Insight into Real-world use and Benefit-risk Profile of Biologics and Frequently Prescribed Drugs in Aging Populations

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Inzicht in het gebruik en het baten-risicoprofiel van biologische medicijnen bij ouderen

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CHAPTER 1.
GENERAL INTRODUCTION

1.1. Rationale for this research

Elderly, comorbidities and politherapy

The significant increase in life expectancy is considered to be one of the greatest demographic achievements. People are living longer lives, and the combination with a decreasing fertility rate seems to lead to a progressive population aging. Globally, there were 727 million persons aged 65 years or over in 2020. Over the next three decades, the number of older persons worldwide is projected to more than double, reaching over 1.5 billion in 2050. Globally, the share of the population aged 65 years or over is expected to increase from 9.3% in 2020 to around 16.0% in 2050 [1].

As the proportion of the world's population in the older ages continues to increase, the burden of chronic diseases increases as well. The complexity of elderly results in functional and cognitive impairment [2, 3] which could increase the risk of geriatric syndromes, such as delirium, falls and incontinence, and, ultimately, it impacts on their quality of life [4, 5].

Elderly patients are characterized by the presence of comorbidities and subsequent polypharmacy that could influence the onset of drug-drug interactions. The report of the World Health Organization in 2019 confirmed that politherapy is a common issue [6]. It is estimated that about 30–40% of subjects over 65 years old take at least 5 drugs in developed countries, while 12% of patients in this age group receive at least 10 different drugs [7]. The result is a higher number of adverse drug events (e.g. as a result of drug interactions) in elderly patients compared to the general population.

Unfortunately, elderly patients are often not included in randomized clinical trials (RCTs) evaluating efficacy and safety of new drugs. Several studies conducted over the past three decades have clearly shown that older patients are underrepresented in RCTs [8-10]. In particular, Gurwitz et al. [8] showed that in over 60% of cases, people over 75 years old were excluded from RCTs performed before 1992. Additionally, papers published after 1980 were more likely to present age-based exclusions from studies published before 1980. These studies enrolled predominantly men, while female sex was predominant among elderly, as women live longer than men. Moreover, in a systematic review, Van Spall H. et al. showed that: common medical conditions were the cause for exclusion in 81.3% of RCTs; patients were excluded due to age in 72.1% of all RTC (38.5% in older adults) and subjects receiving commonly prescribed medications were excluded in 54.1% of trials [11]. Such exclusions impairs the generalizability of RCT results in real-world settings.

Immune-mediated inflammatory diseases and chronic kidney disease

Immune-mediated inflammatory diseases (IMIDs) include a common, clinically different group of conditions, such as rheumatoid arthritis (RA), the spondyloarthritis (SpA), psoriasis, psoriatic arthristis and inflammatory bowel diseases (IBDs), including Crohn's disease (CD) and ulcerative colitis (UC). Patients with IMID are often characterized by comorbidities, including cardiovascular disease, metabolic and bone disorders and cognitive deficit, that further unfavourably impact quality of life and mortality. IMIDs are chronic diseases, affecting also elderly and, with the rising life expectancy worldwide and improvements of the IMID treatments, the number of older individuals with an IMID will continue to expand. Treatment of elderly with

chronic IMID may be a challenge. Advanced age represents a risk factor for several comorbidities, such as cardiovascular disease [12], diabetes [13], and cancer which complicate the use of immunosuppressive therapy [14]. In addition, there may be age-related changes in the pharmacokinetic properties of therapy including absorption, distribution and excretion when compared to the younger age population [15]. The basis of treatment for IMIDs remains life-long immunosuppression. In young patient, while there are recognized risks including that of immunosuppression-related cancers, serious or opportunistic infection, the absolute rate of occurrence of these events is relatively low and the risk-benefit profile favors use in most [16]. However, extrapolation of that safety to older patients is challenging for various reasons. First, older patients were excluded or under-represented in most RCTs of these agents. Moreover, older patients were more likely to withdraw due to drug toxicity [17]. Observational studies examining drug-safety in older patients had small sample sizes limiting generalizability [18-20]. Older age itself increases susceptibility to various therapy related complication, and the consequences of such complications could be more impactful in this population. Thus, there is an important need for systematic study of the safety of biologic therapy in older IMD patients to robustly inform clinical practice.

Chronic kidney disease (CKD) is one of the chronic disease affecting mainly elderly people. In Italy, the prevalence of CKD is 7.5% in men and 6.5% in women, increasing in older CKD patients (from 0.2% in 20–39 year-old to 24.9% in >70 year-old patients) and decreasing in the most severe stages (0.2% and 0.1 in IV and V stage, respectively) [21]. The main related factors may be the aged global population [22] and the type 2 diabetes mellitus [23]. CKD may often progress toward end stage renal disease (ESRD), requiring dialysis or kidney transplantation, which results in a significant reduction of quality of life of the CKD patients due to increasing morbidity and disability, in addition to increasing healthcare costs [24]. In Italy, the annual direct costs of management of a patient on dialysis is estimated to be around €38,821 [25], specifically €29,800 for peritoneal dialysis and €43,800 for hemodialysis [26]. The economic impact of dialysis on the Italian National Health Service (NHS) was estimated to be €2.1 billion per year [26].

Anemia is one of the most clinically important complications of chronic kidney disease and has a negative effect on the patient's quality of life both directly, when symptomatic, and indirectly, increasing the risk of other adverse drug reactions, cardiovascular and mortality risk.

As recommended by the Italian Medicines Agency, erythropoies stimulating agents (ESAs) should be used for the treatment of CKD related anemia and to be started when hemoglobin (Hb) levels are lower than 11 g/dL. Regarding maintenance therapy, ESAs are indicated when Hb levels are between 11 and 12 g/dL [27], but avoiding a rise in Hb greater than 2 g/dl over a four week period, as this may increase the risk of cardiovascular events. Blood transfusions are only recommended when Hb levels are lower than 8 g/dL.

Biologics and biosimilars

In recent years, marketing of highly innovative and costly biologics have improved dramatically the management of high burden diseases, including IMIDs (e.g. TNF-alfa antagonists) and chronic kidney disease (e.g. ESAs). In most therapeutic areas, it is expected a continuously

growing marketing of innovative biotechnological therapies in future years. However, due to their high cost, biologics may have a negative impact on the sustainability of NHS. Since 2006, after the expiration of somatropin patent, the first biosimilar was marketed in Europe. According to European Medicines Agency (EMA) guidelines, a biosimilar is defined as a "*a biological medicinal product that contains a version of the active substance of an already authorized original biological medicinal product (reference medicinal product. A biosimilar demonstrates similarity to the reference medicinal product in terms of quality characteristics, biological, activity, safety and efficacy) based on a comprehensive comparability exercise"* [28].

In general, all biologics produced by recombinant DNA technology share the same type of manufacturing process and they may present a degree of minor variability (i.e., micro-heterogeneity), which must be kept within acceptable ranges to assure positive benefit-risk profiles. This micro-heterogeneity may be detected even within or between batches of the same biologics, especially in the case of changes in the manufacturing process as may happen during the commercial life of the drug. In the pre-marketing phase, a comparability exercise between a biosimilar and a reference product is performed to assess the biosimilarity. The comparability exercise, used to demonstrate the biosimilarity of a biosimilar and the corresponding reference product has been employed for decades to validate that any major manufacturing changes did not impact the quality, safety, and efficacy of the drug [29].

Furthermore, biosimilars can provide around 20−30% purchase cost reduction in comparison to the reference product, thus representing a therapeutic alternative for saving healthcare resources to be reallocated to innovative medicines [30]. To date, up to 67 biosimilars have been authorized by the EMA, and additional 18 biosimilars, are under evaluation [31].

Unfortunately, biosimilars were not immediately well perceived, especially in the first years after their marketing, as demonstrated by the very low penetration of these drugs in most of the European Countries [32-35]. Even though biosimilars were marketed more than 15 years ago, different clinicians and scientific societies are skeptical toward the comparative safety of these drugs versus their reference product and they still need more post-marketing data reassuring about the safety of these drugs.

In light of the concerns still shown by many clinicians, it is essential to conduct post-marketing studies with large study populations in different therapeutic areas (such as chronic kidney disease and IMID) where biologics, and recently also some biosimilars, play an important role, with a special focus in elderly people. In particular, the short treatment period, the reduced and selected number of patients of RCTs highlights the role of post-marketing evidence on the safety of such drugs in real-world setting. In addition, the efficacy and safety data derived from pre-marketing studies of biosimilars usually concern the main indication of use approved. Although this information is often extrapolated to other indications of use, the risk-safety profile of the new indication of a specific drug may differ from the original one. For example, pre-marketing RCTs of the biosimilar infliximab were performed in patients with RA and ankylosing spondylitis and the efficacy and safety data were extrapolated to other indications of use, such as chronic IBDs; similarly, the biosimilar adalimumab has been studied only for the treatment of RA and psoriasis, while the biosimilar etanercept only for the treatment of RA, with subsequent extrapolation to other indications approved for the respective originator.

Another isuue to be addressed in the post-marketing setting concerns the interchangeability of originators and their biosimilars, and, in particular, the risk of immunogenicity by switching between originator and biosimilars, which may cause a lack of effect and toxicity. In clinical practice, the switch between biologics, both originators and biosimilars, is frequent, since about 20% of patients change their therapy during the first year of therapy [32-34, 36]. Data from the NOR-SWITCH study [37] and from spontaneous reporting system databases [38] showed no differences in terms of efficacy and safety between switchers and non-switchers, especially for I generation biosimilars and for infliximab biosimilar. Moreover, Members of the Biosimilar Working Party of the EMA, after exploring the available safety data on switching between a biosimilar and its reference product, concluded that biosimilars licensed in the European Union are interchangeable [39]. However, the safety of switching between originator and biosimilars requires additional investigation in real-world settings and can be further addressed by generating clinical evidence of biosimilarity from pre-marketing studies and post-marketing surveillance [39, 40].

Therefore, with the increasing spectrum of therapeutic options, the paucity of data in older adults and concern about potential safety risk factors affecting this special population, it is essential to critically evaluate and compare the real-world use and the safety of drugs, especially biologics, in elderly patients with chronic kidney disease and IMID.

1.2. Aim and outline of the thesis

The first aims of the research described in the present thesis was to obtain a better understanding of the real-world use of analgesics and biologics approved for the treatment of IMIDs (**Chapter 2**). In particular, in **Chapter 2.1**, the demographic and clinical characteristics of elderly analgesic users, as well as the frequency of analgesic use, including the frequency of potentially inappropriate analgesic use in Caserta Local Health Unit (LHU) (from Southern Italy) were described. **Chapters 2.2** and **2.3** evaluate and compare the baseline characteristics and the pattern of real-world use of drugs (e.g. non-DMARDs and DMARDs) for the treatment of RA, both adult and elderly people, in Southern Italy versus the United States (**Chapter 2.2**) and the real-world use of biologics in elderly patients with inflammatory bowel diseases from Lazio region (**Chapter 2.3**).

Second, in order to evaluate the benefit-risk profile of biologics (**Chapter 3**), an overview of the characteristics and potential challenges in the safety profile assessment of biologics with a focus on the post-marketing setting (**Chapter 3.1**), as well as an overview of the safety and potential drug-drug interaction of immunosuppressive drugs for the treatment of IBD in elderly patients (**Chapter 3.2**) was provided. In this context, the potential of a large Italian multi-database distributed network for conducting post-marketing surveillance of biologics, including biosimilars, approved for the treatment of immune-mediated inflammatory diseases (**Chapter 3.3**) and the potential predictors of ESAs hyporesponsiveness (**Chapter 3.4**) was showed.

Third, **Chapter 4** focused on the interchangeability and switching practices between originators and biosimilars. In general, due to the debate about interchangeability of biosimilar and biological reference product, an overview of the different positions of regulatory authorities on the interchangeability and automatic substitution of biosimilars and reference products as well

as the pharmacological aspects and results from RCT and real-world studies on switching between reference product and biosimilars was provided (**Chapter 4.1**). Moreover, a retrospective analysis investigated the frequency and identified the potential predictors of switching between biosimilar and originator ESAs during the first year of treatment in patients with cancer, CKD, or chemotherapy-related anemia from six large Italian geographic areas in the years 2009-2015 (**Chapter 4.2**). Finally, the comparative effectiveness and safety of switching from ESA α (both originator or biosimilars) to other ESAs versus non-switchers (**Chapter 4.3**) and the impact of biosimilar ESAs in in a large cohort of CKD patients as a strategy to guarantee substainability of the Italian National Health Service (**Chapter 4.4**) were evaluated.

References

1. United Nations. World Population Ageing, Highlights. 2020
2. Marengoni A, Angleman S, Melis R, Mangialasche F, Karp A, Garmen A, Meinow B, Fratiglioni L. Aging with multimorbidity: A systematic review of the literature. Ageing Res. Rev. 2011, 10, 430–439
3. Marengoni A, Von Strauss E, Rizzuto D, Winblad B, Fratiglioni L. The impact of chronic multimorbidity and disability on functional decline and survival in elderly persons. A community-based, longitudinal study. J. Intern. Med. 2009, 265, 288–295
4. Klompstra L, Ekdahl AW, Krevers B, Milberg A, Eckerblad J. Factors related to health-related quality of life in older people with multimorbidity and high health care consumption over a two-year period. BMC Geriatr. 2019, 19, 187
5. Tyack Z, Frakes KA, Barnett A, Cornwell P, Kuys S, McPhail S. Predictors of health-related quality of life in people with a complex chronic disease including multimorbidity: A longitudinal cohort study. Qual. Life Res. 2016, 25, 2579–2592
6. World Health Organization. Medication Safety in Polypharmacy; World Health Organization: Geneva, Switzerland, 2019
7. Kim, J.; Parish, A.L. Polypharmacy and Medication Management in Older Adults. Nurs. Clin. N. Am. 2017, 52, 457–468
8. Gurwitz JH1, Goldberg RJ. Age-based exclusions from cardiovascular clinical trials: implications for elderly individuals (and for all of us): comment on "the persistent exclusion of older patients from ongoing clinical trials regarding heart failure". Arch Intern Med 2011; 171: 557-8
9. Cherubini A, Oristrell J, Pla X, et al. The persistent exclusion of older patients from ongoing clinical trials regarding heart failure. Arch Intern Med 2011; 171: 550-6. https://doi.org/10.1001/archinternmed.2011.31
10. Lee PY, Alexander KP, Hammill BG, et al. Representation of elderly persons and women in published randomized trials of acute coronary syndromes. JAMA 2001; 286: 708-13
11. Van Spall HG, Toren A, Kiss A, et al. Eligibility criteria of randomized controlled trials published in high-impact general medical journals: a systematic sampling review. JAMA 2007; 297: 1233-40
12. Dhingra R, Vasan RS. Age as a risk factor. Med Clin North Am 2012;96:87–91

13. Centers for Disease Control and Prevention. National Diabetes Fact Sheet: General Information and National Estimates on Diabetes in the United States. Atlanta, Georgia, US. 2011
14. Cancer Statistics Working Group. US cancer statistics: 1999 – 2009 incidence and mortality web-based report. Volume http://www.cdc.gov/uscs. Atlanta, Georgia: U.S. 2013
15. Mangoni AA, Jackson SH. Age-related changes in pharmacokinetics and pharmacodynamics: basic principles and practical applications. Br J Clin Pharmacol 2004;57:6–14
16. Siegel CA, Hur C, Korzenik JR, et al. Risks and benefits of infliximab for the treatment of Crohn's disease. Clin Gastroenterol Hepatol 2006;4:1017–24
17. Dahl SL, Samuelson CO, Williams HJ, et al. Second-line antirheumatic drugs in the elderly with rheumatoid arthritis: a post hoc analysis of three controlled trials. Pharmacotherapy 1990;10:79–84
18. Lobaton T, Ferrante M, Rutgeerts P, et al. Efficacy and safety of anti-TNF therapy in elderly patients with inflammatory bowel disease. Aliment Pharmacol Ther 2015;42:441–51
19. Desai A, Zator ZA, de Silva P, et al. Older age is associated with higher rate of discontinuation of anti-TNF therapy in patients with inflammatory bowel disease. Inflamm Bowel Dis 2013;19:309–15
20. Filippini M, Bazzani C, Zingarelli S, et al. Anti-TNF α agents in elderly patients with rheumatoid arthritis: A study of a group of 105 over sixty five years old patients. Reumatismo 2008;60:41–49
21. De Nicola L, Donfrancesco C, Minutolo R, et al. Prevalence and cardiovascular risk profile of chronic kidney disease in Italy: results of the 2008-12 National Health Examination Survey. Nephrol Dial Transplant. 2015;30(5):806-814
22. United States Renal Data System: annual data report: incidence and prevalence of ESRD. Am J Kidney Dis. 2003;42(5):S37–173
23. King H, Aubert RE, and Herman WH. Global burden of diabetes, 1995–2025: prevalence, numerical estimates, and projections. Diabetes Care. 1998;21(9):1414–313
24. Khan S, Amedia CA. Economic burden of chronic kidney disease. J Eval Clin Pract. 2008;14(3):422–34
25. Roggeri A, Roggeri DP, Zocchetti C, et al. Healthcare costs of the progression of chronic kidney disease and different dialysis techniques estimated through administrative database analysis. J Nephrol. 2017; 30(2):263-269
26. Cicchetti A, Ruggeri M, Codella P, Ridolfi A. I costi socio-sanitari dell'insufficienza renale cronica. Farme percorsi Ter. 2011;12(1):21-28
27. Italian Medicines Agency, Determinazione AIFA. Aggiornamento del Piano terapeutico AIFA per prescrizione SSN di Eritropoietine (ex Nota 12). Available from: http://www.agenziafarmaco.gov.it/sites/default/files/2010-07-29_determina_aggiornamento_template_nota_12_g.u._75_del_31-03-2009.pdf
28. European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP): guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/06/WC500144124.pdf

29. Ingrasciotta Y, Cutroneo PM, Marcianò I, Giezen T, Atzeni F, Trifirò G. Safety of Biologics, Including Biosimilars: Perspectives on Current Status and Future Direction. Drug Saf. 2018 Nov;41(11):1013-1022
30. Genazzani AA, Biggio G, Caputi AP, Del Tacca M, Drago F, Fantozzi R, et al. Biosimilar drugs: concerns and opportunities. Biodrugs. 2007; 21:351–6
31. European Medicines Agency. European public assessment reports - biosimilars [Internet]. Available from: https://www.ema.europa.eu/en/medicines/search_api_aggregation_ema_medicine_types/field_ema_med_biosimilar/ema_group_types/ema_medicine
32. Loiacono C, Sgroi C, Coppolino S, Cannata A, Ferrara R, Arcoraci V, et al. How much are biosimilars used in southern Italy? a retrospective analysis of epoetin utilization in the local health unit of Messina in the years 2010–2011. BioDrugs. 2012 Apr 1; 26(2):113–20
33. Ingrasciotta Y, Giorgianni F, Bolcato J, Chinellato A, Pirolo R, Tari DU, Troncone C, Fontana A, Ientile V, Gini R, Santoro D, Santarpia M, Genazzani A, Uomo I, Pastorello M, Addario WS, Scondotto S, Cananzi P, Caputi AP, Trifirò G. How Much Are Biosimilars Used in Clinical Practice? A Retrospective Italian Population-Based Study of Erythropoiesis-Stimulating Agents in the Years 2009-2013. BioDrugs. 2015 Aug;29(4):275-84
34. Marcianò I, Ingrasciotta Y, Giorgianni F, Bolcato J, Chinellato A, Pirolo R, Di Giorgio A, Manna S, Ientile V, Gini R, Santarpia M, Genazzani AA, Uomo I, Pastorello M, Pollina Addario SW, Scondotto S, Cananzi P, Da Cas R, Traversa G, Rossi M, Sottosanti L, Caputi AP, Trifirò G. How did the Introduction of Biosimilar Filgrastim Influence the Prescribing Pattern of Granulocyte Colony-Stimulating Factors? Results from a Multicentre, Population-Based Study, from Five Italian Centres in the Years 2009-2014. BioDrugs. 2016 Aug;30(4):295-306
35. Marcianò I, Ingrasciotta Y, Giorgianni F, Ientile V, Chinellato A, Tari DU, Gini R, Cannavò S, Pastorello M, Scondotto S, Cananzi P, Traversa G, Trotta F, Belleudi V, Addis A, Trifirò G. Pattern of Use of Biosimilar and Originator Somatropin in Italy: A Population-Based Multiple Databases Study During the Years 2009-2014. Front Endocrinol (Lausanne). 2018 Mar 13;9:95
36. D'Amore C, Da Cas R, Rossi M, Traversa G. Switching Between Epoetins: A Practice in Support of Biosimilar Use. BioDrugs. 2016 Feb;30(1):27-32
37. Jørgensen KK, et al. Switching from originator infliximab to biosimilar CT-P13 compared with maintained treatment with originator infliximab (NOR-SWITCH): a 52-week, randomised, double-blind, non-inferiority trial. Lancet. 2017 Jun 10;389(10086):2304-2316
38. Ebbers HC, et al. The safety of switching between therapeutic proteins. Expert Opin Biol Ther. 2012 Nov;12(11):1473-85
39. Kurki P. et al. Interchangeability of biosimilars: a European perspective. BioDrugs. 2017, 31, 83–91
40. Trifirò G, Marcianò I, Ingrasciotta Y. Interchangeability of biosimilar and biological reference product: updated regulatory positions and pre- and post-marketing evidence. Expert Opin Biol Ther. 2018;18(3):309–15

CHAPTER 2.
REAL-WORLD USE OF BIOLOGICS AND ANALGESICS AMONG ELDERLY

2.1. Analgesic drug use in elderly persons: A population-based study

Adapted from:

Ingrasciotta Y[1], Sultana J[1], Giorgianni F[2], Menditto E[3], Scuteri A[4], Tari M[5], Tari DU[5], Basile G[1], Trifiro' G[1,6]. **Analgesic drug use in elderly persons: A population-based study in Southern Italy.** PLoS One. 2019 Sep 19;14(9):e0222836. doi: 10.1371/journal.pone.0222836. PMID: 31536588; PMCID: PMC6752879.

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Abstract

Introduction: Analgesics such as non-steroidal anti-inflammatory drugs (NSAIDs), weak and strong opioids are commonly used among elderly persons. The aim of this study was to describe the demographic and clinical characteristics of elderly analgesic users and to measure the frequency of analgesic use, including the frequency of potentially inappropriate analgesic use.
Methods: The Arianna database was used to carry out this study. This database contains prescription data with associated indication of use for 1,076,486 inhabitants registered with their general practitioners (GPs) in the Caserta Local Health Unit (Caserta district, Campania region in Italy). A cohort of persons aged ≥65 years old with >1 year of database history having at least one analgesic drug (NSAIDs, strong or weak opioids) between 2010 and 2014 were identified. The date of the first analgesic prescription in the study period was considered the index date (ID).
Results: From a source population of 1,076,486 persons, 116,486 elderly persons were identified. Of these, 94,820 elderly persons received at least one analgesic drug: 36.6% were incident NSAID users (N = 36,629), while 13.2% were incident weak opioid users (N = 12,485) and 8.1% were incident strong opioid users (N = 7,658). In terms of inappropriate analgesic use, 9.2% (N = 10,763) of all elderly users were prescribed ketorolac/indomethacin inappropriately, since these drugs should not be prescribed to elderly persons. Furthermore, at least half all elderly persons with chronic kidney disease or congestive heart failure were prescribed NSAIDs, while these drugs should be avoided.
Conclusion: Analgesics are commonly used inappropriately among elderly persons, suggesting that prescribing practice in the catchment area may yet be improved.

Introduction

Pain is common medical problem among older persons and can lead to impaired functionality, depression and a lower quality of life [1]. Mild to moderate acute pain is treated with acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs) as first-line agents [2]. NSAIDs are generally categorized as: a) non-selective compounds which inhibit both cyclo-oxygenase (COX)-1 and COX-2 enzymes; b) COX-2-selective drugs, also known as coxibs, which are associated with a lower risk of gastrointestinal bleeding than non-specific NSAIDs [3]. Due to their strong anti-inflammatory action, NSAIDs are generally indicated in pain of inflammatory origin. On the other hand, opioid analgesics are indicated in pain of visceral origin, in palliative care and in general, in moderate to severe pain not responding to NSAIDs.

Drug use and safety among elderly persons is of importance because this population is more likely to use several drugs concomitantly [4]. Elderly persons are also likely to be frailer in terms of increased multi-morbidity, impaired cognition and reduced independence in activities of daily living [5]. Indeed, the high prevalence of pain in frail elderly persons [6] in addition to the widespread overuse of opioids in some countries [7] creates an urgent need to understand pharmacological pain management approach among the elderly. This is important given the drug risk-benefit profiles may change as a function of cognitive and functional impairment [8].

The Beers criteria for inappropriate analgesic prescribing suggest that the NSAIDs ketorolac and indomethacin should not be prescribed in elderly persons and that non-selective NSAIDs should not be used chronically in elderly persons [9]. Furthermore, several analgesics are contraindicated in conditions which are more frequently present in elderly persons compared to younger ones, such as congestive heart failure (CHF) and chronic kidney disease (CKD). It is therefore important to describe whether analgesic drugs are used appropriately among elderly persons, especially in view of the potential risks in this population, such as falls/ fractures with opioid use [10], and gastric bleeding [11], cardiovascular events [12] or acute kidney disease/CKD [13, 14] with NSAIDs.

Despite the increasing prevalence of pain with increasing age, two leading European clinical guideline organizations, the UK National Institute for Health and Care Excellence (NICE) and the Scottish Intercollegiate Guidelines Network (SIGN) do not have guidelines dedicated to the management of pain in the elderly.

The Italian Geriatric Society (SIGOT) does not have such guidelines on pain management in the elderly while other societies, such as the British Geriatrics Society does [15]. Analgesic drug utilization in this population may therefore be variable. This in addition to the widespread opioid epidemic in some countries is a further incentive to study analgesic use among elderly persons. The appropriateness of analgesic use in Italy has been the topic of limited published research, including the appropriateness of opioid use in cancer patients [16], inappropriate use in chronic pain [17] or in relation to a change in drug prescribing directives [18, 19]. However, to our knowledge, there is no recent Italian study investigating inappropriate analgesic use in the elderly. The aim of this study was therefore to describe the demographic and clinical characteristics of elderly analgesic users and to measure the frequency of analgesic use in this population, including the frequency of potentially inappropriate analgesic use.

Methods

Data source

The Arianna database was used to carry out this study. This database contains prescription data with associated indication of use for 1,076,486 persons living in the catchment area registered with their GPs in the Caserta Local Health Unit (Caserta district, Campania region in Italy). These data are linked with the following patient-level claims data from the same catchment area: demographic registry, pharmacy claims database for drugs acquired through the Italian National Healthcare System (NHS) and a database of hospital discharge diagnoses.
Within the linkage database, diagnoses are recorded using the 9th Edition of the International Classification of Disease codes with clinical modification (ICD-9 CM) while drugs are recorded using Anatomical Therapeutic Chemical (ATC) codes. Pharmacy claims contain prescription data for drugs that are covered by the Italian NHS, including most analgesics. Acetaminophen is not covered by the Italian NHS unless it is found in combination with other drugs. Although most analgesics are covered by the Italian NHS, patients may still opt to buy them out-of-pocket.
In addition to the demographic and clinical patient characteristics mentioned above, the results of a comprehensive geriatric assessment (CGA) concerning cognitive status, mobility, nursing needs and social support were used to further describe the study population. CGA data was extracted for approximately 75% of persons aged 65 and older (N = 116,486 in the study period) registered with the Caserta Local Health Unit. This CGA is carried out yearly for elderly persons in the catchment area by their GPs [20].
The study was carried out using retrospectively collected and anonymized data. In Italy, such studies do not require ethical approval by an Ethics Committee as per the Italian Health Ministry/Italian Drug Agency decree of the 3rd August 2007.

Study population
A cohort of patients from the Caserta catchment area was identified, including patients who had one year of database history, were aged at least 65 years old and received at least one analgesic drug prescription between 2010 and 2014. Patients were censored if transferred out of the database (i.e., changed to a permanent residence outside the catchment area) or if they died. Persons with no analgesic drug dispensing within one year before the index date were considered incident drug users.

Exposure
Analgesic drugs, i.e. NSAIDs, weak opioids and strong opioids were the exposure of interest and were identified within the population of elderly persons using ATC codes. The date of the first analgesic prescription in the study period was considered the index date (ID). Acetaminophen was not included as a main study drug as, this drug is not covered by the Italian NHS unless in combination with codeine and is mainly purchased out-of-pocket as an over-thecounter (OTC) drug. Codeine was considered only in combination with acetaminophen as only this preparation is indicated for pain in Italy.
All analgesic drugs were grouped by pharmacological categories: NSAIDs, including nonselective NSAIDs and coxibs, weak opioids or strong opioids (see ***Online Resource 1*** for further detail). Codeine was considered only in combination with acetaminophen as only this preparation is indicated for pain in Italy. Analgesics were further categorized by formulation (oral, injection, transdermal, rectal or nasal). Indications associated with the analgesic drug prescriptions were reported. The mean prescribed defined daily dose (PDD) for each analgesic

prescription was estimated by dividing the drug doses prescribed (i.e. number of units per day multiplied by the strength prescribed) by the defined daily dose (DDD).
Inappropriate analgesic drug prescribing was identified using Beers criteria [8]. The frequency of inappropriate drug prescriptions in the elderly population was estimated based on the following recommendations: 1) Completely avoid indomethacin and ketorolac in older persons due to an increased risk of GI bleeding and peptic ulcer disease; 2) Avoid chronic use (defined within this study as >90 days) of oral non- selective NSAIDs, i.e. aspirin at doses exceeding 325 mg daily, diclofenac, ibuprofen, ketoprofen, meloxicam, nabumetone, naproxen, oxaprozin or piroxicam, in high risk groups, such as those aged >75 or taking oral or parenteral corticosteroids, anticoagulants, or antiplatelet agents. Inappropriate drug use was also identified based on contraindications in specific disease states: 1) NSAID use in chronic kidney disease (CKD) of any stage, non-selective NSAIDs and coxib use in persons with heart failure; 2) Aspirin at doses exceeding 325 mg daily and non-selective NSAID use in persons with gastric/duodenal ulcers; 3) any pentazocine prescriptions to elderly persons.

Data analysis
For incident analgesic users, demographic and clinical characteristics in terms of age, sex, comorbidities, specifically heart failure, diabetes mellitus, ischemic heart disease (e.g. angina pectoris and acute myocardial infarction), cerebrovascular events (e.g. transient ischemic attack and stroke), chronic kidney disease, gastric and duodenal ulcer, liver disease and gout were identified any time prior to the index date. The number of concomitant drugs used was also estimated within three months before the index date as a proxy of overall disease burden for the following: beta-blockers, diuretics, angiotensin-converting enzyme (ACE) Inhibitors, angiotensin receptor blockers, proton pump inhibitors, misoprostol, statins, lithium, digoxin, methotrexate, gabapentin/pregabalin, tricyclic antidepressants, antipsychotics, selective serotonin reuptake inhibitors (SSRI), anticoagulants, antiplatelet drugs and corticosteroids. The use of analgesics among incident users was described in terms of indication of use median number of daily doses (with interquartile range), formulation used and median number of inappropriate prescriptions (with interquartile range). Incident analgesic users were also described in terms of selected CGA evaluations. Only CGA data regarding elderly incident analgesic users was extracted; results were restricted to the CGAs closest to the index date. The frequency of inappropriate analgesic use was measured without restricting to incident analgesic users since the inappropriate use of these drugs concerns a broader group of patients, i.e. those who are incident as well as those who are not new users. All frequencies related to inappropriate drug use were stratified by age groups: 65–74 years old, 75–84 years old and ≥85 years. Frequencies were calculated both considering number of persons with the disease as a denominator as well as number of elderly persons using the analgesic drugs of interest. A time to event Kaplan-Meier analysis (i.e., time to discontinuation) was performed, stratifying analgesic-naïve users by pharmacological categories, to assess treatment persistence over time. From the beginning of the therapy, for each naïve user we estimated the number of days of continuous analgesic treatment, taking into account dispensed amount of active principle and Defined Daily Dose (DDD) of analgesics. Persistence to analgesics therapy was assessed based on the maximum allowed treatment gap of 60 days, defined as the time between the last day covered by analgesic drug treatment and the time to the next refill. Follow-up of naïve analgesic

users was censored if patients were still on therapy at the end of the study, in case of death or no availability of further data, whichever came first. The Kaplan Meier analysis was carried out and results were stratified by pharmacological categories (non-steroidal anti-inflammatory drugs, weak opioids and strong opioids).

Sub-analyses

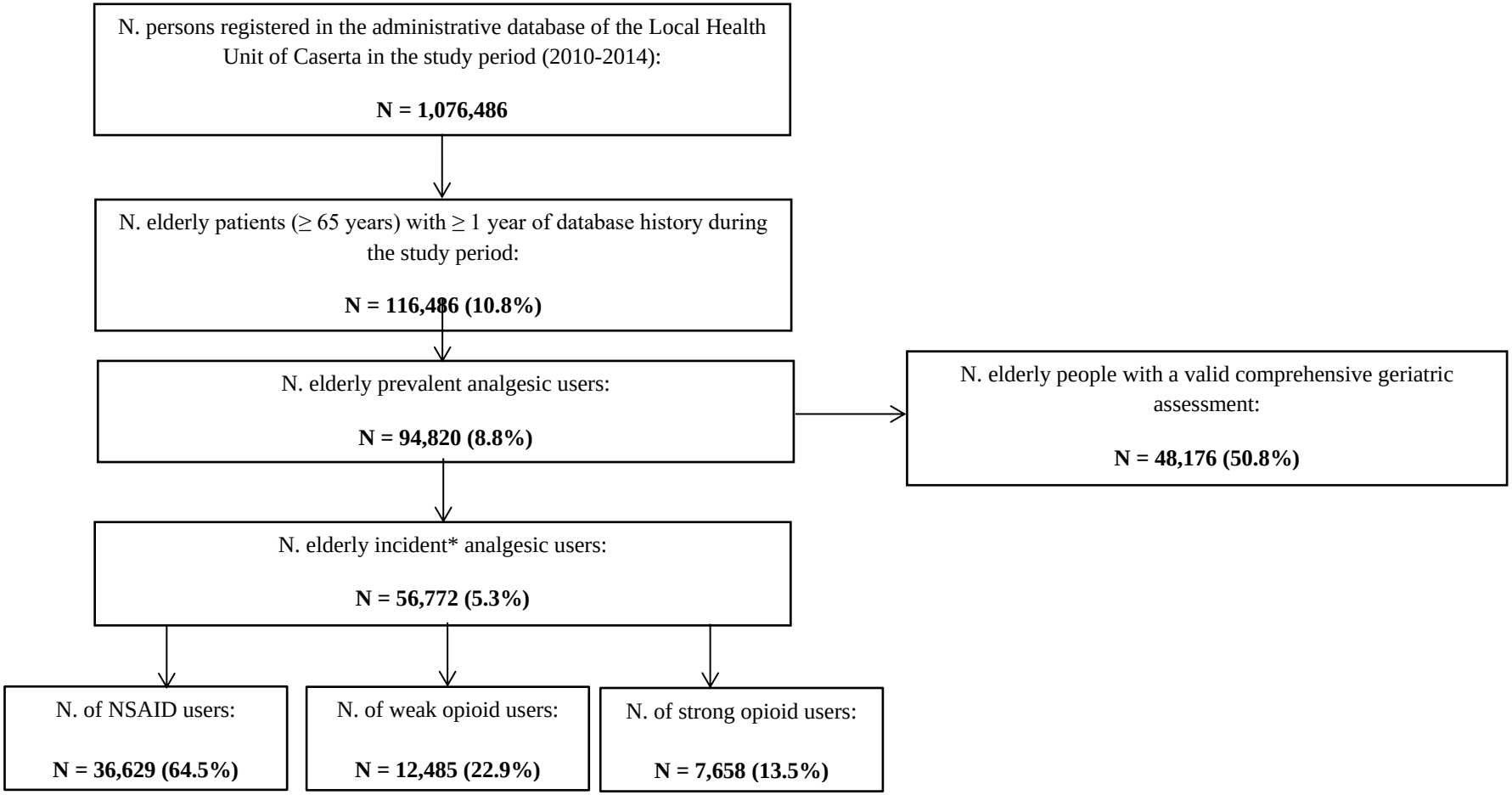
A sub-analysis was carried using a different data source out to find to what extent non-opioid analgesics were purchased over the counter (OTC) from community pharmacies in the catchment area. This analysis was carried out using a database provided by IMS Health on pharmacy sales data for all pharmacies in Caserta. Prescription data from IMS is aggregate prescription-level data through which it is possible to distinguish between units of drugs dispensed through the NHS and those OTC. Data management and analyses were carried out using SAS version 9.2 and SPSS/PC, Version 21 (SPSS Inc., Chicago, Illinois, USA). A p-value of 0.05 was used to denote statistical significance, using the Kruskal-Wallis, Fischer and Chi-square tests, as appropriate.

Results

Prevalence of analgesic use

From a source population of 1,076,486 persons in the catchment area, 116,486 elderly persons were identified. Of these, 94,820 were elderly persons who were dispensed at least one analgesic drug (**Fig. 1**). In 2014, it was seen that NSAIDs were by far the most commonly used analgesics in all age categories (***Online Resource 2***). Up to 50% of all elderly persons aged 75 and over were prescribed an NSAID. The use of all other analgesics was much less common, at less than 15% for all persons aged 65 and over. There was no clear unifying trend concerning the yearly prevalence of non-opioid drugs from 2010 to 2014, although several marked changes in use can be seen for single drugs (***Online Resource 3***). At the beginning of the study period, 2010, the most commonly used non-opioid drug was nimesulide, with a prevalence of approximately 20%, but this decreased by half by 2014. In 2014, the most commonly used non-opioid drugs were ketoprofen (17%), followed by diclofenac (13%) and nimesulide (11%). While the prevalence of several non-opioid drugs did not change notably or decreased during the study period, etoricoxib was the only non-opioid drug whose use increased over the study period, going from 7% to 8%. The most commonly used opioid drug was codeine in combination with acetaminophen, which increased in prevalence from 4 to 5.5% (***Online Resource 4***). The use of oxycodone in combination with naloxone/acetaminophen, and tapentadol increased very markedly over the study period, going from 1 to 3.5% and 0.2 to 1.5%, respectively.

Fig. 1 Identification of elderly persons receiving analgesic drugs during the study period.



Legend: NSAID: non-steroidal anti-inflammatory drug.
*Elderly incident users: no analgesics dispensed within one year prior to the first identified analgesic dispensing.

Incidence of analgesic use: Population characteristics

Overall, 94,820 (81.4% of total elderly) elderly analgesic users were identified, of whom 36,629 (36.6%; mean age 73.1±7.1), 12,485 (13.2%; mean age 74.4±7.0) and 7,658 (8.1%; mean age 74.2±6.8) were incident users of NSAIDs, weak and strong opioids respectively (**Table 1**). More of the incident elderly analgesic users were female rather than male, with the difference being increasingly pronounced in the following order: strong opioids > weak opioids > NSAIDs. The DDD for these three analgesic groups did not decrease linearly, but was highest for non-opioid analgesics > strong opioids > weak opioids. In terms of overall medical condition, defined using number of concomitant medications as a proxy of disease burden, strong opioid users received more concomitant drugs (7.1±4.1) than weak opioid users (6.5±4.0) or non-opioid users (4.2±3.3). Among all three analgesic groups, the most common indication for analgesic prescribing was bone and joint disorders.

Table 1. Characteristics of elderly incident users (≥65 years) of NSAIDs, weak and strong opioids in the years 2010–2014. Numbers in brackets refer to the percentages unless otherwise specified.

	NSAIDs N = 36,629 (%)	**Weak Opioids N = 12,485 (%)**	**Strong Opioids N = 7,658 (%)**	**P-value NSAIDs vs. Strong Opioids**
Demographic characteristics				
Sex				
Male	16,612 (45.4)	4,439 (35.6)	2,592 (33.8)	<0.001
Female	20,017 (54.6)	8,046 (64.4)	5,066 (66.2)	
Median age, years (Q1-Q3)	72 (67-78)	74 (68-79)	74 (69-79)	<0.001
65-74	22,836 (62.3)	6,751 (54.1)	4,184 (54.6)	<0.001
75-84	10,900 (29.8)	4,629 (37.1)	2,866 (37.4)	
≥ 85	2,893 (7.9)	1,105 (8.9)	608 (7.9)	
Median follow-up, years (Q1-Q3)	2.8 (2.2-4.5)	2.8 (2.3-4.9)	2.8 (2.3-4.8)	<0.001
Comorbidities				
Cardiovascular diseases				
Heart failure	2,184 (6.0)	1,055 (8.5)	651 (8.5)	<0.001
Ischemic heart disease	7,319 (20.0)	3,260 (26.1)	2,005 (26.2)	<0.001
Cerebrovascular events	32,031 (87.4)	11,703 (93.7)	7,163 (93.5)	<0.001
Hypertension	29,875 (81.6)	11,172 (89.5)	6,858 (89.6)	<0.001
Metabolic diseases				
Diabetes mellitus	9,268 (25.3)	3,844 (30.8)	2,370 (30.9)	<0.001
Other chronic diseases				
Chronic kidney disease	1,016 (2.8)	554 (4.4)	315 (4.1)	<0.001
Miscellaneous				
Gastric and duodenal ulcer	509 (1.4)	235 (1.9)	159 (2.1)	<0.001
Liver disease	2,762 (7.5)	1,244 (10.0)	815 (10.6)	<0.001
Gout	5,075 (13.9)	2,702 (21.6)	1,690 (22.1)	<0.001
Prior fractures	3,027 (8.3)	1,360 (10.9)	916 (12.0)	<0.001
Previous use of pain relief medications				
NSAIDs	-	5,388 (43.2)	3,973 (51.9)	<0.001
Weak Opioids	950 (2.6)	-	1,378 (18.0)	<0.001

Strong Opiods	404 (1.1)	586 (4.7)	-	<0.001
Median number of concomitant drugs (Q1-Q3)	4 (2-6)	6 (4-9)	7 (4-9)	<0.001
0	3,826 (10.4)	353 (2.8)	145 (1.9)	<0.001
1-2	9,063 (24.7)	1,473 (11.8)	708 (9.2)	
3-5	12,875 (35.1)	3,865 (31)	2,064 (27.0)	
6-10	9,156 (25.0)	5,005 (40.1)	3,274 (42.8)	
>10	1,709 (4.7)	1,789 (14.3)	1,467 (19.2)	
Concomitant drugs	23,419 (63.9)	9,140 (73.2)	5,608 (73.2)	<0.001
Cardiovascular drugs	8,715 (23.8)	3,292 (26.4)	2,007 (26.2)	<0.001
Digoxin	1,110 (3.0)	549 (4.4)	319 (4.2)	<0.001
Central nervous system drugs				
Antidepressant drugs	4,393 (12.0)	2,141 (17.1)	1435 (18.7)	<0.001
Antipsychotics	47 (0.1)	16 (0.1)	14 (0.2)	0.127
Gabapentin/pregabalin	471 (1.3)	407 (3.3)	402 (5.2)	<0.001
Rheumatological drugs				
Methotrexate	83 (0.2)	56 (0.4)	51 (0.7)	<0.001
Corticosteroids	2,273 (6.2)	1,687 (13.5)	1,408 (18.4)	<0.001
Blood thinning drugs				
Anticoagulants	2,784 (7.6)	1,669 (13.4)	1,128 (14.7)	<0.001
Antiplatelet drugs	10,966 (29.9)	4,595 (36.8)	2,612 (34.1)	<0.001
Anticoagulants/antiplatelet drug combination therapy	440 (1.2)	185 (1.5)	123 (1.6)	0.004
Miscellaneous				
Gastroprotectant agents	11,758 (32.1)	6,166 (49.4)	4,320 (56.4)	<0.001
Analgesic use				
Median number of inappropriate analgesic prescriptions (Q1-Q3)*	8 (5–12)	11 (7–15)	11 (8–16)	<0.001
Median number of daily doses, DDD (Q1-Q3)**	0.03 (0.02–0.06)	0.01 (0.00–0.01)	0.01 (00.0–0.02)	<0.001
Median duration of treatment, days (Q1-Q3)	17 days (16–31))	5 days (5–11)	8 days (5–22	
Formulation				
Oral	27,477 (75.0)	11,826 (94.7)	6,699 (87.5)	<0.001
Injection	8,783 (24.0)	610 (4.9)	12 (0.2)	
Transdermal	-	-	849 (11.1)	

Rectal	6 (0.0)	-	-	
Nasal	-	-	13 (0.2)	
More than one	363 (1.0)	47 (0.4)	85 (1.1)	
Indication of use				
Bone and joint diseases	33,230 (90.7)	10,149 (81.3)	5,678 (74.1)	<0.001
Urinary tract disorders (i.e. renal colic)	833 (2.3)	78 (0.6)	19 (0.3)	
Cancer pain	392 (1.1)	952 (7.6)	1,154 (15.1)	
Other and unclassified	2,162 (5.9)	1,305 (10.5)	807 (10.5)	

*inappropriate drug prescriptions were defined as: 1) use of indomethacin and ketorolac among elderly persons; 2) chronic use of oral non- selective NSAIDs (aspirin at doses exceeding 325 mg daily, diclofenac, ibuprofen, ketoprofen, meloxicam, nabumetone, naproxen, oxaprozin or piroxicam, among patients aged >75 or those taking oral or parenteral corticosteroids, anticoagulants, or antiplatelet agents; 3) any NSAID use in chronic kidney disease; 4) non-selective NSAID and coxib use in patients with heart failure; 5) aspirin at doses exceeding 325 mg daily and non-selective NSAID use in persons with gastric/duodenal ulcers; 6) any pentazocine prescriptions to elderly persons.
Abbreviations: NSAID: non-steroidal anti-inflammatory drugs; Q1-Q3: 25th percentile to 75th percentile.

Incidence of analgesic use: drug utilization in frail elderly persons

Overall, strong opioid users showed more factors indicating frailty status than weak opioid or non-opioid users. For example, a larger proportion of elderly strong opioid users had mild cognitive impairment compared to weak opioids and non-opioid drug users, while there was no difference in the proportion of persons with moderate and severe cognitive impairment among the three analgesic groups. With regard to nursing needs, non-opioid users were more commonly those with no additional nursing needs, compared to the other two analgesic groups; conversely, strong opioid users more commonly required nursing assistance than the other two analgesic groups. Strong opioid users were also more likely to be required assistance regarding mobility (**Table 2**).

Table 2. Comprehensive geriatric assessment for elderly incident analgesic users.

	NSAID users N=11,409 (%)	**Weak opioid users N= 4,033 (%)**	**Strong opioids users N= 2,528 (%)**	**P-value**
Cognitive status: SPMSQ results				
Intact Intellectual Functioning	9,152 (80.3)	3,062 (75.9)	1,915 (75.8)	<0.001
Mild Intellectual Impairment	1,340 (11.7)	604 (15.0)	380 (15.0)	
Moderate Intellectual Impairment	573 (5.0)	249 (6.2)	155 (6.1)	
Severe Intellectual Impairment	344 (3.0)	118 (2.9)	78 (3.1)	
Nursing needs				
High	537 (4.7)	270 (6.7)	197 (7.8)	<0.001
Low	1,345 (11.8)	678 (16.8)	488 (19.3)	
No nursing need	9,527 (83.5)	3,085 (76.5)	1,843 (72.9)	
Social support				
Good	11,015 (96.5)	3,840 (95.2)	2,431 (96.2)	<0.001
Not good	394 (3.5)	193 (4.8)	97 (3.8)	
Mobility				
Independent	9,953 (87.2)	3,301 (81.8)	1,972 (78.0)	<0.001
Requires assistance	688 (6.1)	350 (8.7)	274 (10.8)	
No mobility at all	768 (6.7)	382 (9.5)	282 (11.2)	

Abbreviations: SPMSQ: short portable mental status questionnaire.

Inappropriate analgesic use

Overall, a total of 10,763 (9.2%) of all elderly analgesic users were considered to have an inappropriate prescription for the NSAIDs (ketorolac or indomethacin), although this appeared to be more widespread for ketorolac (9,748 patients, 8.4%) compared to indomethacin (1,237 patients, 8.4%) (**Table 3**). In contrast, the chronic use of non-selective non-steroidal anti-inflammatory drugs, defined as that exceeding 90 days, was less common (1,1611 patients, 1.4%). There were only 4 elderly persons with a prescription for pentazocine. With regards to disease-specific indicators of prescribing appropriateness, the degree of inappropriate prescribing was similar for NSAIDs use in CKD, non-selective NSAID or coxib use in heart failure and non-selective NSAID use in gastric/duodenal ulcers (**Table 4**).

Table 3. Frequency of inappropriate drug prescriptions in the elderly population according to the Beers criteria, stratified by age groups.

		Patients 65-74 years old N = 70,406		**Patients 75-84 years old N = 34,612**		**Patients ≥85 years old N = 11,468**		**Total N = 116,486**	
Drugs/drug classes	**Inappropriate drug use criteria**	**Patients N (%)**	**Prescriptions N**	**Patients N (%)**	**Prescriptions N**	**Patients N (%)**	**Prescriptions N**	**Patients N (%)**	**Prescriptions N**
Indomethacin or ketorolac	Avoid in elderly persons	6,345 (9.0)	12,375	3,553 (10.3)	7,428	865 (7.5)	1,686	**10,763 (9.2)**	**21,489**
Indomethacin		733 (1.0)	1,422	425 (1.2)	977	79 (0.7)	193	**1,237 (1.1)**	**2,592**
Ketorolac		5,745 (8.2)	10,953	3,201 (9.3)	6,451	802 (7.0)	1,493	**9,748 (8.4)**	**18,897**
All oral non COX 2-selective NSAIDs	Avoid chronic use if no gastroprotectant agents* are used	977 (1.4)	5,728	526 (1.5)	3,573	108 (0.9)	717	**1,611 (1.4)**	**10,018**

*proton pump inhibitor or misoprostol

Abbreviations: COX-selective NSAIDs: cyclo-oxygenase 2 selective non-steroidal anti-inflammatory agents

Table 4. Frequency of inappropriate drug prescriptions in the elderly population with a specific disease, stratified by age groups.

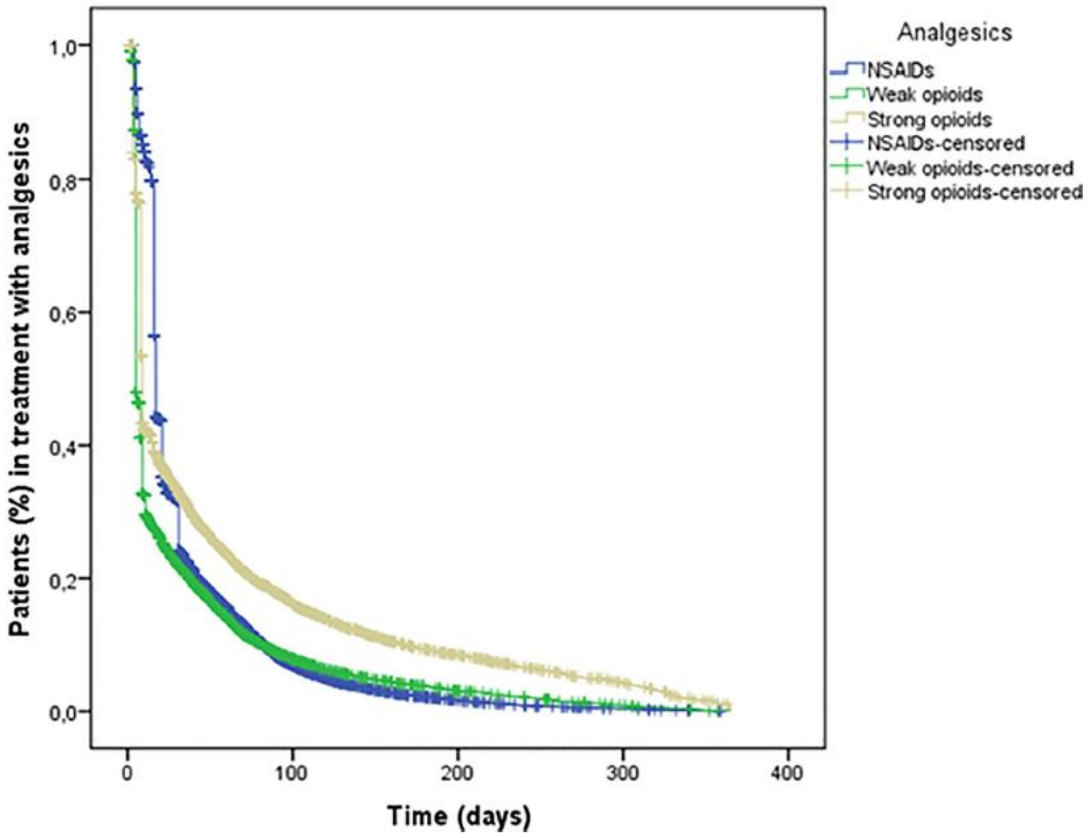
	Patients 65-74 years old		**Patients 75-84 years old**		**Patients ≥85 years**		**Total**	
	Patients N = 70,406 (% on all population; % on patients with the disease)	**Prescriptions N**	**Patients N = 34,612 (% on all population; % on patients with the disease)**	**Prescriptions N**	**Patients N = 11,468 (% on all population; % on patients with the disease)**	**Prescriptions N**	**Patients N = 116,486 (% on all population; % on patients with the disease)**	**Prescriptions N**
Chronic kidney disease any stage								
Non-selective NSAIDs and COX-2 inhibitors	1,993 (2.8; 55.0)	12,173	1,966 (5.7; 51.8)	10,892	733 (6.4; 44.1)	3,277	4,692 (4.0; 51.7)	26,342
Heart failure								
Non-selective NSAIDs and COX-2 inhibitors	2,891 (4.1; 58.0)	18,292	3,492 (10.1; 56.3)	21,077	1,472 (12.8; 47.6)	7,052	7,855 (6.7; 55.0)	46,421
Gastric/duodenal ulcers								
Aspirin >325 mg/day	47 (0.1; 0.7)	77	32 (0.1; 0.8)	42	9 (0.1; 0.7)	33	88 (0.1; 0.7)	152
Non-selective NSAIDs	4,269 (6.1; 62.2)	24,832	2,562 (7.4; 62.6)	14,846	727 (6.4; 53.7)	3,910	7,558 (6.5; 61.4)	43,588

Abbreviations: COX-selective NSAIDs: cyclo-oxygenase 2 selective non-steroidal anti-inflammatory agents; NSAIDs: non-steroidal anti-inflammatory drugs

Persistence

The median duration of treatment was 17 days (IQR: 16–31) for NSAIDs, 5 days (IQR: 5–11) for weak opioids and 8 days (IQR: 5–22) for strong opioids. Overall, 91.01% (N = 51,370) of elderly patients discontinued their analgesic medication using a 60 day treatment gap to define discontinuation; this decreased to 84.09% (N = 48,946) on using a 120 day treatment gap definition. Using any definition, persistence was always slightly higher for strong opioid use. None of the analgesic users were persistent at 1 year from the start of analgesic use (**Fig. 2**). Persistence for strong opioids was always highest while that for weak opioids and NSAIDs was lower.

Fig. 2 Time to discontinuation of analgesic therapy among incident analgesic users.



Sub-analysis

The analysis on analgesic dispensing using IMS pharmacy sales data confirmed that by and large, about half of non-opioid analgesic drugs acquired in community pharmacies was indeed bought over-the-counter and could not have been captured by the NHS administrative drug dispensing databases (***Online Resource 5***).

Discussion

To our knowledge, the present study is the first to describe analgesic use and appropriateness among elderly persons in Italy. Among the incident elderly analgesic users identified, more persons were prescribed non-opioid analgesics than opioid analgesics, and among opioid analgesics, weak opioids were more commonly used than strong opioids. This is in line with the

recommended stepped use of analgesic drugs, where non-opioids are first-line agents, followed by weak and strong opioids. Recent years have seen an 'opioid crisis' take place in the U.S.A., with widespread over-use and misuse of opioids, leading to a large number of overdose-related deaths [21]. In Italy there has been a four-fold increase in the number opioid prescriptions from 2007 to 2017, as reported by the Italian Society of Pharmacology, however this increase is odest compared to other European countries [22]. Indeed, the cautious use of opioids is confirmed by the very short median duration of these drugs: 5 days (IQR: 5–11) for weak opioids and 8 days (IQR: 5–22) for strong opioids; there is no study to which these results can be compared at the time of writing. The trend in opioid use in Italy may be related to a law passed in 2010 known as Law 38/2010 in which the Italian government commits to improving the access to palliative care and pain relief. While a recently published study using data from pharmacy sales on a national level confirmed a relative increase in opioid use in Italy from 2000 to 2010, this study reported that opioid use is overall low; the most commonly used drug was codeine, which was used at 5 DDD per day per 1,000 persons in 2010 [23].

Evaluating the appropriateness of opioid prescribing is a challenge, as this depends on an accurate classification of the severity of pain. For example, the present study found that weak and strong opioids were commonly used for bone and joint disorders, although less commonly than non-opioid analgesics. Although opioids can be used appropriately in joint and bonerelated pain, they should only be used for moderate to severe pain [24]. On the other hand, opioids were commonly used in persons with cancer as an indication, in line with the indication of these drugs in palliative care [25]. In the context of frailty, it is surprising that strong opioids were used more commonly in frailer persons compared to persons with a better cognition and functional status because elderly persons who are frail are likely to have poorer mobility [26]. This is likely to predispose such elderly persons to ADRs such as falling with risk of facture, increasing the risk of hospitalization and disability [27].

The decreasing prevalence of nimesulide among elderly persons is perhaps the most notable trend among non-opioid analgesics. This may be related to concerns as early as 2007, when EMA reviewed nimesulide after the government of Ireland suspending the marketing authorization for this drug due to concerns about drug-induced liver disease [28]. Uncertainty about this drug remained unresolved, because in 2010, EMA requested the Committee for Medicinal Products for Human Use to evaluate the nimesulide risk-benefit profile and recommend a regulatory course of action such as changing, suspending or withdrawing the marketing authorization of the drug throughout the European Union. The Italian Drug Agency published a notice on the risk of hepatotoxicity with use of NSAIDs, with specific mention of nimesulide in 2012, however the reduction in the use of nimesulide after 2012 was minimal compared to the reduction from 2010 to 2012 [29].

On the other hand, the mild increase in the prevalence of etoricoxib use from 2010 to 2014 may make sense in the context of sequence of safety concerns about this drug, and indeed the whole class of COX-2 inhibitors. The controversy surrounding these drugs culminated in the withdrawal of rofecoxib; it may be hypothesized that the subsequent evaluation of the safety of etoricoxib in 2008 by EMA [30], published in Italian by the Italian Drug Agency [31], may have been an important factor leading prescribers to prescribe this drug more confidently.

In terms of absolute numbers, ketorolac and indomethacin were commonly inappropriately prescribed, that is, they were prescribed in 10,763 elderly persons whereas they should not be

prescribed in this population at all. Nevertheless, when considered in terms of relative frequency, this population consisted of 9.2% of the elderly persons considered. Non-selective NSAIDs were prescribed inappropriately, that is chronically and without concomitant gastroprotective drugs, in a smaller number of elderly persons (N = 1,611, 1.4% of the study population). As expected the inappropriate use of pentazocine, defined as the prescription of this drug to an elderly person, was very low, amounting to only 4 persons during the study period.

However, we suggest that this does not reflect the appropriateness of use of this drug as much as the low prevalence of this drug; the clinical relevance of this finding is limited. The appropriateness of other opioid drugs was not treated in Beers criteria, and was seldom mentioned in START-STOPP criteria [32], except with regard to the recommended concomitant use of laxatives if opioids are used chronically and concerning the treatment of pain in the appropriate clinical context, i.e. not treating mild pain with strong transdermal opioids as a first line of treatment. It was not possible to evaluate this criterion for inappropriate use since the level of pain was not quantifiable as mild, moderate or severe. Similarly, the appropriateness of other analgesic drugs in the context of pain severity was not possible. It is worth noting that the appropriate use of medications in frail persons may go beyond the available guidance on the appropriate use of medications. For example, while acute and chronic kidney disease may be caused, exacerbated or worsened by non-opioid analgesics, it may be misleading to monitor renal function renal function in elderly persons through creatinine levels alone in patients with sarcopenia, i.e. reduced muscle mass and strength. Sarcopenia is often a component of frailty especially in very old patients; in patients with this condition it is essential to use equations such as CKD EPI or MDRD to monitor renal function [33]. Results on medication appropriateness in the present study do not take this into account.

The main strength of this study is the use of real-world clinical data reflecting the actual use of analgesic drug prescribing in clinical practice and the large size of the elderly population studied. Another important strength of this study is the detailed description of elderly analgesic users in terms of frailty. This is approach combines traditional drug utilization research using healthcare databases with data from comprehensive geriatric assessments. The latter is rarely available in large-scale databases and is even more rarely used. A further strength is the detail provided not only regarding the prevalence of analgesic drug use but also regarding use of these drugs in elderly persons with varying degrees of cognitive or physical impairment, which is not commonly available or used in secondary healthcare data. Furthermore, the potentially inappropriate use of these drugs in elderly persons was described in detail, including the duration of drug use as well as the use of analgesics in specific populations such as the use of NSAIDs and COX-2 inhibitors not concomitantly prescribed gastroprotective drugs.

However this study also has some limitations. Although we assume that a prescription for analgesics covers the patient for the duration equivalent to finishing all the doses in a package, it is possible that this leads to an over-estimation of drug exposure, as analgesic use may be sporadic. Furthermore, it is possible that persons in the catchment area buy the analgesic drugs out of pocket, rather than through the Italian NHS. In this case, such drug use would not be captured. However, it is unlikely that persons chronically using these drugs would buy them out-of-pocket as over the counter drugs, particularly concerning strong NSAIDs, coxibs and opioids. Acetaminophen, along with other medications which are not covered by the Italian NHS or which are covered but which patients prefer to buy out of pocket, such as inexpensive medications, are

not captured by the present data. Furthermore, the diagnoses identified in the present study may be underestimated, since these are only captured on hospital admission. As a result, inappropriate medication use may also be underestimated. Finally, it should be borne in mind that the present study is descriptive in nature and predictors of drug utilization were not explored. Future studies may want to build on findings from the present study by investigating predictors of using non-opioid and/or opioid medications as well as describe analgesic polypharmacy and its implications in elderly populations.

Conclusions

Analgesics are commonly used in elderly persons, with weak non-opioid analgesics being most used. In particular these drugs were commonly used in persons having varying degrees of cognitive and physical impairment. Overall, at least half all elderly persons with chronic kidney disease or congestive heart failure were prescribed NSAIDs inappropriately. Both non-opioid and opioid analgesics should be used with caution in elderly persons, and the need and appropriateness of such drugs should be evaluated regularly.

References

1. Kaye AD, Baluch A, Scott JT. Pain management in the elderly population: a review. Ochsner J. 2010 Fall; 10(3):179–87.
2. Blondell RD, Azadfard M, Wisniewski AM. Pharmacologic therapy for acute pain. Am Fam Physician. 2013 Jun 1; 87(11):766–72.
3. Bacchi S, Palumbo P, Sponta A, Coppolino MF. Clinical pharmacology of non-steroidal anti-inflammatory drugs: a review. Antiinflamm Antiallergy Agents Med Chem. 2012; 11(1):52–64.
4. Onder G, Bonassi S, Abbatecola AM, Folino-Gallo P, Lapi F, Marchionni N et al. High prevalence of poor quality drug prescribing in older individuals: a nationwide report from the Italian Medicines Agency (AIFA). J Gerontol A Biol Sci Med Sci. 2014; 69(4):430–7.
5. Sultana J, Fontana A, Giorgianni F, Basile G, Patorno E, Pilotto A et al. Can information on functional and cognitive status improve short-term mortality risk prediction among community-dwelling older people? A cohort study using a UK primary care database. Clin Epidemiol. 2017; 10:31–39.
6. McLachlan AJ, Bath S, Naganathan V, Hilmer SN, Le Couteur DG, Gibson SJ et al. Clinical pharmacology of analgesic medicines in older people: impact of frailty and cognitive impairment. Br J Clin Pharmacol.2011; 71(3):351–64.
7. Skolnick P. The Opioid Epidemic: Crisis and Solutions. Annu Rev Pharmacol Toxicol. 2018 Jan 6;58:143–159.
8. Routledge PA, O'Mahony MS, Woodhouse KW. Adverse drug reactions in elderly patients. Br J Clin Pharmacol. 2004; 57(2):121–6.
9. American Geriatrics Society 2012 Beers Criteria Update Expert Panel. American Geriatrics Society updated Beers Criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc. 2012; 60(4):616–31.
10. Miller M, Stu¨rmer T, Azrael D, Levin R, Solomon DH. Opioid analgesics and the risk of fractures in older adults with arthritis. J Am Geriatr Soc. 2011; 59(3):430–8.

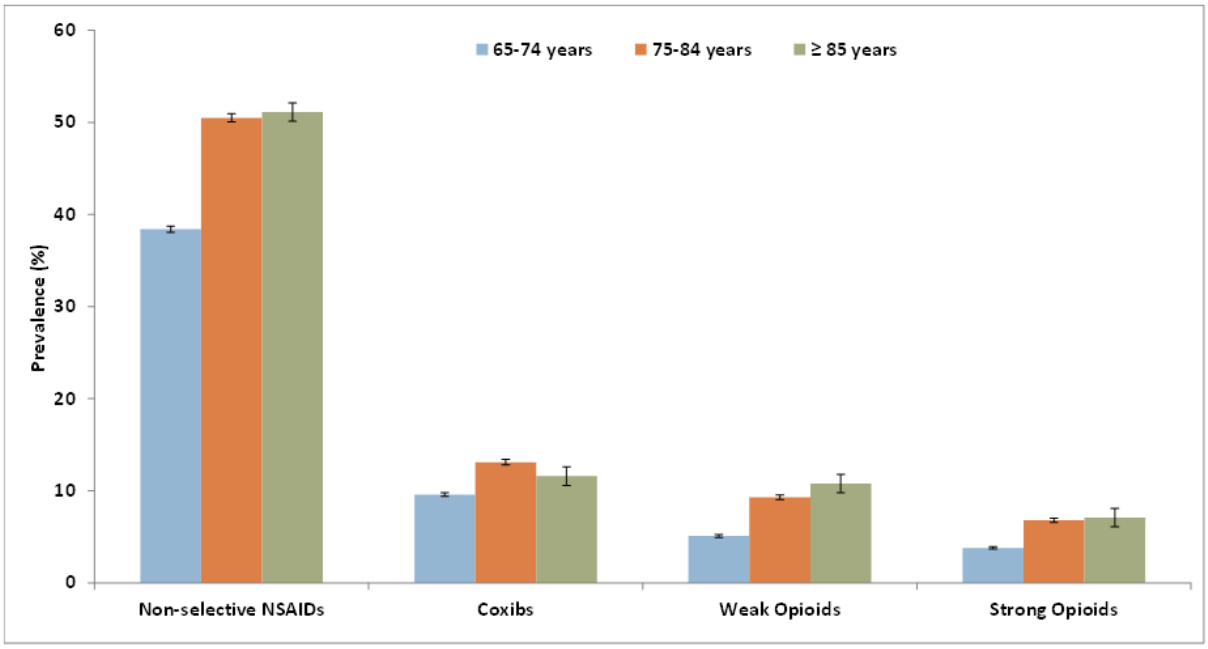
11. Kocoglu H, Oguz B, Dogan H, Okuturlar Y, Hursitoglu M, Harmankaya O et al. NSAIDs and ASA Cause More Upper Gastrointestinal Bleeding in Elderly than Adults? Gastroenterol Res Pract. 2016:8419304.
12. Solomon DH, Rassen JA, Glynn RJ, Lee J, Levin R, Schneeweiss S. The comparative safety of analgesics in older adults with arthritis. Arch Intern Med. 2010; 170(22):1968–76.
13. Ungprasert P, Cheungpasitporn W, Crowson CS, Matteson EL. Individual non-steroidal anti-inflammatory drugs and risk of acute kidney injury: A systematic review and meta-analysis of observational studies. Eur J Intern Med. 2015; 26(4):285–91.
14. Ingrasciotta Y, Sultana J, Giorgianni F, Fontana A, Santangelo A, Tari DU et al. Association of individual non-steroidal anti-inflammatory drugs and chronic kidney disease: a population-based case control study. PLoS One. 2015; 10(4):e0122899.
15. Abdulla A, Adams N, Bone M, Elliott AM, Gaffin J, Jones D et al. Guidance on the management of pain in older people.Age Ageing. 2013 Mar; 42 Suppl 1:i1–57.
16. Ripamonti C, Fagnoni E, Campa T, Brunelli C, De Conno F. Is the use of transdermal fentanyl inappropriate according to the WHO guidelines and the EAPC recommendations? A study of cancer patients in Italy. Support Care Cancer. 2006 May; 14(5):400–7.
17. Ussai S, Miceli L, Pisa FE, Bednarova R, Giordano A, Della Rocca G et al. Impact of potential inappropriate NSAIDs use in chronic pain. Drug Des Devel Ther. 2015 Apr 9; 9:2073–7.
18. Viola E, Trifirò G, Ingrasciotta Y, Sottosanti L, Tari M, Giorgianni F et al. Adverse drug reactions associated with off-label use of ketorolac, with particular focus on elderly patients. An analysis of the Italian pharmacovigilance database and a population based study. Expert Opin Drug Saf. 2016 Dec; 15 (sup2):61–67.
19. Lombardi N, Vannacci A, Bettiol A, Marconi E, Pecchioli S, Magni A et al. Prescribing Trends of Codeine-containing Medications and Other Opioids in Primary Care After A Regulatory Decision: An Interrupted Time Series Analysis. Clin Drug Investig. 2019 May; 39(5):455–462.
20. Guerriero F, Orlando V, Tari DU, Di Giorgio A, Cittadini A, Trifirò G et al. How healthy is communitydwelling elderly population? Results from Southern Italy. Transl Med UniSa. 2015; 13: 59–64.
21. Skolnick P. The Opioid Epidemic: Crisis and Solutions. Annu Rev Pharmacol Toxicol. 2018; 58:143–159.
22. Società Italiana di Farmacologia. Trattamento del dolore cronico in Italia: appropriatezza terapeutica con oppiacei e timore di addiction: situazione italiana vs USA. Apr18. Available from: https://sif-website.s3.amazonaws.com/uploads/position_paper/attachment/139/sif_position_paper_dolore_oppiacei_apr18.pdf
23. Musazzi UM, Rocco P, Brunelli C, Bisaglia L, Caraceni A, Minghetti P. Do laws impact opioids consumption? A breakpoint analysis based on Italian sales data. J Pain Res. 2018 Aug 29; 11:1665–1672.
24. Marras F, Leali PT. The role of drugs in bone pain. Clin Cases Miner Bone Metab. 2016 May-Aug; 13 (2):93–96.
25. Bruera E, Paice JA. Cancer pain management: safe and effective use of opioids. Am Soc Clin Oncol Educ Book. 2015:e593–9.

26. Sultana J, Fontana A, Giorgianni F, Basile G, Patorno E, Pilotto A et al. Can information on functional and cognitive status improve short-term mortality risk prediction among community-dwelling older people? A cohort study using a UK primary care database. Clin Epidemiol. 2017 Dec 19; 10:31–39.
27. Daoust R, Paquet J, Moore L,E´ mond M, Gosselin S, Lavigne G et al. Recent opioid use and fall-related injury among older patients with trauma. CMAJ. 2018 Apr 23; 190(16):E500–E506.
28. European Medicines Agency (EMA). Nimesulide summary. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Nimesulide/human_referral_000275.jsp&mid=WC0b01ac0580024e99
29. Agenzia Italiana del Farmaco (AIFA—Italian Drug Agency). Nota 66. Available from: http://www.aifa.gov.it/sites/default/files/determinazione_nota_66.pdf
30. European Medicines Agency (EMA). Questions and answers on the review of etoricoxib-containing medicines. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Etoricoxib/human_referral_000104.jsp
31. Agenzia Italiana del Farmaco (AIFA—Italian Drug Agency). Domande e Risposte predisposte dall'EMEA in merito alla revisione dei medicinali contenenti ETORICOXIB (2008). Available from: http://www.aifa.gov.it/sites/default/files/faq_comunicato_etoricoxib260608.pdf
32. O'Mahony D, O'Sullivan D, Byrne S, O'Connor MN, Ryan C, Gallagher P. STOPP/START criteria for potentially inappropriate prescribing in older people: version 2. Age Ageing. 2015; 44(2):213–8.
33. Carter JL, Stevens PE, Irving JE, Lamb EJ. Estimating glomerular filtration rate: comparison of the CKD-EPI and MDRD equations in a large UK cohort with particular emphasis on the effect of age. QJM. 2011; 104(10):839–47.

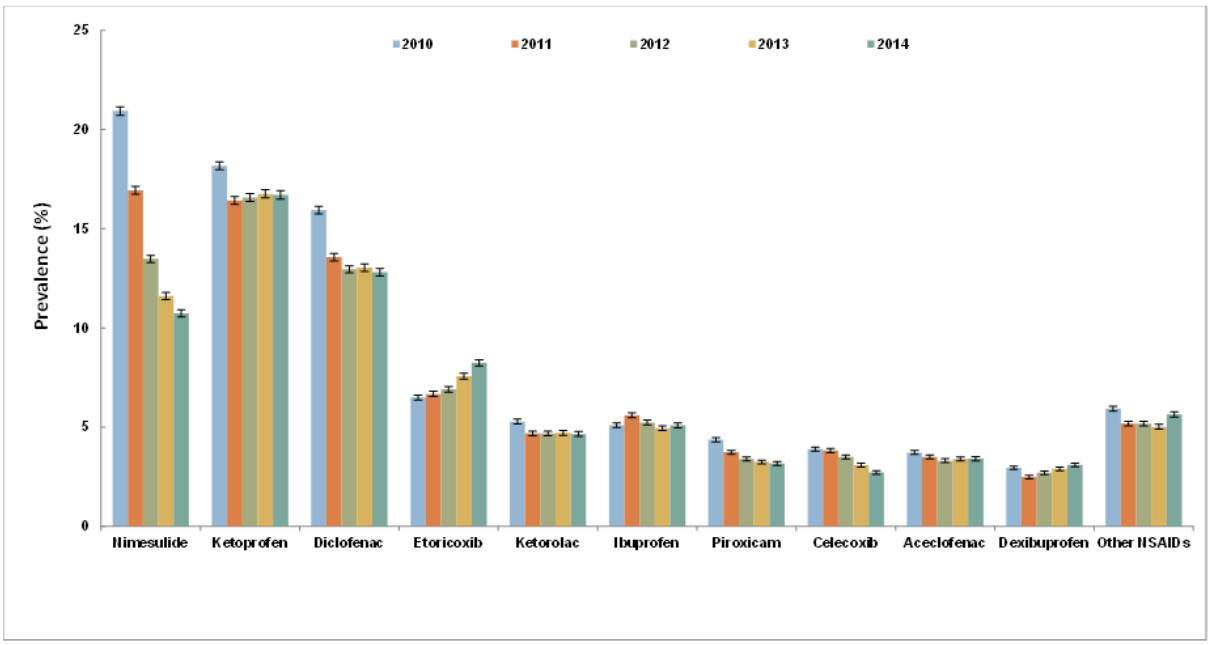
Online Resource 1: Analgesics identified by ATC codes and generic name.

Category	ATC	Generic name
Non-steroidal anti-inflammatory drugs	M01AB01	Indometacin
	M01AB05	Diclofenac
	M01AB14	Proglumetacin
	M01AB15	Ketorolac
	M01AB16	Aceclofenac
	M01AB55	Diclofenac, combinations
	M01AC01	Piroxicam
	M01AC02	Tenoxicam
	M01AC05	Lornoxicam
	M01AC06	Meloxicam
	M01AE01	Ibuprofen
	M01AE02	Naproxen
	M01AE03	Ketoprofen
	M01AE09	Flurbiprofen
	M01AE11	Tiaprofenic acid
	M01AE12	Oxaprozin
	M01AE14	Dexibuprofen
	M01AE17	Dexketoprofen
	M01AE52	Naproxen and esomeprazole
	M01AE53	Ketoprofen, combinations
	M01AE91	Carprofen
	M01AG01	Mefenamic acid
	M01AH01	Celecoxib
	M01AH05	Etoricoxib
	M01AX01	Nabumetone
	M01AX02	Niflumic acid
	M01AX05	Glucosamine
	M01AX17	Nimesulide
	M01AX22	Morniflumate
	N02BA01	Acetylsalicylic acid
	N02BA51	Acetylsalicylic acid, combinations excl. psycholeptics
Weak opioids	N02AA59	Codeine
	N02AX02	Tramadol
Strong opioids	N02AA01	Morphine
	N02AA03	Hydromorphone
	N02AA05	Oxycodone
	N02AA55	Oxycodone and naloxone
	N02AB03	Fentanyl
	N02AE01	Buprenorphin
	N02AX06	Tapentadolo
	N07BC02	Methadone

Online Resource 2. Prevalence of elderly analgesic users, stratified by age group in 2014.

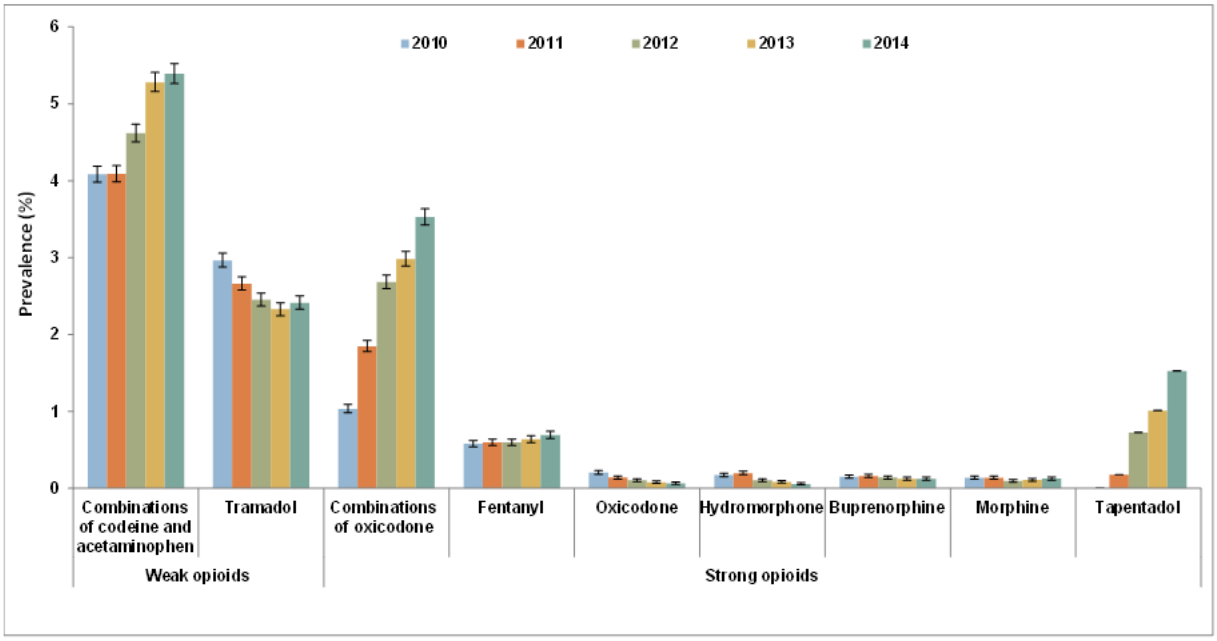


Online Resource 3. Prevalence of elderly NSAID users, stratified by calendar year and individual nonselectiveNSAIDs and coxibs.



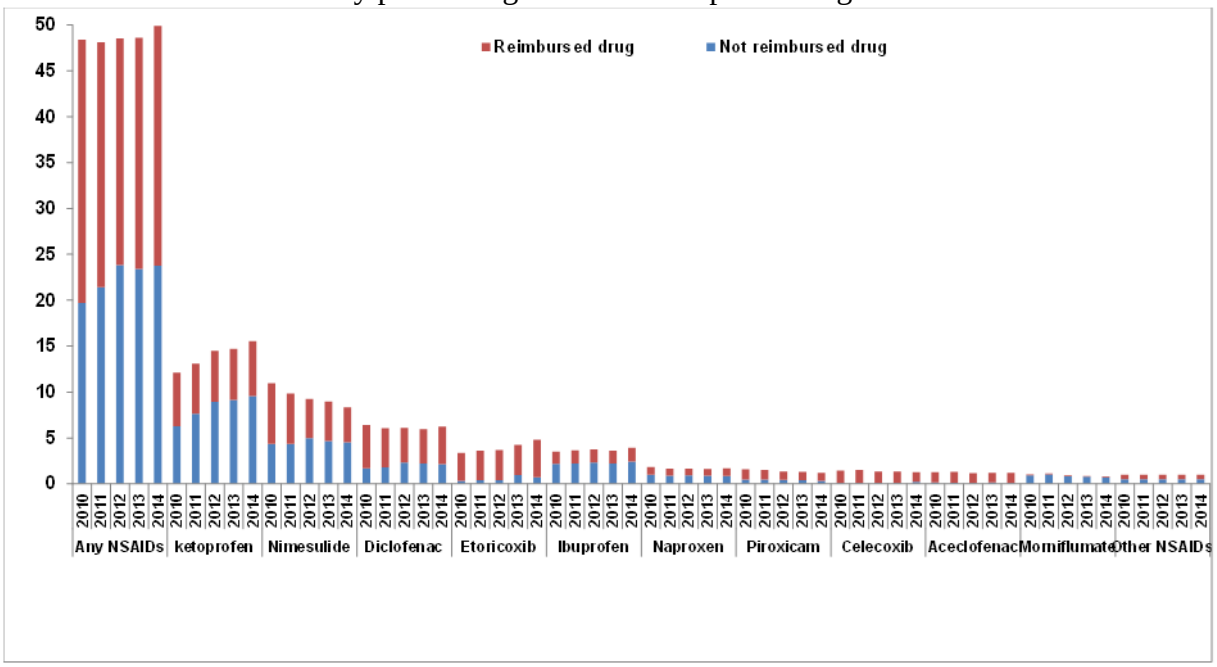
Other NSAIDs: lornoxicam, meloxicam, diclofenac and misoprostol, ketoprofen sucralfate, ketoprofen and omeprazole, dexketoprofen, naproxen, nabumetone, flurbiprofen, acetylsalicylic acid, acetylsalicylic acid combinations excl. Psycholeptics, indomethacin, mefenamic acid, niflumic acid, tenoxicam, morniflumate, tiaprofenic acid, oxaprozin, naproxen and esomeprazole, amtolmetine guacil, proglumetacin, cinnoxicam

Online Resource 4. Prevalence of elderly opioid users, stratified by calendar year and individual drug.



Combinations of oxycodone: oxycodone and naloxone, oxycodone and acetaminophen.

Online Resource 5. Yearly purchasing trend of non-opioid analgesics.



Other NSAIDs: Dexketoprofen, mefenamic acid, niflumic acid, tiaprofenic acid, dexibuprofen, diclofenac combination, flurbiprofen, indomethacin, ketoprofen combination, ketorolac, lornoxicam, meloxicam, nabumetone, oxaprozin, tenoxicam.

2.2. Real-world patient characteristics and use of disease-modifying anti-rheumatic drugs in patients with rheumatoid arthritis

Adapted from:

Ylenia Ingrasciotta[1-3], Yinzhu Jin[4], Saveria S. Foti[2], Joan E. Landon[4], Michele Tari[5], Francesco Mattace-Raso[3], Seoyoung C. Kim[4,6], Gianluca Trifirò[2,7]. **Real-world patient characteristics and use of disease-modifying anti-rheumatic drugs in patients with rheumatoid arthritis: a cross-national study**. *[Submitted to: Journal of Clinical Medicine]*

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2.3. Real-world use of biologics among elderly patients with inflammatory bowel disease

Adapted from:

Ylenia Ingrasciotta[1, 2], Valentina Isgrò[3], Valentina Ientile[2], Matilde Tanaglia[3], Luca L'Abbate[3], Valeria Belleudi[4], Francesca Poggi[4], Elena Sofia Fiore[3], Gianluca Trifirò[3], Francesco Mattace-Raso[1]. **Real-world use of biologics among elderly patients with inflammatory bowel disease**. *[To be submitted]*

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CHAPTER 3.
MONITORING OF THE BENEFIT-RISK PROFILE OF BIOLOGICS

3.1. Safety of biologics, including biosimilars: perspectives on current status and future direction

Adapted from:

Ylenia Ingrasciotta[1], Paola M. Cutroneo[2,3], Ilaria Marcianò[2], Thijs Giezen[4], Fabiola Atzeni[5], Gianluca Trifiro'[1,2]. **Safety of Biologics, Including Biosimilars: Perspectives on Current Status and Future Direction.** Drug Saf. 2018 Nov;41(11):1013-1022. doi: 10.1007/s40264-018-0684-9. PMID: 29796832.

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Abstract

In recent years, marketing of highly innovative and costly biologics improved the management of highburden diseases such as autoimmune diseases, cancers, and chronic renal failure. Several widely prescribed biologics have recently lost or will shortly lose their patents, thus opening avenues to the marketing of a growing number of biosimilars worldwide, which are products similar in terms of quality, safety, and efficacy to already licensed reference products, thus allowing for potential savings in pharmaceutical expenditure. Numerous debates about the interchangeability between biosimilars and reference products are still ongoing, owing to concerns about potentialimmunogenicity raised by switching, which may cause a lack of effect and toxicity. Patients successfully treatedwith biologic therapy may theoretically receive biosimilars to contain costs, if reference product and related biosimilar are judged as interchangeable. However, the positions of regulatory agencies on the interchangeability and automatic substitution of biologics with biosimilars are very different. The benefit-risk profile of biosimilars has been often questioned by clinicians owing to the limited amount of pre-marketing information on clinical efficacy and safety, despite biosimilarity being based on a comparability exercise with the reference product to gain the biosimilar approval. Nevertheless, after more than 10 years of marketing from the first biosimilar approval in Europe, no proof of differences in terms of the safety profile of biosimilars and originators has been reported. In this context, post-marketing evaluation of both biologics and biosimilars safety profiles through analyses from spontaneous reporting databases and claims databases is crucial. An important issue for the pharmacovigilance of biologics concerns the traceability, indicating the brand name and batch number in spontaneous adverse drug reaction reports, but this requirement is not frequently addressed. This review aims to provide an overview of the characteristics and potential challenges in the safety profile assessment of biologics with a focus on the post-marketing setting.

Introduction

Highly innovative and costly biologics significantly improved the management of high-burden diseases such as autoimmune disorders (e.g., tumor necrosis factor-a antagonists), cancers (e.g., rituximab, trastuzumab), and chronic renal failure (e.g.,. epoetins). Knowledge about the safety profile of new drugs, including biologics, is not complete at approval time, owing to intrinsic limitations of pre-marketing clinical trials. Furthermore, during the preapproval phase, the safety profile assessment is more difficult for biologics than for chemically synthetized molecules because of limited predictability of animal studies and a high immunogenicity potential. Post-marketing safety data therefore become essential to evaluate new potential safety concerns in clinical practice. Moreover, the biologics manufacturing or formulating process may change over time [1, 2]. The potential impact of these changes on quality, efficacy, and safety should always be evaluated by the company and assessed by the regulatory agencies.

To date, a variety of important safety issues have been detected in the post-marketing setting with the use of biologics. Generally, adverse events related to these agents are attributed to an augmentation of the known pharmacologic actions, such as the risk of infections and malignancies, or are related to immunologic and infusion reactions, including anti-drug antibody development as a result of the protein nature of these agents.

Because of their specific characteristics, biologics require the implementation of distinctive strategies in pharmacovigilance and risk management. Given the growing number of innovative biologics, and the marketing of biosimilars in new therapeutic areas such as oncology, there is a need to put in place a more efficient post-marketing surveillance system of these drugs, which may profit from the availability of a large amount of electronic healthcare databases to complement spontaneous reporting systems.

This review aims to provide an overview of the characteristics and potential challenges in the safety profile assessment of biologics with a focus on the post-marketing setting. As vaccines are a very heterogenous group with their own characteristics, their safety profile is beyond the scope of this review.

Definitions and pharmacologic and regulatory considerations

Biologics contain one or more active substances, produced by or extracted from a biologic source (i.e., living cells or organisms), including products manufactured by recombinant DNA techniques [3, 4]. Targets of biologics are specific proteins or receptors playing a key role in disease progression [5], thus offering substantial benefits in terms of response rate and quality of life [6]. Biologics include a wide variety of molecules, e.g., hormones, growth factors, interleukins, monoclonal antibodies, which differ in size and structural complexity (e.g., their molecular mass ranges from 5 kDa for insulin to more than 150 kDa for monoclonal antibodies) [3]. The manufacturing process is therefore much more complex for biologics than for chemically synthetized drugs [4], thus leading to higher development costs. As a consequence, many biologics are listed among the top 30 molecules accounting for the pharmaceutical expenditure in public hospitals [7].

All biologics produced by recombinant DNA technology share the same type of manufacturing process and they may present a degree of minor variability (i.e., microheterogeneity), which must be kept within acceptable ranges to assure positive benefit-risk profiles. This micro-heterogeneity may be detected even within or between batches of the same biologic, especially

in the case of changes in the manufacturing process as may happen during the commercial life of the drug. As mentioned by the European Medicines Agency (EMA), ‘‘natural variability is inherent to all biologics and strict controls are always in place during manufacturing to ensure that it does not affect the way the medicine works or its safety’’ [3]. Specifically, biologics often undergo postmarketing changes in their production process [1, 2], which need to be assessed by the regulatory agencies.

Once a biologic loses its patent, the corresponding biosimilar may be marketed. According to the World Health Organization, a biosimilar is defined as a biotherapeutic product that is similar in terms of quality, safety, and efficacy to an already licensed reference biotherapeutic product [8].

In the pre-marketing phase, a comparability exercise between a biosimilar and a reference product is performed to assess the biosimilarity. Furthermore, biosimilars guarantee a reduction of 20–30% of the purchase cost, compared to the reference product, thus representing a therapeutic alternative while contributing to the National Health Service’s sustainability. By January 2018, up to 38 biosimilars have been authorized by the EMA, the first being approved in 2006 (somatropin) [9], while only nine biosimilars are available in USA since 2015 [10]. Recently, the first biosimilars of rituximab, bevacizumab, and trastuzumab, approved for hematologic malignancies, rheumatoid arthritis, and different neoplasms, have been approved by the EMA.

The comparability exercise, used to demonstrate the biosimilarity of a biosimilar and the corresponding reference product, has been employed for decades to validate that any major manufacturing changes did not impact the quality, safety, and efficacy of the drug. As compared to the approval procedure of the reference product, most of the emphasis in the biosimilar approval is placed on the physicochemical and biologic characterization. Biosimilar companies are advised to apply a stepwise approach starting with quality evaluation and, if biosimilarity is demonstrated, continue with pre-clinical and clinical evaluations, pharmacokinetic and/or pharmacodynamic studies, and generally one controlled clinical trial comparing the short-term efficacy and safety of a biosimilar and a reference product. Biosimilar product labeling incorporates relevant data and information from the reference product labeling, with appropriate product-specific modifications [11, 12].

There have been numerous debates about the interchangeability of biosimilars and reference products based on concerns of immunogenicity due to switching, which may cause a lack of effect and toxicity. Patients successfully treated with biologic therapy may theoretically receive biosimilars to contain costs, if reference product and related biosimilar are judged as interchangeable. However, regulatory agencies have different positions on defining interchangeability, which are described below (Sect. 5).

Concerning safety evaluations, data related to biosimilars are collected during the clinical development phase using pharmacokinetic/pharmacodynamic studies and clinical trials. The previously documented safety data for the reference product are taken into consideration and should be the basis for the safety assessment of biosimilars. Adverse events should be evaluated in terms of type, severity, and frequency to allow a comparison to the reference product. A risk management plan (RMP) must be submitted as part of the application dossier for all biologics, including biosimilars, followed by periodic safety update reports and a collection of the adverse events identified and reported during the post-marketing phase [13].

The RMP of the biosimilar is initially based on the reference product RMP, taking into consideration known and potential safety concerns associated with the reference product use. The RMP should, generally, include identified and/or potential risks and further pharmacovigilance activities to identify any adverse drug reactions (ADRs). Immunogenicity should be mentioned in the RMP of a biologic in case of expected safety problems. Any specific safety monitoring strategy used for the reference product should be applied to the biosimilar as well. Such information needs to be periodically integrated with post-marketing data, to provide as much complete as possible overview of the benefit-risk profile of all biologics [14].

Post-marketing monitoring of safety of biologics including biosimilars

In general, the safety profile of biologics includes adverse reactions related to their pharmacologic actions and immunologic reactions, such as immunogenicity and administration-site reactions [13, 15, 16]. Unlike small chemically synthetized molecules, systemic adverse effects of biologics are more often caused by the pharmacodynamics effects of the drug (so-called 'on-target risks'). Most biologics, such as monoclonal antibodies, have a prolonged half-life and increased durations of action in comparison with small molecules and are usually injectable drugs, frequently associated with mild, cutaneous, or hypersensitivity reactions.

Immunogenicity is considered an important safety concern for biologics, which may induce immune responses, including mild hypersensitivity, infusion reactions, or cross-reactions to endogenous molecules. This may result in a loss of efficacy or deficiency syndromes (e.g., thrombocytopenia as a result of neutralizing antibodies blocking endogenous thrombopoietin after treatment with recombinant thrombopoietin or neutralizing antibodies with human growth hormone) [17].

Immunogenicity can be induced by active substance, impurities, structural modifications, protein aggregation, and patient factors, such as co-morbidities, genetics, and previous or concomitant drug exposures. One of the best-known examples of biologic-related immunogenicity was the development of pure red cell aplasia, sustained by cross-reacting neutralizing antibodies against endogenous erythropoietin, associated with the subcutaneous administration of recombinant epoetin alpha in patients with chronic kidney disease [18, 19]. Pure red cell aplasia was ascribed to a combination of factors related to the production, handling, and route of administration of one particular formulation of an epoetin alpha reference product, in which the stabilizer albumin was substituted by polysorbate 80 and glycine. Organic compounds leached by polysorbate 80 from the stoppers used in the prefilled
syringes of the biologic may have had a role in the product's immunogenicity [20].

Biologic-related immunologic reactions also include systemic inflammatory reactions, such as cytokine release syndrome (CRS) or cytokine storms. Cytokine release syndrome occurs as a result of notable immune activation and release of inflammatory cytokines. The most famous example is TGN1412, a humanized anti-CD28 monoclonal antibody. No proinflammatory reactions were detected during pre-clinical studies, but in the phase I clinical trial, the enrolled patients developed multiorgan failure, lymphopenia, thrombocytopenia, and elevations in cytokine levels, outlining the clinical picture of a CRS [21, 22].

Such reactions have also been documented for infliximab, rituximab, and alemtuzumab [23], and with chimeric antigen receptor T cell therapy. Although chimeric antigen receptor T cells lead to significant remissions of hematologic malignancies, their use is limited because of CRS-related

severe organ damage and deaths [24–26]. In 2017, the US Food and Drug Administration (FDA) approved the use of tocilizumab for patients experiencing severe or life-threatening CRS induced by chimeric antigen receptor T cells [27].

Particular ADRs are associated with individual biologics as a result of their mechanism of action. For example, immunomodulatory biologics are associated with serious infections, including tuberculosis reactivation, malignancies (e.g., anti-tumor necrosis factor-a agents), and progressive multifocal leukoencephalopathy (e.g., natalizumab, rituximab), as well as wound-healing complications or arterial thromboembolic events observed for angiogenesis inhibitors (e.g., bevacizumab), dermatologic toxicities observed for epidermal growth factor receptor inhibitors (cetuximab, panitumumab), and B-cell lymphocyte depletion from anti-CD20 antibodies (rituximab) [15, 28–32].

Post-marketing studies confirmed that biologics, as a result of their expected effects on selected targets, have different safety reporting trends as compared with non-biologics. An analysis on Vigibase [16], reported that suspected ADRs for biologics concerned more frequently 'Infections and infestations', 'Surgical and medical procedures', and 'Neoplasms benign, malignant and unspecified'. Similarly, in the Italian Spontaneous Reporting System, administration-site conditions, infections, and neoplasms were more likely reported with biologics than with non-biologics [30]. Substantial differences exist also across various mechanistic classes of biologics: monoclonal antibodies, fusion proteins, enzymes, and coagulation factors were mainly associated with cutaneous reactions; cytokines and antagonists with hematologic disorders; and hormones with disorders of metabolism and nutrition. About two-thirds of all Italian ADR reports involved anti-cancer monoclonal antibodies, tumor necrosis factor-a inhibitors, and interferons.

Downing et al. analyzed the frequency of post-marketing safety events (i.e., withdrawals because of safety concerns; incremental boxed warnings; safety communications) among 222 biologics and non-biologics, approved by the FDA between 2001 and 2010. Post-marketing safety events were significantly more frequent among biologics and among therapeutics receiving accelerated approval, which included several anti-cancer biologics [31].

Pharmacovigilance for Biologics

Although biologics require specific risk management strategies, current methods of post-marketing safety evaluation for small molecules and biologics are comparable. Information about drug safety is generally collected in the post-marketing period from spontaneous reporting systems, post-marketing observational studies, and pragmatic clinical trials. The spontaneous reporting system represents an important tool for the detection of safety signals and consequences of immunogenicity (especially if mild to moderate), even if an improvement in specific tools and algorithms to identify potential cases is still needed. For biologics, further complications raised in the case-causality assessment related to spontaneous ADR reports. Patients treated with biologics are often in polytherapy and affected by severe and/or life-threatening diseases, which may complicate adequate causality assessment. Channeling bias (i.e., allocation bias, in which patients having specific susceptibility to problems or specific co-morbidities are channeled to receive a drug, rather than another with similar therapeutic indications) is also of concern in the causality assessment of adverse events related to biologics, as the disease state can be incorrectly

attributed to the use of a drug, which was instead prescribed to patients who were most likely to develop that adverse reaction [33].
Another important issue for the pharmacovigilance of biologics concerns the manufacturing variability over time in the post-authorization phase. Consequently, a key requirement is the need to ensure product and batch traceability in clinical use. Regulatory agencies required clinicians to indicate in spontaneous ADR reports the brand name and batch number of biologics, but this requirement is not frequently addressed [34].
Beyond the above-mentioned RMP, based on European Pharmacovigilance legislation, additional pharmacovigilance activities (including post-authorization safety studies) may be required for all new biologics and biosimilars [35]. Similarly, in USA, the FDA requires the submission of a Risk Evaluation and Mitigation Strategy from manufacturers to ensure that the benefits of a drug or biologic outweigh its risks [36].
Concerning biosimilars, their benefit-risk profile has been often questioned by clinicians because of the limited amount of pre-marketing information on clinical efficacy and safety, despite biosimilarity approval being based on an extensive comparability exercise with the reference product [37]. Nevertheless, after more than 10 years of marketing from the first biosimilar in Europe, no proof of differences in terms of the safety profile of biosimilars and originators has been reported. However, monitoring the use of biologics, including biosimilars, is particularly needed in the pediatric setting as risks and co-morbidity profiles in children may be different from adults [38, 39].

Sources for Post-Marketing Monitoring of Biologics and Biosimilars
The spontaneous reporting system still represents the main tool for the early detection of safety signals of all biologics, including immunogenicity and its consequences. However, the spontaneous reporting system may be less valuable in detecting less severe consequences or in the case of antidrug antibody development, thus highlighting the need for specific algorithms to rapidly and easily identify potential cases of immunogenicity.
Beyond the spontaneous reporting system, post-marketing evaluation of the safety profile of biologics may profit from a wide variety of data sources, ranging from patients' registries to paper or electronic medical charts, claims databases, and distributed database networks, thus allowing the conduction of prospective/retrospective observational studies, cross-sectional studies, and surveys. Such data sources have to be wisely chosen in light of the type of included data, based on the specific research question to be addressed with a specific study design.
Numerous healthcare administrative databases are currently available in Europe and are often used for pharmacoepidemiologic purposes. For instance, Italian administrative healthcare databases include demographic and mortality registries, drug dispensing, hospital discharge diagnosis and emergency department visits, healthcare service payment exemptions, outpatient diagnostic tests and specialists' visits and, in some cases, laboratory findings, as previously described [40].

Traceability of biologics
Biologics are subject to frequent manufacturing changes after a product is marketed [32]. Most often, these changes have no negative impact on clinical efficacy and safety, but the example of epoetin-induced pure red cell aplasia illustrates the potential impact of a substantial change in

formulation.
For these reasons, one of the key requirements for the pharmacovigilance of biologics as well as of biosimilars is the need to ensure continuous product and batch traceability in clinical practice [41]. The specific product and batch administered to the patient should be traced in case an adverse event occurs, to easily detect and evaluate emerging product-specific safety issues and immunogenicity. In the pharmacovigilance legislation described in Directive 2010/84/EU and adopted by the European Parliament and Council of Ministers, it is clearly stated that Member States shall ensure, through both data collection and follow-up of suspected ADRs, that all appropriate measures are taken to clearly identify biologics that are subjects of a suspected ADR, with due focus to the brand name (to distinguish the biosimilar and the reference product) and to the batch number [42]. A previous study [34] showed that 21.1 and 24% of the spontaneously reported ADRs for biologics to the European Union Eudravigilance database and the FDA adverse event reporting system contains information on the batch number, respectively. A sub-analysis of the reports showed that the administered product could be traced back to the manufacturer by brand name in 96.2% of the cases. However, the batch number was only available for 5.7% of the cases. Furthermore, reports from consumers contained batch numbers more often than reports from clinicians and pharmacists [34]. Similarly, a recent study on the Italian spontaneous reporting system [30] documented that the brand name was reported in 94.8% of biologic-related reports, while the batch number was reported in only 8.6% of the reports. A higher level of completeness was available for those biologics with expired patents (brand name was reported in 98.7% of reports; batch number in 13.4%).
The product name and batch number are included in the product packaging, as printed in ‘‘human-readable’’ format, but batch numbers are not included in barcodes. To ensure biologics traceability, this information may therefore be recorded at all levels in the supply chain from manufacturer release to prescriptions, dispensing, and patient administration. A recent study aimed at identifying determinants influencing brand name and batch number recording in ADRs in a Dutch hospital setting [43], highlighted the co-existence of different types of information-recording systems (i.e., at dispensing phase, at administration phase, and administrative claims databases about the patient), which included data collected for different
aims and by different healthcare professionals. Such systems may or may not exchange information with each other, may or may not require the specific brand name information or the batch number collection, and may or may not be incorporated in one integrated system, thus leading to fragmented data collection along the supply chain.
It is therefore known that traceability needs to be improved and several initiatives have been proposed, including barcode-controlled administration/delivery to the patient and storage of these data in the electronic patient files. To date, information about the batch number is not included in the barcodes and the possibility to store the information in the electronic patient files is rather limited [44]. However, in 2016, the European Commission published a regulation [45] requesting companies place a two-dimensional barcode on most human medicine packaging, thus allowing the storage of more information than the data elements of the previously used unique identifier, such as batch numbers. The requirement for a two-dimensional barcode supplements the Falsified Medicines Directive (Directive 2001/83/EC, regarding the prevention of the entry into a legal supply chain of falsified medicinal products) and involves only the outer (i.e., secondary) packaging of human medicines. Further concerted actions are needed to build a

system able to support the achievement of the public health objectives and the implemented regulations.

Interchangeability and switching practices of biologics including biosimilars

Most of the regulatory agencies and scientific societies indicate that biosimilars can be prescribed to naıve patients or to patients affected by chronic diseases and already successfully treated with biologics, who may receive biosimilars as a switch from the reference product as a cost containment strategy [46, 47]. The term 'naıve' usually refers to never-treated patients ('primary naive') or patients previously treated with a biologic who have had an adequate wash-out period [48].

Considering interchangeability, the positions of regulatory agencies are heterogeneous worldwide. The EMA defines interchangeability as the property of a drug to be exchanged with another, which is expected to have the same clinical effects. This exchange may occur from a reference product to a biosimilar or vice versa, or from one biosimilar to another and may be achieved by switching (i.e., the prescriber decides to exchange one drug for another having the same therapeutic effect) or by automatic substitution (i.e., the practice of dispensing one drug instead of another equivalent and interchangeable drug at the pharmacy level, without previously consulting the prescriber) [3]. However, each European Union member state is responsible for the interchangeability status and the allowance of switching and/or automatic substitution is undertaken by the national regulatory authorities [49].

The European Generic Medicines Association reported that more than 12 countries across the EU have introduced rules to avert the automatic substitution of innovator biologics with biosimilars [50]. France allowed the substitution of biosimilars for naıve patients (but never implemented a corresponding decree), allowing interchangeability provided transparency, monitoring, and traceability of biosimilars can be guaranteed [51]. In Germany, a pharmacist may substitute a biosimilar as part of the obligatory generic substitution referred to as 'Autidem-Regelung'. Nevertheless, there is no authorized legislation in the country to substitute biologics from different manufacturers [52]. In the UK, pharmacists are not allowed to dispense biosimilars in place of reference products and clinicians are required to prescribe biologics by brand name and not by International Nonproprietary Names [53].

In Spain, automatic substitution in community pharmacies is not allowed. The Netherlands and Austria have a more neutral approach. In the Netherlands, substitution is allowed with other biosimilars but never with the originator molecule. In Austria, substitution is promoted for naıve patients and this discretion usually lies with the prescribing physician. Although these countries have accepted the significance of biosimilars, the legislation for interchangeability is far from visible [54]. In the last position paper, the Italian Medicines Agency (Agenzia Italiana del Farmaco, AIFA) states that the benefit-risk profile of biosimilars is the same as that for a reference product. Thus, biosimilars are interchangeable with reference products for naıve and treated patients [55].

In Latin America, a biologic is defined as interchangeable with another one if the two show similar safety and effectiveness. In this case, the substitution is acceptable, otherwise only the physician can allow it [56]. In India, the biosimilar substitution is automatic as soon as the drug is approved; this is not allowed in other countries such as Japan, Australia, and Canada and has yet to be addressed in South Korea [19, 57].

In contrast, based on the FDA approach, the term ‘‘‘interchangeable’’ means that ‘‘the biological product may be substituted for the reference product without the intervention of the healthcare provider who prescribed the reference product’’ [58]. To grant the interchangeable status, the FDA requests the drug companies to conduct pre-marketing studies on multiple and reverse switching of biosimilars and reference products, in addition to the studies demonstrating biosimilarity [59]. The FDA draft guidance for industries recommends the evaluation of at least three switches between the reference product and biosimilar, back and forward. As study endpoints, the FDA asks for clinical pharmacokinetic and pharmacodynamic
tests and assays to be validated early in a product’s development. Such a validation should consider both the reference product and the proposed interchangeable biosimilar. In comparison to efficacy endpoints, relevant pharmacodynamic measures may represent more sensitive indicators of the potential impact of switching and may highlight multiple domains of activity, thus reducing residual uncertainty about interchangeability. The FDA will therefore define the biologic interchangeable with the reference product if submitted data demonstrate that ‘‘for a biological product that is administered more than once, the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch’’. The FDA allows automatic substitution without prescriber intervention if the biosimilar has been considered interchangeable with the reference product [59].

To date, several randomized clinical trials have been conducted including patients experiencing a switch from a reference product to a biosimilar and/or vice versa, highlighting that switching has no impact on the efficacy and safety of therapies [60–65]. The NOR-SWITCH study [66] was a non-inferiority, double-blind, phase II randomized trial that included patients affected by rheumatoid arthritis, spondyloarthritis, psoriatic arthritis, ulcerative colitis, Crohn’s disease, and chronic plaque psoriasis. The study showed the non-inferiority of switching from an originator to a biosimilar infliximab vs. continuous treatment with the originator infliximab, according to a pre-specified non-inferiority margin of 15%, which was chosen based on previous clinical trials as well as discussions with the Norwegian Medicines Agency. However, the study was not powered to demonstrate the non-inferiority within each disease group. In addition, although the 15% margin may include clinically important differences, it has been defined as sufficient to define non-inferiority by the EMA but too wide based on the FDA requirement.

In routine care, the switching practice is frequent (e.g., 15–20% for epoetins and 20% for filgrastim, considering also reverse and multiple switches, during the first year of treatment), occurring mostly among various originators with the same indications [67–70]. The frequency of switching may limit the correct causality assessment of the ADRs. Furthermore, this practice has recently become more complex owing to the increasing number of available biosimilars for the same reference product and of different reference product versions. Several data from observational studies are already available on the maintenance of efficacy and safety after the switching, thus confirming results from RCTs. In addition, a review of clinical trials conducted worldwide and of ADRs reported to the EudraVigilance database found no evidence that the switching practice leads to safety concerns [71]. As explicitly stated by Kurki et al., ‘‘a state-of-the-art demonstration of biosimilarity, together with intensified post-marketing surveillance, is a sufficient and realistic way of ensuring interchangeability of European Union-approved biosimilars under supervision of the prescriber’’ [72]. The up-to-date available evidence

highlights that a single switch from an originator to the corresponsing biosimilar is safe and effective and there are no reasons why switching among biosimilars of the same originator would lead to different clinical outcomes [73].

Based on the published data, the switch from the reference product to the corresponding biosimilar has been defined as acceptable by the European Crohn and Colitis Organization in its last position paper on the use of biosimilars for inflammatory bowel diseases. The European Crohn and Colitis Organization highlighted that studies on switching can provide reliable evidence for efficacy and safety, but further evaluations about reverse, multiple, and cross-switching among biosimilars are needed [74]. The European League Against Rheumatism and the American College of Rheumatology do not recommend switching can provide reliable evidence for efficacy and safety, but further evaluations about reverse, multiple, and cross-switching among biosimilars are needed [74]. The European League Against Rheumatism and the American College of Rheumatology do not recommend switching between biologics for non-medical reasons. The European League Against Rheumatism clearly stated that in the case of treatment failure with a biologic, another biologic can be as effective as changing the mechanism of action; however, the switch should not occur toward the biosimilar of the same molecule as its efficacy and safety are similar to the reference product [75]. The American College of Rheumatology position on switching is in line with the FDA, strongly supporting the FDA requirements for clinical trials focusing on immunogenicity, antidrug antibody development, loss of clinical efficacy, as well as adverse effects following the switch between drugs. The American College of Rheumatology further recommends the long-term collection of post-marketing registry-based data to monitor less frequent, but possibly significant adverse events [76].

Conclusions

In the next few years, a growing number of biologics and biosimilars will be available on the market, thus highlighting the need for specific post-marketing short- and long-term monitoring programs for these drugs. It is essential to understand how the concept of interchangeability will be managed and regulated in the future. Further efforts should be directed at implementing strategies to improve traceability and to evaluate the benefits and risks of multiple switches between originators and biosimilars to better explore the issue of interchangeability.

In clinical practice, spontaneous reporting and healthcare databases represent valid instruments for post-marketing surveillance of biologics, including biosimilars. Future directions include developing policies that further improve the safety monitoring of biologics and biosimilars, involving payers, healthcare professionals, and patients in the real-world evidence generation. Strategies to disseminate the correct information on biosimilars to healthcare professionals and patients are needed.

Furthermore, specific pharmacovigilance programs should be established for innovative drugs used in therapeutic areas that need further investigation, such as rare diseases and orphan drugs and biosimilar monoclonal antibodies in the oncology setting. An important issue for future clinical practice will be how to approach the safety evaluation of gene or cell therapy, such as chimeric antigen receptor T-cell therapies, considering a life-long follow-up of patients to define a long-term safety profile.

References

1. Veze´r B, Buza´s Z, Sebeszta M, et al. Authorized manufacturing changes for therapeutic monoclonal antibodies (mAbs) in European Public Assessment Report (EPAR) documents. Curr Med Res Opin. 2016;32(5):829–34.

2. European Medicines Agency. Remicade: procedural steps taken and scientific information after authorization. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Procedural_steps_taken_and_scientific_information_after_authorisation/human/000240/WC500050890.pdf. Accessed 20 Nov 2017.

3. European Medicines Agency; European Commission. Biosimilars in the EU: information guide for health care professionals. http://www.ema.europa.eu/docs/en_GB/document_library/Leaflet/2017/05/WC500226648.pdf. Accessed 28 Sep 2017.

4. US Food and Drug Administration. Biological product definitions. https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/UCM581282.pdf. Accessed 6 Nov 2017.

5. Dos Reis C, Teixo R, Mendes F, Cruz RS. Biosimilar medicines: review. Int J Risk Saf Med. 2016;28(1):45–60.

6. Mach JP. Introduction to monoclonal antibodies. Cancer Immun. 2012;12:11.

7. Italian Medicines Agency. L'uso Nazionale dei Farmaci in Italia: Rapporto OsMed 2016. http://www.aifa.gov.it/sites/default/files/Rapporto_OsMed_2016_AIFA.pdf. Accessed 20 Nov 2017.

8. GaBi Online. WHO definitions of biosimilars. 2012. http://gabionline.net/Biosimilars/General/WHO-definitionsofbiosimilars. Accessed 23 Apr 2018.

9. http://www.ema.europa.eu/ema/index.jsp?curl=pages%2Fmedicines%2Flanding%2Fepar_search.jsp&mid=WC0b01ac058001d124&searchTab=searchByAuthType&alreadyLoaded=true&isNewQuery=true&status=Authorised&keyword=Enter?keywords&-searchType=name&taxonomyPath=&treeNumber=&searchGenericType=biosimilars&genericsKeywordSearch=Submit. European Medicines Agency. European Public Assessment Reports: biosimilars. Accessed 7 Dec 2017.

10. US Food and Drug Administration. Purple book: lists of licensed biological products with reference product exclusivity and biosimilarity or interchangeability evaluations. Available from: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm411418.htm. [Accessed 20 Nov 2017].

11. European Medicines Agency. QRD general principles regarding the SmPC information for a generic/hybrid/biosimilar product. EMA/627621/2011. 3 May 2012. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2012/05/WC500127589.pdf. [Accessed 23 Jan 2017].

12. US Department of Health and Human Services Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). Labeling for biosimilar products: guidance for industry. March 2016. Available from: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM493439.pdf. [Accessed 3 May 2018].
13. Giezen T, Schneider CK. Safety assessment of biosimilars in Europe: a regulatory perspective. GaBI J. 2014;3(4):180–3.
14. European Medicines Agency. Guideline on good pharmacovigilance practices (GVP). Module V: risk management systems (Rev 2). Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129134. pdf. [Accessed 12 Jan 2018].
15. Giezen TJ, Mantel-Teeuwisse AK, Straus SMJM, Schellekens H, Leufkens HG, Egberts AC. Safety-related regulatory actions for biologicals approved in the United States and the European Union. JAMA. 2008;300(16):1887–96.
16. Giezen TJ, Mantel-Teeuwisse AK, Meyboom RH, Straus SM, Leufkens HG, Egberts TC. Mapping the safety profile of biologicals: a disproportionality analysis using the WHO adverse drug reaction database. VigiBase. Drug Saf. 2010;33(10):865–78.
17. Sharma B. Immunogenicity of therapeutic proteins. Part 3: impact of manufacturing changes. Biotechnol Adv. 2007;25(3):325–31.
18. Bennett CL, Luminari S, Nissenson AR, Tallman MS, Klinge SA, McWilliams N, McKoy JM, Kim B, Lyons EA, Trifilio SM, Raisch DW, Evens AM, Kuzel TM, Schumock GT, Belknap SM, Locatelli F, Rossert J, Casadevall N. Pure red-cell aplasia and epoetin therapy. N Engl J Med. 2004;351(14):1403–8.
19. Bennett CL, Chen B, Hermanson T, Wyatt MD, Schulz RM, Georgantopoulos P, Kessler S, Raisch DW, Qureshi ZP, Lu ZK, Love BL, Noxon V, Bobolts L, Armitage M, Bian J, Ray P, Ablin RJ, Hrushesky WJ, Macdougall IC, Sartor O, Armitage JO. Regulatory and clinical considerations for biosimilar oncology drugs. Lancet Oncol. 2014;15(13):e594–605.
20. Boven K, Stryker S, Knight J, Thomas A, van Regenmortel M, Kemeny DM, Power D, Rossert J, Casadevall N. The increased incidence of pure red cell aplasia with an Eprex formulation in uncoated rubber stopper syringes. Kidney Int. 2005;67(6):2346–53.
21. Suntharalingam G, Perry MR, Ward S, Brett SJ, Castello-Cortes A, Brunner MD, Panoskaltsis N. Cytokine storm in a phase 1 trial of the anti-CD28 monoclonal antibody TGN1412. N Engl J Med. 2006;355(10):1018–28.
22. Khan DA. Hypersensitivity and immunologic reactions to biologics: opportunities for the allergist. Ann Allergy Asthma Immunol. 2016;117(2):115–20.
23. Lee DW, Gardner R, Porter DL, et al. Current concepts in the diagnosis and management of cytokine release syndrome. Blood. 2014;124(2):188–95.
24. Neelapu SS, Tummala S, Kebriaei P, et al. Chimeric antigen receptor T-cell therapy: assessment and management of toxicities. Nat Rev Clin Oncol. 2018;15(1):47–62.
25. Brudno JN, Kochenderfer JN. Toxicities of chimeric antigen receptor T cells: recognition and management. Blood. 2016;127(26):3321–30.
26. Frey N. Cytokine release syndrome: who is at risk and how to treat. Best Pract Res Clin Haematol. 2017;30(4):336–40.

27. US Food and Drug Administration. FDA approves tisagenlecleucel for B-cell ALL and tocilizumab for cytokine release syndrome. Available from: https://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm574154.htm. [Accessed 31 Jan 2018].
28. Erdman A, Nickas J, Brown B. Safety of biotherapeutics. In: Talbot J, Aronson JK, editors. Stephens' detection and evaluation of adverse drug reactions: principles and practice. 6th ed. Chichester: Wiley-Blackwell; 2011.
29. Giezen TJ, Mantel-Teeuwisse AK, Leufkens HGM. Pharmacovigilance of biopharmaceuticals. Drug Saf. 2009;32(10):811–7.
30. Cutroneo PM, Isgro` V, Russo A, Ientile V, Sottosanti L, Pimpinella G, Conforti A, Moretti U, Caputi AP, Trifiro` G. Safety profile of biological medicines as compared with non-biologicals: an analysis of the Italian spontaneous reporting system database. Drug Saf. 2014;37(11):961–70.
31. Downing NS, Shah ND, Aminawung JA, Pease AM, Zeitoun JD, Krumholz HM, Ross JS. Postmarket safety events among novel therapeutics approved by the US Food and Drug Administration between 2001 and 2010. JAMA. 2017;317(18):1854–63.
32. Stanculeanu DL, Zob D, Toma OC, Georgescu B, Papagheorghe L, Mihaila RI. Cutaneous toxicities of molecular targeted therapies. Maedica (Buchar). 2017;12(1):48–54.
33. Petri H, Urquhart J. Channeling bias in the interpretation of drug effects. Stat Med. 1991;10(4):577–81.
34. Vermeer NS, Straus SMJM, Mantel-Teeuwisse AK, Domergue F, Egberts TCG, Leufkens HGM, De Bruin ML. Traceability of biopharmaceuticals in spontaneous reporting systems: a cross sectional study in the FDA Adverse Event Reporting System (FAERS) and EudraVigilance Databases. Drug Saf. 2013;36:617–25.
35. European Medicines Agency. Pharmacovigilance: post-authorisation. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_001819.jsp&mid=WC0b01ac05800241de. [Accessed 20 Dec 2017].
36. US Food and Drug Administration. Approved Risk Evaluation and Mitigation Strategies (REMS). Available from: https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm. [Accessed 20 Dec 2017].
37. Gulacsi L, Pentek M, Rencz F, et al. Biosimilars for the management of inflammatory bowel diseases: economic considerations. Curr Med Chem. 2017. https://doi.org/10.2174/0929867324666170406112304 (Epub ahead of print).
38. Fiorino G, Girolomoni G, Lapadula G, Orlando A, et al. The use of biosimilars in immune-mediated disease: a joint Italian Society of Rheumatology (SIR), Italian Society of Dermatology (SIDe-MaST), and Italian Group of Inflammatory Bowel Disease (IGIBD) position paper. Autoimmun Rev. 2014;13(7):751–5.
39. Atzeni F, Sebastiani M, Ricci C, Celano A, et al. Position paper of Italian rheumatologists on the use of biosimilar drugs. Clin Exp Rheumatol. 2015;33(1):1–4.
40. Trifiro` G, Marciano` I, Ingrasciotta Y, Genazzani A. Biosimilars in Italy: what do real-world data reveal? GABI J. 2017;6(3):114–9.
41. European Medicine Agency. Guideline on good pharmacovigilance practices (GVP): product traceability.

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/08/WC500211728.pdf. Accessed 20 Dec 2017.
42. European Parliament and Council. Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010 amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community Code Relating to Medicinal Products for Human Use (text with EEA relevance). http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2010:348:0074:0099:EN: PDF. Accessed 19 Apr 2018.
43. Klein K, Scholl JH, Vermeer NS, Broekmans AW, et al. Traceability of biologics in the Netherlands: an analysis of information-recording systems in clinical practice and spontaneous ADR reports. Drug Saf. 2016;39(2):185–92.
44. Vermeer NS, Spierings I, Mantel-Teeuwisse AK, et al. Traceability of biologicals: present challenges in pharmacovigilance. Expert Opin Drug Saf. 2015;14(1):63–72.
45. European Commission. Commission Delegated Regulation (EU) 2016/161 of 2 October 2015 supplementing Directive 2001/83/EC of the European Parliament and of the Council by laying down detailed rules for the safety features appearing on the packaging of medicinal products for human use. http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=uriserv:OJ.L_.2016.032.01.0001.01.ENG. Accessed 12 Jan 2018.
46. Italian Medicines Agency (AIFA). Position paper sui farmaci biosimilari (28/05/2013). http://www.agenziafarmaco.gov.it/sites/default/files/AIFA_POSITION_PAPER_FARMACI_BIOSIMILARI.pdf. Accessed 11 May 2018.
47. US Food and Drug Administration. Prescribing biosimilar products. https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/UCM581341.pdf. Accessed 11 May 2018.
48. Biggioggero M, Danova M, Genovese U, et al. The challenging definition of naı¨ve patient for biological drug use. Autoimmun Rev. 2015;14:543–6.
49. European Medicines Agency. Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues. 2014. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/01/WC500180219.pdf. Accessed 20 Nov 2017.
50. GaBI Online. Generics and biosimilars initiative: efficacy, extrapolation and interchangeability of biosimilars. 2013. http://www.gabionline.net/Biosimilars/Research/Efficacyextrapolation-and-interchangeability-of-biosimilars. Accessed 11 May 2018.
51. GaBI Online. France to allow biosimilars substitution. 2014. http://www.gabionline.net/Policies-Legislation/France-to-allowbiosimilars-substitution. Accessed 11 May 2018.
52. GaBI Online. Generics and biosimilars initiative: use of biosimilars in Europe. www.gabionline.net/Reports/Use-of-biosimilarsin-Europe. Accessed 11 May 2018.
53. FederSanita`Anci. Per creare cultura su un approccio corretto dei farmaci biosimilari: position paper. 2015. http://www.federsanita.it/. Accessed 11 May 2018.
54. Thimmaraju PK, Rakshambikai R, Farista R, Juluru K. Legislations on biosimilar interchangeability in the US and EU: developments far from visibility. 2015.

http://www.gabionline.net/Sponsored-Articles/Legislations-on-biosimilarinterchangeability-in-the-US-and-EU-developments-far-fromvisibility. Accessed 11 May 2018.
55. Italian Medicines Agency. Secondo position paper AIFA sui Farmaci Biosimilari. March 2018. http://www.agenziafarmacogov.it/sites/default/files/2_Position-Paper-AIFA-Farmaci-Biosimilari.pdf. Accessed 11 May 2018.
56. Pineda C, Caballero-Uribe CV, de Oliveira MG, et al. Recommendations on how to ensure the safety and effectiveness of biosimilars in Latin America: a point of view. Clin Rheumatol. 2015;34(4):635–40.
Nagai S, Yanagihara R, Kishioka Y. Japanese regulatory authority's perspective on biosimilars. Lancet Oncol. 2015;16(3):e101.
58. Food and Drug Administration. Public Health Service Act. Title III: General Powers and Duties of Public Health Service. USA. Section 351(i)(3). 2013. http://legcounsel.house.gov/Comps/PHSA_CMD.pdf. Accessed 28 Sep 2017.
59. US Food and Drug Administration. Considerations in demonstrating interchangeability with a reference product: guidance for industry. 2017. https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM537135.pdf. Accessed 28 Sep 2017.
60. Wie¸cek A, Ahmed I, Scigalla P, et al. Switching epoetin alfa and epoetin zeta in patients with renal anemia on dialysis: posthoc analysis. Adv Ther. 2010;27(12):941–52.
61. Romer T, Zabransky M, Walczak M, et al. Effect of switching recombinant human growth hormone: comparative analysis of phase 3 clinical data. Biol Ther. 2011;1:5.
62. Park W, Yoo DH, Miranda P, et al. Efficacy and safety of switching from reference infliximab to CT-P13 compared with maintenance of CT-P13 in ankylosing spondylitis: 102-week data from the PLANETAS extension study. Ann Rheum Dis. 2017;76(2):346–54.
63. Yoo DH, Prodanovic N, Jaworski J, et al. Efficacy and safety of CT-P13 (biosimilar infliximab) in patients with rheumatoid arthritis: comparison between switching from reference infliximab to CT-P13 and continuing CT-P13 in the PLANETRA extension study. Ann Rheum Dis. 2017;76(2):355–63.
64. Buer LCT, Moum BA, Cvancarova M, et al. Switching from Remicade to Remsima is well tolerated and feasible: a prospective, open-label study. J Crohns Colitis. 2017;11(3):297–304.
65. Sieczkowska J, Jarze¸bicka D, Banaszkiewicz A, et al. Switching between infliximab originator and biosimilar in paediatric patients with inflammatory bowel disease: preliminary observations. J Crohns Colitis. 2016;10(2):127–32.
66. Jørgensen KK, Olsen IC, Goll GL, Lorentzen M, Bolstad N, Haavardsholm EA, et al. Switching from originator infliximab to biosimilar CT-P13 compared with maintained treatment with originator infliximab (NOR-SWITCH): a 52-week, randomised, double-blind, non-inferiority trial. Lancet. 2017;389(10086):2304–16.
67. Ingrasciotta Y, Giorgianni F, Bolcato J, et al. How much are biosimilars used in clinical practice? A retrospective Italian population-based study of erythropoiesis-stimulating agents in the years 2009–2013. BioDrugs. 2015;29(4):275–84.
68. D'Amore C, Da Cas R, Rossi M, et al. Switching between epoetins: a practice in support of biosimilar use. BioDrugs. 2016;30(1):27–32.
69. Marciano` I, Ingrasciotta Y, Giorgianni F, et al. How did the introduction of biosimilar filgrastim influence the prescribing pattern of granulocyte colony-stimulating factors? Results

from a multicentre, population-based study, from five Italian centres in the years 2009–2014. BioDrugs. 2016;30(4):295–306.
70. Loiacono C, Sgroi C, Coppolino S, et al. How much are biosimilars used in southern Italy? A retrospective analysis of epoetin utilization in the local health unit of Messina in the years 2010–2011. BioDrugs. 2012;26(2):113–20.
71. Ebbers HC, Muenzberg M, Schellekens H. The safety of switching between therapeutic proteins. Expert Opin Biol Ther. 2012;12(11):1473–85.
72. Kurki P, Van Aerts L, Wolff-Holz E, et al. Interchangeability of biosimilars: a European perspective. BioDrugs. 2017;31(2):83–91.
73. Kay J, Schoels MM, Do¨rner T, Emery P, Kvien TK, et al. Consensus-based recommendations for the use of biosimilars to treat rheumatological diseases. Ann Rheum Dis. 2018;77(2):165–74.
74. Danese S, Fiorino G, Raine T, et al. ECCO position statement on the use of biosimilars for inflammatory bowel disease: an update. J Crohns Colitis. 2017;11(1):26–34.
75. Smolen JS, Landewe´ R, Bijlsma J, Burmester G, Chatzidionysiou K, Dougados M, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. Ann Rheum Dis. 2017;76(6):960–77.
76. American College of Rheumatology. Comments on draft guidance considerations in demonstrating interchangeability with a reference product (FDA 2017-01042). https://www.rheumatology.org/Portals/0/Files/ACR-Comments-FDAInterchangeability-May-2017.pdf. Accessed 24 Jan 2018.

3.2. Safety and potential interaction of immunosuppressive drugs for the treatment of inflammatory bowel disease in elderly patients

Adapted from:

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Abstract

Inflammatory bowel diseases, including Crohn's disease and ulcerative colitis, are chronic diseases associated with increased morbidity and reduced quality of life. Age may represent a risk factor for adverse events, due to the multimorbidity and polypharmacy, common in elderly patients. Elderly are often not included in clinical trials evaluating efficacy and safety of study drugs for the treatment of inflammatory bowel diseases. Several drugs, such as aminosalicylates, systemic corticosteroids, immunosuppressant drugs, biological drugs and Janus Kinase inhibitors, are available for the management of inflammatory bowel diseases. With the increasing spectrum of therapeutic options, it is therefore important to analyze the evidence regarding the safety of the use of these agents in elderly patients. Selection of immunosuppressive therapy is a challenge in the management of elderly patients with inflammatory bowel diseases, for whom biologics with a lower risk of infection or cancer, such as vedolizumab and ustekinumab, may be preferred in elderly patients. Concomitant therapies and comorbidities must be thoroughly investigated before initiating any immunosuppressive or biological therapy in order to minimize the risk of drug-drug interactions. This review aims to provide an overview of the safety of thiopurines, methotrexate and target therapies as well as their drug-drug interactions in patients with inflammatory bowel diseases.

Introduction

Among patients with inflammatory bowel disease (IBD), 25–35% are over 60 years old [1, 2]. Elderly patients are characterized by the presence of comorbidities and subsequent polypharmacy, an altered physiological state, possible cognitive decline, reduced motility and concomitant risk factors that could influence an optimal therapy in this peculiar population of IBD patients [3]. Moreover, elderly patients with IBD are often not included in clinical trials evaluating efficacy and safety of study drugs for the treatment of IBD. Therefore, the overall quality of the evidence is often judged as low or very low, as several data come from cohorts and case-control studies with different methodologies, sample sizes, and lengths of follow-up [4].

The result is a change in the outcomes and a higher number of adverse drug effects (e.g. as a result of drug interactions) in elderly patients compared to the general population with IBD. Over the years, many studies have reported an increased risk of adverse events (AEs) or severe adverse events (SAEs) in elderly patients with IBD treated with immunosuppressants or biological therapies, including malignancies and infections, which have a significant impact especially in a population that is more likely to be frail. Age has been reported as a risk factor for AEs or SAEs in various studies [5-8]. This risk has many possible causes, which range from differences in pharmacokinetics due to polypharmacy to immunosenescence. Notably, the fear of side effects, combined with the perception of a milder course of the disease in patients with late onset IBD [9] has led to less aggressive management of this subgroup of patients, as physicians are more reluctant to use immunosuppressants and biologics with elderly patients. The role of comorbidities emerged in two recent Dutch multicentre studies assessing the safety of biological therapies in elderly patients with IBD. In the first, infliximab (IFX)-exposed patients were not found to be at a higher risk of infection when compared with their younger, equally exposed counterparts, and the rates of any infection and hospitalization were not associated with age but with the burden of comorbidities, especially cardiovascular disease [10]. Similar results were reported in a prospective study in patients treated with vedolizumab (VDZ) and ustekinumab (UST): again, comorbidities, not age, were found to be associated with an increased risk of hospitalization and infections [11]. Polypharmacy was found to be associated with a higher risk of infection [5].

According to recent guidelines, several drugs are available for the medical management of IBD, including aminosalicylates (i.e. mesalazine, sulfasalazine, balsalazide), locally active steroids (budesonide, beclomethasone), systemic corticosteroids (i.e. prednisolone, hydrocortisone, methylprednisolone), immunosuppressants (i.e. azathioprine (AZA), mercaptopurine (MP), methotrexate (MTX)), biological drugs (TNF-alpha inhibitors, anti-integrins, anti-interleukins 12/23) and Janus Kinase (JAK) inhibitors (Tofacitinib) [12,13]. With the increasing spectrum of therapeutic options and concern about potential safety risk factors affecting IBD patients, it is therefore important to critically analyse the available evidence concerning the safety of use of these agents in this special population of patients with chronic inflammatory diseases.

Safety of thiopurines and methotrexate

In elderly patients, thiopurines (azathioprine/6-mercaptopurine) may be used to maintain IBD remission as steroid-sparing agents; however, they are currently underused in clinical practice due to safety issues [14] and the availability of other, different, medical options. Among the elderly, thiopurines are associated with a higher rate of adverse events such as myelotoxicity,

hepatotoxicity and digestive intolerance often resulting in discontinuation of treatment [15]. Moreover, several studies have reported a higher risk of malignancies such as lymphomas [16], non-melanoma skin cancers (NMSC) [17] and urinary tract cancers [18], raising concerns about their use in this population. More specifically, the CESAME study showed that older age is an independent risk factor for lymphoproliferative disorders in thiopurine-treated patients, with a yearly incidence rate of 5.41 per 1000 patient-years (PY) in patients >65 years compared with 2.58 in patients aged 50 to 65 years [16]. Similarly, the incidence rate of NMSC, such as basalioma and spinocellular skin cancer was also higher with thiopurine exposure and highest among patients >65 years (12.2 per 1000 PY vs 4.8 per 1000 PY without exposure) [19]. There is limited evidence regarding the role of MTX in older patients with IBD. The dose-dependent side effects of MTX in elderly patients with rheumatoid arthritis (RA) tend to be more frequent and severe compared with those in younger patients, so a lower dose may be considered [20].

Drug–drug interactions of methotrexate and thiopurines

Allopurinol/oxipurinol/thiopurinol and other xanthine oxidase inhibitors (e.g. febuxostat) may prolong the activity of AZA, due to an inhibitory effect on the metabolism of AZA by blocking the xanthine oxidase enzyme, resulting in enhanced bone marrow suppression [21]. Concomitant administration is not recommended as data are not sufficient to determine an adequate dose reduction of AZA. An increase of the risk of myelosuppression with the concomitant use of angiotensin-converting enzyme (ACE) inhibitors, trimethoprim/sulfamethoxazole, cimetidine, indomethacin and aminosalicylate derivatives such as olsalazine, mesalazine and sulfasalazine, was also observed [22, 23]. Co-administration of cyclosporine and thiopurine has also been associated with enhancement of cyclosporine plasma levels [24] and consequent myelosuppression. Furthermore, Peyrin-Biroulet *et al.* found that the use of AZA and ribavirin (in combination with pegylated interferon) concomitantly can be associated with myelotoxicity, caused by the inhibition of the inosine-5′-monophosphate dehydrogenase (IMPDH) enzyme catalysing the conversion of inosine 5'-phosphate (IMP) to xanthosine 5'-phosphate (XMP) [25, 26].

There is also clinical evidence that AZA antagonizes the effect of non-depolarizing muscle relaxants (curare, d-tubocurarine and pancuronium), confirming that AZA reverses the neuromuscular blockade produced by non-depolarizing agents, and shows that AZA potentiates the neuromuscular blockade caused by depolarizing agents [27].

Other known drug-drug interactions of thiopurine were related to warfarin and consequent reduction of anticoagulant effects [28] and MTX that can increase levels of 6-mercaptopurine (6-MP) and other active metabolites of AZA associated with induction of leukopenia [29].

Other drug-drug interactions with AZA were observed with co-administration of IFX in the treatment of patients with Crohn's disease. In particular, a transient increase in levels of 6-thioguanine nucleotide (6-TGN, an active metabolite of AZA) and a reduction in the mean leukocyte count in the first weeks after IFX infusion was registered [30]. Moreover, the immunosuppressive activity of AZA can lead to an atypical and potentially dangerous response to live vaccines and therefore, theoretically, the administration of live vaccines to patients receiving AZA should be contraindicated [31]. Concerning MTX, pharmacokinetic interactions with co-administration of anticonvulsant medicinal products (reduced MTX blood levels), 5-fluorouracil (increased t½ of 5--fluorouracil), salicylates, phenylbutazone, phenytoin,

barbiturates, tranquilizers, oral contraceptives, tetracyclines, amidopyrine derivatives, sulfonamides and p-aminobenzoic acid (displace MTX from serum albumin binding, increasing bioavailability) have been observed. Patients taking potentially hepatotoxic medicinal products during MTX therapy (e.g. leflunomide, AZA, sulphasalazine, and retinoids) should be closely monitored for possibly increased hepatotoxicity [22, 32-34].

The effects of MTX may be enhanced by drugs that decrease its renal excretion, such as NSAIDs and salicylates, probenecid, and some penicillins [35-37]. In detail, antibiotics can reduce the renal clearance of MTX, increasing serum concentrations with consequent haematological and gastro-intestinal toxicity [35-38].

The co-administration of MTX and sulfasalazine may enhance MTX efficacy by sulfasalazine related inhibition of folic acid synthesis, leading to an increased risk of adverse reactions. Co-administration of proton-pump inhibitors such as omeprazole or pantoprazole can also lead to interactions [39]: MTX and omeprazole can lead to a delay in the renal elimination of MTX; combination with pantoprazole inhibits renal elimination of the 7-hydroxymethotrexate metabolite, resulting in myalgia and shivering.

Furthermore, concurrent use of MTX and warfarin may result in an increased risk of elevated international normalised ratio (INR) and subsequent bleeding [40].

The combined use of MTX and leflunomide may increase the risk for pancytopenia. MTX leads to increased plasma levels of mercaptopurines. Therefore, the combination of these may require dose adjustment [41, 42].

During MTX therapy, concurrent vaccination with live vaccines must not be carried out.

All the main drug-drug interactions related to thiopurines and methotrexate, reported in IBM Micromedex ®, are described in **Table 1** and **Table 2**.

Table 1. Main drug-drug interactions of thiopurines.

Interacting drugs	Mechanism of interaction	Effects of interaction
Xantine oxidase inhibitors	Inhibition of xanthine oxidase	Bone marrow suppression
ACE inhibitors Trimethoprim Cimetidine Sulfamethoxazole Indomethacin Aminosalicylate derivatives	n.a.	↑ risk of myelosuppression
Doxorubicin	n.a.	↑ risk of hepatotoxicity
Cyclosporine	↓ cyclosporine absorption	↓ cyclosporine plasma levels
Ribavirin (in combination with pegylated interferon)	IMPDH enzyme inhibition	Myelotoxicity
Non-depolarizing muscle relaxants	Reverses the neuromuscular blockade induced by azathiopurine	Antagonism towards to non-depolarizing muscle relaxants
Methotrexate	↑ levels of 6-MP	Leucopenia
Infliximab	transient ↑ of 6-TGN levels	↑ tofacitinib plasma levels
Live Vaccines	↓ immune response	↑ risk of infection live vaccines-induced
Warfarin	Impaired warfarin absorption Enhanced warfarin metabolism	↓ anticoagulant effect

Legend: ACE: Angiotensin-converting enzyme; IMPDH: inosine-5′-monophosphate dehydrogenase; n.a.: not available; 6-MP: 6-mercaptopurine; 6-TNG: 6-thioguanine nucleotide.

Table 2. Main drug-drug interactions of methotrexate.

Interacting drugs	Mechanism of interaction	Effects of interaction
Leflunomide	Inhibition of OAT-mediated transport of methotrexate	
Salicylates Phenylbutazone Phenytoin Barbiturates Tranquilizers Oral contraceptives Tetracyclines Amidopyrine derivatives Sulfonamides P-aminobenzoic acid	Displace methotrexate from serum albumin binding, ↑ bioavailability	↑ plasma concentration and subsequently ↑ the side effects
Cotrimoxazole	Synergistic anti-folate effects, protein binding displacement, ↓ renal tubular elimination	↑ risk of methotrexate toxicity *(myelotoxicity, pancytopenia, megaloblastic anemia. leukopenia, thrombocytopenia, anemia, nephrotoxicity, mucosal ulcerations)*
Proton pump inhibitors	Inhibition of H+, K+-ATPase in the kidney by proton pump inhibitors blocks the active secretion of methotrexate	
NSAIDs Probenecid Penicillins	↓ renal clearance	
Levetiracetam	Delay of methotrexate elimination	
Bentiromide	PABA competition for methotrexate binding sites	
Tamoxifen	n.a.	↑ risk of thromboembolism
Enasidenib Simeprevir Lasmiditan Darolutamide Capmatinib	Inhibition of OATP1B1 and BCRP transport	↑ exposure of OATP1B1 and/or BCRP substrate
Asparaginase	Asparaginase inhibits the cell replication for methotrexate antineoplastic activity	↓ methotrexate antineoplastic activity
Sapropterin	Inhibition of DHPR	↓ BH4 levels and ↑ phenylalanine levels
Foscarnet	Additive nephrotoxicity	nephrotoxicity
Antifolate agents	n.a.	↑ methotrexate exposure, decreased metabolite formation and increased risk of adverse events and decreased efficacy
Tegafur (5-fluorouracil after absorption)	Inhibition of thymidylate synthase and dihydrofolate reductase by methotrexate	↑ 5-fluorouracil toxicity
Azathioprine Sulphasalazine	Additive hepatotoxicity	↑ risk of hepatotoxicity
Live vaccines	↓ immune response	↑ risk of infection live vaccines-induced
Warfarin	n.a.	↑ risk for elevated INR and subsequent bleeding

Legend: BCRP: Breast cancer resistance protein; BH4: tetrahydrobiopterin; DHPR: dihydropteridine reductase; INR: International Normalized Ratio; n.a.: not available; NSAIDs: nonsteroidal anti-inflammatory drugs; OAT: organic anion transporter; OATP: organic anion transporting polypeptide; PABA: para-aminobenzoic acid.

Safety of target therapies

TNF-α antagonists, vedolizumab, ustekinumab and tofacitinib

TNF-α antagonists have been available for over a decade as treatment for IBD, and many studies attempted to assess their safety in elderly patients. Khan *et al.* conducted a retrospective database analysis of 63,759 patients (54,971 non-elderly and 8,788 elderly) treated with corticosteroids, immunosuppressants or anti-TNFs, and observed that immunosuppressants and anti-TNF therapy were associated with a higher risk of infection, as well as age [5]. In this cohort, the most frequent infections in the elderly group were pneumonia (39.8%), sepsis (13.2%), candidiasis (12.9%), herpes zoster (12.7%), and *Clostridioides difficile* colitis (8.3%).

A multicentre nested case-control study performed by the Italian Group for Inflammatory Bowel Disease [6] reported a higher rate of severe infections and mortality in elderly patients treated with anti-TNFs as compared with younger patients (13% vs 2.6% and 10% vs 1%, respectively) with the same treatment and with patients of the same age that did not receive these therapeutics. Similar results were reported by Lobatón et al. [7], whose observational study concluded that elderly patients treated with these drugs had a higher rate of SAEs than younger patients under the same treatment, regardless of concomitant treatment with immunosuppressants or corticosteroids. Data from 4 randomized clinical trials (RCTs) were summarized in a pooled analysis conducted by Cheng et al.: the analysis included 2,257 patients and compared older (≥ 60 years old, 10.2% of the cohort) and younger (< 60 years old) patients with ulcerative colitis (UC) treated with either anti-TNF agents (IFX) or golimumab (GOL) or placebo; older patients had an increased risk of SAEs (20% vs 10.2%,) and hospitalization (14.4% vs 5.2%) when compared to younger patients, but a high rate of SAEs was also found in older patients treated with placebo (25.4%), suggesting that elderly patients have a baseline increased risk of SAEs, which was not increased by anti-TNF therapy [8]. However, these data were extracted from clinical trials, which have very strict inclusion and exclusion criteria, possibly impairing the generalizability of these results. A recent Dutch, retrospective, multicentre cohort study found that the use of anti-TNF therapy in older patients with IBD was associated with serious infections (HR 3.92), but in their analysis comorbidities were also found to be related with safety outcomes [10]. A meta-analysis was conducted by Borren et al. pooling data of patients with immune-mediated disease treated with TNFα antagonists, including 14 studies (6 studies in IBD, 7 in rheumatoid arthritis and 1 in psoriasis). The authors showed a higher prevalence of infections in older users of biologics than in younger users (13% vs 6%), as well as a more than 3-fold increased risk of infection when compared to patients who did not use biologics43. However, no significant differences were found in odds of death, compared to older patients not on biological therapy. These results are in contrast with another meta-analysis conducted by Piovani et al. [4], which included 15 studies (9 cohort studies, 5 case-control studies and 1 post-hoc analysis of an RCT, mostly regarding TNFα antagonists) and found no evidence of increased risk of infection in elderly patients exposed to biologics, while reporting an increased risk of serious infections and opportunistic infections.

Regarding cancer and exposure to anti-TNFs, the evidence is controversial: three meta-analysis of RCTs in patients with RA [44-46] did not confirm the increased risk of malignancy previously reported in another meta-analysis [47]. An Italian real-world observational study in patients with spondylarthritis found a higher incidence of malignancies in patients treated with anti-TNFs than

in the general population and having had a previous solid cancer was predictive of a new malignancy [48], while a later study did not find the same increased risk of cancer [49]. In IBD, a Danish nationwide study found no association between TNFα use and occurrence of cancer over a median follow-up of 3.7 years [50]. Data from the ENEIDA registry in over 11,000 patients reported no increased risk of extracolonic cancer in patients treated with TNFα inhibitors [51]. The evidence of biological therapy and risk of malignancy in elderly patients was synthesized in the two previously cited meta-analyses [4, 20], which found no significant association between occurrence of cancer and TNFα exposure.

Another focal point in elderly patients is represented by safety in patients with prior malignancies [52], which is a common exclusion criterion in RCTs. Axelrad et al. conducted a retrospective study which did not report an increased risk of new malignancy or recurrence of a previous malignancy in patients treated with anti-TNFs; more recently, another Danish nationwide study in patients with immune-mediated diseases and previous cancer treated with anti-TNF concluded that the use of anti-TNFα therapy was not associated with recurrent or new primary cancer development and that the timing of anti-TNFα therapy after an initial cancer diagnosis did not influence recurrence or occurrence of a new primary cancer [53]. Regarding combination therapy, while a post-hoc analysis of the REACT trial showed no increased risk in patients treated with anti-TNFα and thiopurines [54], Desai et al. concluded that combination therapy was associated with a double risk of cessation in this population [55]. Pooled analysis from clinical trials and an observational cohort confirmed the increased risk of infection and malignancy [53, 56]. Kirschgesner et al. conducted a database-based analysis to assess the risk of infections in patients treated with anti-TNFα, thiopurines or combo therapy. Compared with anti-TNFα monotherapy, combination therapy was associated with increased risks of serious infection (HR 1.23) and opportunistic infection (HR 1.96). Compared with thiopurine monotherapy, anti-TNF monotherapy was associated with increased risks of serious infection (HR 1.71), mycobacterial infection (HR 1.98), and bacterial infection (HR 2.38). Conversely, anti-TNF monotherapy was associated with decreased risk of opportunistic viral infection compared with thiopurine monotherapy (HR 0.57; 95% CI, 0.38–0.87), suggesting a different interaction between these drugs and the immune system [57].

Still few data are available regarding anti-integrins, anti-interleukins and small molecules in elderly patients with IBD. VDZ is usually considered a safe option in this population; however, due to the usual strict inclusion criteria of RCTs, elderly patients were underrepresented in the GEMINI 1 and GEMINI 2 trials, which enrolled only 4% and 2% of patients > 65 years58,59. A post-hoc analysis of these two trials was conducted by Yajnik et al. [60] who concluded that no difference in safety was found when stratifying patients for age, though the subgroup of patients > 65 was substantially smaller than its comparison. A systematic review addressing the safety profile of VDZ was conducted by Bye et al. [61], which included 2,830 VDZ-exposed patients from registration studies and subsequent post-marketing cohorts, and interestingly reported lower incidence rates of infection and SAEs in patients treated with VDZ compared to placebo. A recent case-control study which included 25 elderly patients and 100 matched younger patients for comparison reported a similar profile of safety for VDZ in patients of all ages [62]. Another study conducted with 1,087 patients treated with VDZ confirmed its overall favourable safety profile: the rates of adverse events were comparable between VDZ monotherapy and VDZ in combination with an immunomodulator, but it was the addition of corticosteroids to both groups

which resulted in an incremental increase in risk of infection and SAEs (OR 1.72 per agent); additionally, they observed that being an active smoker was independently associated with infections (OR 3.39) [63]. A recent observational study from the cohort of SN-IBD also demonstrated the effectiveness and safety of VDZ as a first-line biologic, particularly among elderly patients [64]. A retrospective study on 131 elderly patients with IBD initiating anti-TNF or VDZ therapy concluded that there was not difference in occurrence of infection (20% for anti-TNF, 17% for VDZ) or malignancy (3% vs 1%) between the two therapeutic classes after the first year of treatment [65]. Another comparison was made by a Dutch multicentre study which prospectively included 410 patients treated with VDZ and UST to assess their safety, and concluded that the rates of any infection and hospitalization were associated with the burden of comorbidities and not with age [8].
The safety data on UST and tofacitinib rely on studies from dermatology and rheumatology, while data on IBD are still under evaluation. PSOLAR is an observational disease-based registry that assessed efficacy and safety among psoriasis patients treated with biologics: a recent analysis showed that patients in the UST cohort had lower severe infection rates than the anti-TNFs and MTX cohorts; age was associated with an increased risk for infection, irrespective of biologic exposure [66]. A previous study of 24 elderly patients with psoriasis treated with UST showed no severe infection at one year [67]. Regarding JAK inhibitors, Curtis et al. [68] pooled data from 5 phase III trials and two long term extension studies, identifying approximately 1,000 elderly patients with RA on tofacitinib: the risk of SAEs was higher in older than younger patients even in the placebo group, suggesting no incremental age-related risk due to tofacitinib exposure.
In July 2019, FDA approved a black-box warning for the 10 mg twice-daily dose of tofacitinib noting an increased risk for pulmonary embolism among older RA patients with a cardiovascular risk factor.

Drug-drug interactions of target therapies used in IBD patients

Drug-drug interactions can also occur with target therapies used in IBD patients, although no specific interaction studies have been performed during pre-marketing clinical studies, according to the summary of product characteristics (SmPCs) of these agents.
Regarding TNFα inhibitors, concomitant administration of two or more biological disease-modifying antirheumatic drugs [e.g. adalimumab (ADA) and IFX] or other TNF-inhibitors is not recommended based upon the possible increased risk for infections, including serious infections and other potential pharmacological interactions. It is also known that there is an interaction between the drugs belonging to this class and live vaccines, leading to a reduced efficacy of immunization and the issuing of a recommendation of non-concomitant administration. ADA has been studied in several diseases (e.g. rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, psoriatic arthritis) in monotherapy and in patients taking concomitant MTX. Antibody development was lower when ADA was given together with MTX in comparison with use as monotherapy [69-72].
Similarly, concomitant use of MTX and other immunomodulators may reduce the production of antibodies against IFX and increase the plasma concentrations of this drug. However, results are uncertain due to limitations in the methods used for serum analyses of IFX and antibodies against IFX. Corticosteroids do not affect the pharmacokinetics of IFX to a clinically relevant extent. Some clinical studies reported a higher prevalence of serious infections occurring in patients

aging 65 years and older treated with IFX compared with younger patients treated with the same drug. Furthermore, use of IFX showed a potential risk of development of hepatosplenic T-cell lymphoma in association with thiopurine, and the interaction of CYP450 substrates (e.g. tyrosin kinase inhibitors) with IFX increases the metabolism of these drugs [73-76].
Regarding UST, pharmacokinetics are not affected by the concomitant use of MTX, non-steroidal anti-inflammatory drugs, 6-mercaptopurine, AZA and oral corticosteroids in patients with psoriatic arthritis, IBD, also those with a prior exposure to TNFα inhibitors. VDZ has been studied in adult UC and Crohn's disease patients with concomitant administration of corticosteroids, immunomodulators (AZA, 6-mercaptopurine, and MTX), and aminosalicylates suggesting no clinically meaningful effect of co-administration of such agents. Live vaccines should not be given concurrently with UST or VDZ.
Tofacitinib total daily dose should be reduced by half in patients receiving moderate or potent inhibitors of CYP3A4 (e.g., ketoconazole) as well as potent inhibitors of CYP2C19 (e.g. fluconazole), due to an increase of Cmax of tofacitinib observed during co-administration with these agents. In contrast, co-administration of tacrolimus, cyclosporine or rifampicin reduced the tofacitinib Cmax. Moreover, concomitant use of tofacitinib and immunosuppressants has been associated with an increase in the immunosuppressive effect [77, 78].
All the main drug-drug interactions related to target therapies, reported in IBM Micromedex ®, are described in **Table 3**.

Table 3. Main drug-drug interactions of target therapies.

Interacting drugs	Effects of interaction	Molecule
Biologic agents	↑ immunosuppression ↑ risk of infections	Infliximab Adalimumab
Methotrexate	↓ antibody level	Adalimumab
	↑ infliximab plasma levels	Infliximab
Warfarin	↓ warfarin plasma concentrations	Infliximab
CYP450 substrate	↓ CYP450 substrate plasma concentrations	Infliximab
Live vaccines	↑ risk of infection live vaccines-induced ↓ effectiveness of immunization	Adalimumab Infliximab Ustekinumab Vedolizumab Tofacitinib
Strong CYP3A4 Inducers	↓ tofacitinib plasma levels	Tofacitinib
Strong CYP3A4 Inhibitors	↑ tofacitinib plasma levels	Tofacitinib
Strong CYP2C19 inhibitors	↑ tofacitinib plasma levels	Tofacitinib
Tacrolimus Cyclosporine Rifampicin	↓ Cmax of tofacitinib	Tofacitinib

Legend: bDMARDs: Biological disease-modifying antirheumatic drugs; Cmax: maximum serum concentration.

Conclusion

Selection of immunosuppressive therapy is a challenge in the management of elderly patients with IBD. Thiopurine safety issues include an increased risk of lymphoma and NMSC, while anti-TNFα therapy is associated with higher rate of opportunistic infection in this population. Therefore, when possible, biologics with lower infection or malignancy risk (vedolizumab and ustekinumab) may be preferred in elderly patients. Concomitant therapies and comorbidities

should be thoroughly investigated before starting any immunosuppressive or biological therapy in order to minimize the risk of drug-drug interactions.

References

1. Jeuring SF, van den Heuvel TR, Zeegers MP, et al. Epidemiology and long-term outcome of inflammatory bowel disease diagnosed at elderly age – an increasing distinct entity? Inflamm Bowel Dis 2016;22:1425–34.
2. Taleban S, Colombel JF, Mohler MJ, Fain MJ. Inflammatory bowel disease and the elderly: A review. J Crohns Colitis 2015;9:507–15.
3. Kim M, Katz S, Green J. Drug Management in the Elderly IBD Patient. Curr Treat Options Gastroenterol. 2015;13(1):90-104.
4. Piovani D, Danese S, Peyrin-Biroulet L, Nikolopoulos GK, Bonovas S. Systematic review with meta-analysis: biologics and risk of infection or cancer in elderly patients with inflammatory bowel disease. Aliment Pharmacol Ther. 2020;51(9):820-830.
5. Khan N, Vallarino C, Lissoos T, Darr U, Luo M. Risk of Infection and Types of Infection Among Elderly Patients With Inflammatory Bowel Disease: A Retrospective Database Analysis. Inflamm Bowel Dis. 2020;26(3):462-468.
6. Cottone M, Kohn A, Daperno M, et al. Advanced age is an independent risk factor for severe infections and mortality in patients given anti-tumor necrosis factor therapy for inflammatory bowel disease. Clin Gastroenterol Hepatol. 2011;9(1):30-35.
7. Lobatón T, Ferrante M, Rutgeerts P, Balle V, Van Assche G, Vermeire S. Efficacy and safety of anti-TNF therapy in elderly patients with inflammatory bowel disease. Aliment Pharmacol Ther. 2015;42(4):441-451.
8. Cheng D, Cushing KC, Cai T, Ananthakrishnan AN. Safety and Efficacy of Tumor Necrosis Factor Antagonists in Older Patients With Ulcerative Colitis: Patient-Level Pooled Analysis of Data From Randomized Trials [published online ahead of print, 2020 May 1]. Clin Gastroenterol Hepatol. 2020;S1542-3565(20)30615-7.
9. Ananthakrishnan AN, Shi HY, Tang W, et al. Systematic Review and Meta-analysis: Phenotype and Clinical Outcomes of Older-onset Inflammatory Bowel Disease. J Crohns Colitis. 2016;10(10):1224-1236.
10. Asscher VER, van der Vliet Q, van der Aalst K, et al. Anti-tumor necrosis factor therapy in patients with inflammatory bowel disease; comorbidity, not patient age, is a predictor of severe adverse events. Int J Colorectal Dis. 2020;35(12):2331-2338.
11. Asscher VER, Biemans VBC, Pierik MJ, et al. Comorbidity, not patient age, is associated with impaired safety outcomes in vedolizumab- and ustekinumab-treated patients with inflammatory bowel disease-a prospective multicentre cohort study. Aliment Pharmacol Ther. 2020;52(8):1366-1376.
12. Torres et al. ECCO Guidelines on Therapeutics in Crohn's Disease: Medical Treatment. Journal of Crohn's and Colitis. 2020, 4–22.
13. Rubin DT et al. ACG Clinical Guideline: Ulcerative Colitis in Adults. Am J Gastroenterol. 2019 Mar;114(3):384-413.
14. Juneja M, Baidoo L, Schwartz MB, et al. Geriatric inflammatory bowel disease: phenotypic presentation, treatment patterns, nutritional status, outcomes, and comorbidity. Dig Dis Sci. 2012;57(9):2408-2415.

15. Calafat M, Mañosa M, Cañete F, et al. Increased risk of thiopurine-related adverse events in elderly patients with IBD [published correction appears in Aliment Pharmacol Ther. 2020 Mar;51(6):674]. Aliment Pharmacol Ther. 2019;50(7):780-788.
16. Beaugerie L, Brousse N, Bouvier AM, et al. Lymphoproliferative disorders in patients receiving thiopurines for inflammatory bowel disease: a prospective observational cohort study. Lancet. 2009;374(9701):1617-1625.
17. Peyrin-Biroulet L, Khosrotehrani K, Carrat F, et al. Increased risk for nonmelanoma skin cancers in patients who receive thiopurines for inflammatory bowel disease. Gastroenterology. 2011;141(5):1621-28.e285.
18. Bourrier A, Carrat F, Colombel JF, et al. Excess risk of urinary tract cancers in patients receiving thiopurines for inflammatory bowel disease: a prospective observational cohort study. Aliment Pharmacol Ther. 2016;43(2):252-261.
19. Abbas AM, Almukhtar RM, Loftus EV Jr, Lichtenstein GR, Khan N. Risk of melanoma and non-melanoma skin cancer in ulcerative colitis patients treated with thiopurines: a nationwide retrospective cohort. Am J Gastroenterol. 2014;109(11):1781-1793.
20. Yoshii I, Chijiwa T, Sawada N. Efficacy and Safety of Targeted Strategy for Treating Rheumatoid Arthritis Patients Aged 75 Years or Older. Tohoku J Exp Med. 2020 Jan;250(1):13-23. doi: 10.1620/tjem.250.13.
21. Cummins D, Muthasamy S, Halil O et al. Myelosuppression associated with azathioprine-allopurinol interaction after heartand lung transplantation. Transplantation 1996; 61:1661-1662.
22. John, E.S., Katz, K., Saxena, M. et al. Management of Inflammatory Bowel Disease in the Elderly. Curr Treat Options Gastro 14, 285–304 (2016).
23. Gossmann J, Kachel HG, Schoeppe W et al. Anemia in renal transplant recipients caused by concomitant therapy with azathioprine and angiotensin-converting enzyme inhibitors. Transplantation 1993; 56:585-589
24. Grekas D, Nikolaidis P, Karamouzis M et al. Effects of azathioprine on ciclosporin metabolism (letter). Nephron 1992;60:489.
25. Peyrin-Biroulet L, Cadranel JF, Nousbaum JB et al. Interaction of ribavirin with azathioprine metabolism potentiallyinduces myelosuppression. Aliment Pharmacol Ther Oct 15, 2008; 28(8):984-993.
26. Product Information: COPEGUS(R) oral tablets, ribavirin oral tablets. Genentech, Inc, South San Francisco, CA, Jun,2010. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/021511s029lbl.pdf (Accessed on April 26,2021)
27. Product Information: IMURAN(R) oral tablets, azathioprine oral tablets. Prometheus Laboratories Inc., SanDiego, CA, Feb, 2014. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/016324s034s035lbl.pdf (Accessed on April 26,2021)
28. Vazquez SR, et al. Azathioprine-induced warfarin resistance. Ann Pharmacother Jul, 2008; 42(7):1118-1123.
29. Lowry PW, et al. Leucopenia resulting from a drug interaction between azathioprine or 6-mercaptopurine and mesalamine, sulphasalazine, or balsalazide. Gut. 2001 Nov;49(5):656-64.

30. Yarur AJ, et al. Concentrations of 6-thioguanine nucleotide correlate with trough levels of infliximab in patients with inflammatory bowel disease on combination therapy. Clin Gastroenterol Hepatol. 2015 Jun;13(6):1118-24.e3.
31. Centers for Disease Control and Prevention: General Recommendations on Immunization. MMWR Jan 28, 2011;60(2):1-60. Available at: "https://www.cdc.gov/mmwr/preview/mmwrhtml/rr6002a1.htm" (Accessed on April 26, 2021)
32. Groenendal H & Rampen FHJ. Methotrexate and trimethoprim-sulphamethoxazole-a potentially hazardous combination. Clin Exp Dermatol 1990; 15:358-360.
33. Product Information: FOSCAVIR(R) intravenous injection solution, foscarnet sodium intravenous injection solution. Hospira, Inc. (per DailyMed), Lake Forest, IL, Nov, 2014. Available at: https://www.pfizer.com/products/product-detail/foscavir (Accessed on April 26,2021)
34. Liddle BJ, Marsden JR. Drug interactions with methotrexate. Br J Dermatol 1989; 120: 582-3.
35. Zuik M, Mandel MA. Methotrexate-salicylate interaction: a clinical and experimental study. Surg Forum 1975; 26: 567-9.
36. Paxton JW. Interaction of probenecid with the protein binding of methotrexate. Pharmacology 1984; 28: 86-9. (PubMed id:6709690)
37. Dawson JK, Abernethy VE & Lynch MP. Methotrexate and penicillin interaction (letter). Br J Rheumatol 1998; 37:807.
38. Gabrielli A, et al. Methotrexate and nonsteroidal anti-inflammatory drugs. BMJ 1987; 294: 776.
39. Santucci R, Leveque D, Kemmel V et al. Severe intoxication with methotrexate possibly associated with concomitant use of proton pump inhibitors. Anticancer Res Mar, 2010; 30(3):963-965.
40. Seifter EJ, et al. Possible interactions between warfarin and antineoplastic drugs. Cancer Treat Rep Feb 1, 1985; 69(2):244-245.
41. Chan J, Sanders DC, Du L et al. Leflunomide-associated pancytopenia with or without methotrexate. Ann Pharmacother2004; 38:1206-1211.
42. Product Information: ARAVA(R) oral tablets, leflunomide oral tablets. sanofi-aventis U.S. LLC, Bridgewater, NJ,Aug, 2015. Available at: https://products.sanofi.us/arava/arava.html (Accessed on April 26, 2021)
43. Borren NZ, Ananthakrishnan AN. Safety of Biologic Therapy in Older Patients With Immune-Mediated Diseases: A Systematic Review and Meta-analysis. Clin Gastroenterol Hepatol. 2019;17(9):1736-1743.e4.
43. Askling J, van Vollenhoven RF, Granath F, et al. Cancer risk in patients with rheumatoid arthritis treated with anti-tumor necrosis factor alpha therapies: does the risk change with the time since start of treatment? Arthritis Rheum. 2009;60(11): 3180-3189
45. Lopez-Olivo MA, Tayar JH, Martinez-Lopez JA, et al. Risk of malignancies in patients with rheumatoid arthritis treated with biologic therapy: a meta-analysis. JAMA. 2012;308(9):898-908.
46. Moulis G, Sommet A, Béné J, et al. Cancer risk of anti-TNF-α at recommended doses in adult rheumatoid arthritis: a meta-analysis with intention to treat and per protocol analyses. PLoS One. 2012;7 (11):e48991

47. Bongartz T, Sutton AJ, Sweeting MJ, Buchan I, Matteson EL, Montori V. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. JAMA. 2006;295(19):2275-2285
48. Atzeni F, Carletto A, Foti R, et al. Incidence of cancer in patients with spondyloarthritis treated with anti-TNF drugs. Joint Bone Spine. 2018;85(4):455-459.
49. Hellgren K, Dreyer L, Arkema EV, et al. Cancer risk in patients with spondyloarthritis treated with TNF inhibitors: a collaborative study from the ARTIS and DANBIO registers. Ann Rheum Dis. 2017;76(1):105-111.
50. Nyboe Andersen N, Pasternak B, Basit S, et al. Association between tumor necrosis factor-α antagonists and risk of cancer in patients with inflammatory bowel disease. JAMA. 2014;311(23):2406-2413.
51. Chaparro M, Ramas M, Benítez JM, et al. Extracolonic Cancer in Inflammatory Bowel Disease: Data from the GETECCU Eneida Registry. Am J Gastroenterol. 2017;112(7):1135-1143.
52. Lawlor G, Katz S. Management of IBD in the Elderly Patient With Cancer. Curr Treat Options Gastroenterol. 2015;13(3):301-307.
53. Waljee AK, Higgins PDR, Jensen CB, et al. Anti-tumour necrosis factor-α therapy and recurrent or new primary cancers in patients with inflammatory bowel disease, rheumatoid arthritis, or psoriasis and previous cancer in Denmark: a nationwide, population-based cohort study. Lancet Gastroenterol Hepatol. 2020;5(3):276-284.
54. Singh S, Stitt LW, Zou G, et al. Early combined immunosuppression may be effective and safe in older patients with Crohn's disease: post hoc analysis of REACT. Aliment Pharmacol Ther 2019;49:1188-1194.
55. Desai A, Zator ZA, de Silva P, et al. Older age is associated with higher rate of discontinuation of anti-TNF therapy in patients with inflammatory bowel disease. Inflamm Bowel Dis 2013;19:309-15.
56. Lemaitre M, Kirchgesner J, Rudnichi A, et al. Association Between Use of Thiopurines or Tumor Necrosis Factor Antagonists Alone or in Combination and Risk of Lymphoma in Patients With Inflammatory Bowel Disease. JAMA. 2017;318(17):1679-1686.
57. Kirchgesner J, Lemaitre M, Carrat F, Zureik M, Carbonnel F, Dray-Spira R. Risk of Serious and Opportunistic Infections Associated With Treatment of Inflammatory Bowel Diseases. Gastroenterology. 2018;155(2):337-346.e10.
58. Feagan BG, Rutgeerts P, Sands BE, et al. Vedolizumab as induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2013;369(8):699-710.
59. Sandborn WJ, Feagan BG, Rutgeerts P, et al. Vedolizumab as induction and maintenance therapy for Crohn's disease. N Engl J Med. 2013;369(8):711-721.
60. Yajnik V, Khan N, Dubinsky M, et al. Efficacy and Safety of Vedolizumab in Ulcerative Colitis and Crohn's Disease Patients Stratified by Age. Adv Ther. 2017;34(2):542-559.
61. Bye WA, Jairath V, Travis SPL. Systematic review: the safety of vedolizumab for the treatment of inflammatory bowel disease. Aliment Pharmacol Ther. 2017;46(1):3-15.
62. Shashi P, Gopalakrishnan D, Parikh MP, Shen B, Kochhar G. Efficacy and safety of vedolizumab in elderly patients with inflammatory bowel disease: a matched case-control study. Gastroenterol Rep (Oxf).

63. Meserve J, Aniwan S, Koliani-Pace JL, et al. Retrospective Analysis of Safety of Vedolizumab in Patients With Inflammatory Bowel Diseases. Clin Gastroenterol Hepatol. 2019;17(8):1533-1540.e2.
64. Macaluso FS, Fries W, Renna S, et al. Effectiveness and safety of vedolizumab in biologically naïve patients: A real-world multi-centre study. United European Gastroenterol J. 2020;8(9):1045-1055.
65. Adar T, Faleck D, Sasidharan S, et al. Comparative safety and effectiveness of tumor necrosis factor α antagonists and vedolizumab in elderly IBD patients: a multicentre study. Aliment Pharmacol Ther. 2019;49(7):873-879.
66. Ritchlin CT, Stahle M, Poulin Y, et al. Serious infections in patients with self-reported psoriatic arthritis from the Psoriasis Longitudinal Assessment and Registry (PSOLAR) treated with biologics. BMC Rheumatol. 2019;3:52. Published 2019 Nov 28.
67. Hayashi M, Umezawa Y, Fukuchi O, Ito T, Saeki H, Nakagawa H. Efficacy and safety of ustekinumab treatment in elderly patients with psoriasis. J Dermatol. 2014;41(11):974-980.
68. Curtis JR, Schulze-Koops H, Takiya L, et al. Efficacy and safety of tofacitinib in older and younger patients with rheumatoid arthritis. Clin Exp Rheumatol. 2017;35(3):390-400.
69. Weinblatt M, Schiff M, Goldman A et al. Selective costimulation modulation using abatacept in patients with activerheumatoid arthritis while receiving etanercept: a randomised clinical trial. Ann Rheum Dis Feb 1, 2007; 66(2):228-234.
70. Product Information: ORENCIA(R) intravenous, subcutaneous injection, abatacept intravenous, subcutaneous injection.Bristol-Myers Squibb Company, Princeton, NJ, Jun, 2020. Available at: https://www.orencia.com/ (Accessed on April 26,2021)
71. Product Information: KINERET(R) subcutaneous injection, anakinra subcutaneous injection. Amgen,Inc, Thousand Oaks,CA, Dec 1, 2006. Available at: https://www.kineretrx.com/ (Accessed on April 26,2021)
72. Product Information: AMJEVITA(TM) subcutaneous injection, adalimumab atto subcutaneous injection. Amgen Inc., Thousand Oaks, CA, Sep, 2016. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/761024lbl.pdf (Accessed on April 26,2021)
73. Product Information: REMICADE(R) intravenous injection, infliximab intravenous injection. Janssen Biotech Inc, Horsham, PA, Oct, 2017. Available at: https://www.remicadehcp.com/ (Accessed on April 26,2021)
74. Product Information: RENFLEXIS(TM) intravenous injection powder for solution, infliximab-abda intravenous injection powder for solution. Merck Sharp & Dohme Corp, Kenilworth, NJ, Apr, 2017. Available at: https://www.renflexis.com/ (Accessed on April 26,2021)
75. Product Information: INFLECTRA intravenous injection, infliximab-dyyb intravenous injection. Hospira, LakeForest, IL, Apr, 2016. Available at: https://www.pfizer.com/products/product-detail/inflectra (Accessed on April 26,2021)
76. Product Information: ACTEMRA(R) IV injection, tocilizumab IV injection. Genentech, Inc, South San Francisco, CA, Jan,2011. Available at: https://www.actemrahcp.com/ (Accessed on April 26,2021)
77. Product Information: XELJANZ(R) oral tablets, tofacitinib oral tablets. Pfizer Labs, New York, NY, May, 2018. Available at: https://www.xeljanz.com/ (Accessed on April 26,2021)

78. Gupta, P. et al (2014). Evaluation of the effect of fluconazole and ketoconazole on the pharmacokinetics of tofacitinib in healthy adult subjects. Clinical Pharmacology in Drug Development, 3: 72-77.

3.3. Large-scale postmarketing surveillance of biological drugs for immune-mediated inflammatory diseases through an italian distributed multi-database healthcare network: the VALORE Project

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Abstract

Background: Biological drugs improved the management of immune-mediated inflammatory diseases (IMIDs), despite they have been associated to important safety issues such as immunogenicity, infections and malignancies in real-world setting.

Objective: Aim of this study was to explore the potential of a large Italian multi-database distributed network for post-marketing surveillance of biological drugs, including biosimilars, in IMID patients.

Methods: A retrospective cohort study was conducted using 13 Italian regional claims databases during 2010-2019. A tailor-made R-based tool developed for distributed analysis of claims data using a study-specific common data model was customized for this study. Yearly prevalence of biological drug users as well as frequency of switches between originator and biosimilar for infliximab, etanercept and adalimumab separately was measured and stratified by calendar year and region. Cumulative number of users and number of person-years (PYs) of exposure to individual biological drugs approved for IMIDs was calculated. For a number of safety outcomes (e.g. SARS-COV-2 infection), sample power calculation was carried out to estimate the amount of PYs of exposure required for investigating the association with individual biological drugs approved for IMIDs, considering different strengths of association.

Results: From a total underlying population of almost 50 million of inhabitants from 13 Italian regions, 143,602 (0.3%) biological drug users were identified, with a cumulative exposure of 507,745 PYs during the entire follow-up. The mean age (±standard deviation) of biological drug users was 49.3 (±16.3) with a female to male ratio of 1.2. Age-adjusted yearly prevalence of biological drug users increased three-fold from 0.7 per 1,000 in 2010 to 2.1 per 1,000 in 2019. Overall, 40,996 users of biosimilar of Tumor Necrosis Factor (TNF)-alpha inhibitors (i.e. etanercept, adalimumab and infliximab) were identified in the years 2015-2019. Of these, 46% (N=18,845) switched at any time between originator and biosimilars, or viceversa. To investigate a moderate association (Incidence Rate Ratio=2) of use of biological drugs approved for IMIDs and safety events of interest such as optic neuritis (lowest background incidence rate: 10.4/100,000 PYs) or severe infection (highest background incidence rate: 4,312/100,000 PYs), a total of 43,311 PYs and 104 PYs of exposure to individual biological drug, respectively, would be required. As such, using this network, out of 15 individual biological drugs approved for IMIDs, the association with those adverse events could be investigated for 4 (27%) and 14 (93%) respectively.

Conclusion: The VALORE project multi-database network has access to data on more than 140,000 biological drug users (and >0.5 million PYs) from 13 Italian regions during the years 2010-2019, which will be further expanded with the inclusion of data from other regions and more recent calendar years. Overall, the cumulated amount of person-time of exposure to biological drugs approved for IMIDs provides enough statistical power to investigate weak/moderate associations of almost all individual compounds and the most relevant safety outcomes. Moreover, this network may offer the opportunity to investigate interchangeability of originator and biosimilars of several TNF-alpha inhibitors in different therapeutic areas in real-world setting.

Introduction

Recent years have seen the introduction into the market of highly innovative biological drugs, leading to an improvement in the management of immune-mediated inflammatory diseases (IMIDs) in dermatologic, rheumatologic and gastroenterological settings. Since 2006, in parallel, several widely prescribed biological drugs have lost their patents, opening the market to a growing number of biosimilars [1]. Biological drugs, including biosimilars, approved for IMID treatment may be associated to important safety issues that have been mostly detected in the post-marketing setting [2]. In particular, immunogenicity (e.g. hypersensitivity and infusion reactions) as well as infections, malignancies and other serious adverse reactions have been repeatedly documented for several biological drugs [3-5].

More recently, with the current severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) pandemic causing coronavirus disease 2019 (COVID-19), there is uncertainty about the risk of SARS-COV-2 infection and COVID-19 prognosis in patients receiving chronic treatment with biological drugs interfering with the immune system [6,7]. Specifically, it has been debated among clinicians whether treatment with biological drugs should be interrupted to prevent severe complications of the COVID-19, such as interstitial pneumonia [8,9]. The American College of Rheumatology recommends continuing the treatment with biological drugs in patients with stable rheumatic diseases in absence of COVID-19 or SARS–CoV-2 exposure [10]. On the other hand, several biological drugs (e.g. tocilizumab, sarilumab) have been proposed as repurposed treatments for COVID-19 patients and have been investigated in a number of ongoing experimental studies [11-14].

Another important issue to be addressed in the post-marketing setting concerns the interchangeability of biological drug originators and biosimilars and, specifically, on the presumed risk of immunogenicity by switching between biological drugs, which may cause lack of effect and toxicity. Members of the Biosimilar Working Party of the European Medicine Agency (EMA), after exploring the available safety data on switch between a biosimilar and its reference product, concluded that biosimilars licensed in the European Union are interchangeable. However, the safety of the switch between originator and biosimilars requires additional investigation in real life and can be further addressed generating clinical evidence of biosimilarity provided from pre-marketing studies and from intensified post-marketing surveillance [15, 16].

It is therefore imperative to set-up large-scale real-world data infrastructures for generating real-world evidence on the comparative benefit-risk profiles of individual biological drugs (including biosimilars) in IMIDs, integrating evidence from pivotal clinical trials as well as rapidly investigating emerging safety issues, such as COVID-19.

In general, claims databases and clinical registries are sources of real-world data with potential and limitations for monitoring the benefit–risk profile of biological drugs. In some European Countries, established registries of IMID patients, such as the British Association of Dermatologists Biologic Interventions (BADBIR Register) and the British Society for Rheumatology Biologics Registry (BSRBR), the Antirheumatic Therapies (ARTIS) and Psoriasis Registry (PsoReg) in Sweden and the Danish Registry for Biologic Therapies in Rheumatology (DANBIO) [17-19] have been used in European Union for post-authorization safety studies, but these sources lack power and length of follow-up. Likewise, the Biologic and Biosimilar Collective Intelligence Consortium (BBCIC) is a non-profit research consortium that

was established in the US in 2015 to conduct observational studies on the safety and the effectiveness of biological drugs, including biosimilars using claims data [*available at: https://bbcic.org/*].
Irrespective of the data source, monitoring of the appropriate prescribing and the benefit-risk profile of (newly-marketed) biological drugs as well as of the interchangeability of originators and biosimilars call for the implementation of large-scale real-world data networks for rapid, systematic and comparative assessment of biological drugs in post-marketing setting [20].
The Italian project "Post-marketing evaluation of the benefit-risk profile of originator biological drugs vs. biosimilars in dermatology, rheumatology, gastroenterology through healthcare database network, active surveillance and clinical registries" (VALORE project), funded by the Italian Medicine Agency, set up a distributed multi-database network of claims databases linked to clinical registries from almost the entire Country. The aim of this study was to demonstrate the enormous potential of the VALORE project network for conducting post-marketing surveillance of biological drugs, including biosimilars, in Italian patients with IMIDs.

Methods

A retrospective, cohort, multi-database study was performed. Fully anonymized data were extracted from the claims databases of 13 Italian regions (Abruzzo, Apulia, Basilicata, Campania, Emilia-Romagna, Friuli Venezia Giulia, Lazio, Lombardy, Sardinia, Sicily, Tuscany, Umbria and Veneto), which covers almost 50 million of inhabitants (83.3% of Italian population).

Data sources

In this study, the following regional claims databases have been considered: a) inhabitant registry, including demographic information about the date of birth, gender, date of registration in the regional healthcare system; b) drug dispensing from pharmacy claims database; c) birth registry (**Fig. 1**). Data about biological drugs were recorded using Anatomical Therapeutic Chemical classification system (ATC) and National Drug Code (NDC), while the Defined Daily Dose (DDD) was used as the unit to estimate drug exposure [21].
Biological drugs having subcutaneous formulations are dispensed to the patients by hospital pharmacists for outpatient use, whereas intravenous biological drugs (e.g. infliximab) are administered to patients in dedicated hospital ambulatory care centres. In each region, claims data collect information on dispensing of biological drugs, irrespective of the formulations.
In Italy, for each biological drug being prescribed to outpatients, a therapeutic plan must be filled by a specialist physician employed by the national healthcare systems. The therapeutic plan includes the drug name, dosing regimen and indication for use. In five Italian regions (i.e. Apulia, Lazio, Friuli Venezia Giulia, Veneto and Campania) electronic therapeutic plans can be linked at the individual level to the claim data sources.

Study population

All persons residing in the catchment areas of all participating regions between January 1st, 2010 (or first available data) and December 31st, 2019 (or last available date) were identified. Based on the data availability at the time of the study, Apulia and Campania (2014–2019), Sicily (2011-2018), Lazio (2010-2017), Basilicata (2017-2019) and Veneto (2015-2019) could contribute a

lower number of observation years. All subjects in the source population having at least one biological drug dispensing during the observation years were included in the study.
The date of the first biological drug dispensing (index drug) was used as index date (ID). As a patient could potentially start multiple treatments with biological drugs during the entire study period, multiple individual biological drug-specific IDs per patient were considered, if appropriate.
Each patient was followed up from the ID until the occurrence of one of the following events, whichever came first: a) patient's death; b) transfer out of the database; c) end of the study period/end of data collection of the database. The characteristics (total size, mean age and sex distribution) of the underlying population of each region participating to VALORE project network [22] were provided in the ***Online Resource 1***.

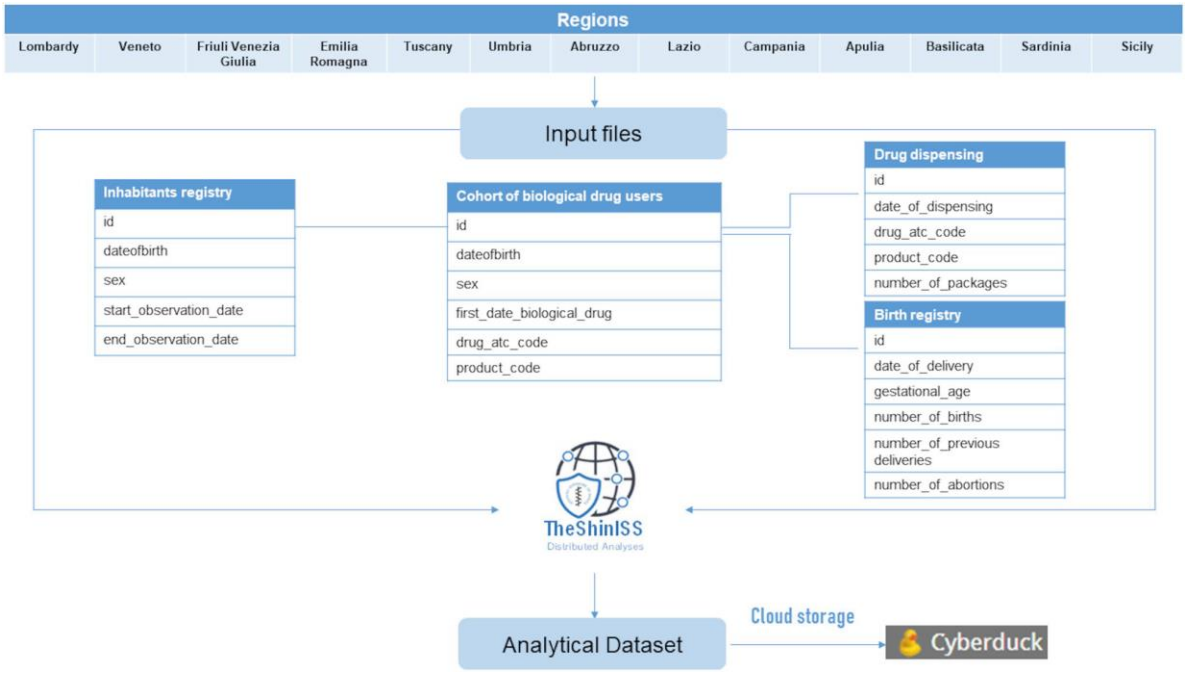
Drugs of interest

Drugs of interest were biological drugs (originator and biosimilar) approved in Italy for IMIDs up to 31st December 2019: a) Tumor Necrosis Factor (TNF)-alpha inhibitors (i.e. infliximab, etanercept, adalimumab, golimumab and certolizumab pegol); b) interleukin inhibitors (i.e. anakinra, tocilizumab, secukinumab, ustekinumab, ixekinumab, brodalumab, sarilumab, guselkumab, tildrakizumab, risankizumab); c) selective immunosuppressants (i.e. abatacept, vedolizumab). Rituximab was not included in the analysis as this drug is mainly used in the onco-haematological setting. At the time of this study the biosimilars of infliximab, etanercept and adalimumab were available in the Italian market.
The ATC and NDC codes of the study drugs are included in ***Online Resource 2***.

Distributed Analyses

A distributed analyses approach based on a "study-specific" Common Data Model (CDM) strategy was used [23]. An R-based open-source tool "TheShinISS", developed by the Italian National Institute of Health for conduction of distributed analyses, was customized for the purposes of the study. TheShinISS has been already described elsewhere [14,24-26]. Specifically, it was delivered to regions for elaborating and processing, at local level, data on a cohort of biological drug users approved for IMIDs, which were previously extracted and loaded into a study-specific CDM. This tool performs quality controls of data and ultimately generates anonymized and harmonized analytic dataset to be shared for the centralized data analyses. A project-specific cloud storage browser, Cyberduck, was used for the latter purpose (**Fig. 1**).

Fig. 1 VALORE project multi-database network using common data model.



ID: index date, ATC: anatomical therapeutic chemical.

Analysis of safety outcomes

Based on safety information reported in the summary of product characteristics (SmPCs) and the Risk Management Plan (RMP), a list of the most relevant safety outcomes associated to the study drugs was produced. Specifically, all the safety outcomes reported in the *Important identified or potential risks* sections of the RMP and in the Paragraph 4.4 *Special warnings and precautions for use* of the SmPCs were collected. Safety outcomes from SmPCs and RMP were grouped according to mechanistic classes of biological drugs (i.e. TNF-alpha inhibitors, interleukin inhibitors and selective immunosuppressants) and included in **Table 1.** Hierarchical attributions (i.e. important identified risk > important potential risk > safety risk from SmPCs) were considered. Further identification of these safety outcomes, stratified by active substance, was provided in ***Online Resource 3-5.***

Table 1. Major safety outcomes for TNF-alpha inhibitors, selective immunosuppressants and interleukin inhibitors, as reported on SmPC and RMP.

Safety outcome	TNF-alpha inhibitors	Selective immunosuppressants	Interleukin inhibitors
Immune system disorders			
Hypersensitivity (incl. anaphylaxis or anaphylactoid reactions)[a,b,c]	•	•	•
Infections and infestations			
Tuberculosis [a,b]	•	•	•
Sepsis[a,b]	•	•	
Pneumonia[a,b]	•	•	
Invasive fungal infections[a,b]	•	•	
Hepatitis B virus (HBV) reactivation[a,b,c]	•	•	•
Gastrointestinal infections[c]		•	
Upper Respiratory Tract Infections[a,b]		•	•
Diverticulitis aggravated[a,b]			•
Conjunctivitis[a,b]			•
Fungal infections[a,b]			•
Cardiac disorders			
Congestive heart failure[a,b]	•		
Hyperlipidaemia[a]			•
Major Adverse Cardiac Events (MACE)[c]			•
Gastrointestinal disorders			
Inflammatory bowel disease (including Crohn's disease and ulcerative colitis)[a,b,c]			•
Gastrointestinal perforation[b]			•
Hepatobiliary disorders			
Worsening of hepatitis C[a]	•		
Autoimmune hepatitis[a]	•		
Acute liver failure[b]			•
Hepatitis[b]			•
Jaundice[a]			•
Respiratory, thoracic and mediastinal disorders			
Eosinophilic pneumonia[a]			•
Pulmonary alveolar proteinosis[a,c]			•
Pulmonary hypertension[a,c]			•
Interstitial lung disease[a,c]			•
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)			
Lymphomas[a,b,c]	•		•
Leukaemia[a,b]	•		
Melanoma[a,b]	•		
Nonmelanoma skin cancer[a,b,c]	•	•	•
Merkel cell carcinoma[a,b]	•		
Colon cancer/dysplasia [a,c]	•	•	
Lung cancer[a,c]	•		•
Cervical cancer[b]	•		
Breast cancer[a]	•		
Blood and lymphatic system disorders			
Pancytopenia, leukopenia, neutropenia and thrombocytopenia[a,b]	•		•
Wegener's granulomatosis[a]	•		
Musculoskeletal and connective tissue disorders			
Lupus and lupus-like illness [a,b]	•		
Nervous system disorders			

Guillain-Barré syndrome[a,b]	•		
Multiple Sclerosis[a,b]	•		
Serious depression (including suicidality)[c]	•		•
Optic neuritis[b]	•		
Progressive multifocal leukoencephalopathy (PML)[a,c]	•	•	
Reversible posterior leukoencephalopathy syndrome[c]	•		•
Encephalitis/Leukoencephalomyelitis[c]	•		
Facial palsy[b]			•
Skin and subcutaneous tissue disorders			
Exfoliative dermatitis[a]			•
Psoriasis[b]			•
Immuno system disorders			
Macrophage activation syndrome (MAS)[a]			•
Investigations			
Transaminase elevations[a]			•
Increases in lipid parameters[a,c]			•
Vascular disorders			
Venous thromboembolism[c]			•
Metabolism and nutrition disorders			
Hypoglycaemia[a]	•		
Hyperlipidaemia[a]			•

[a] Paragraph 4.4 Special warnings and precautions for use, Summary of products characteristics.

[b] Risk Management Plan, Important identified risk

[c] Risk Management Plan, Important potential risk

Legend: RMP=risk management plan; SmPC= summary of product characteristics

To assess the potential of the multi-database network for investigating the association of clinically relevant safety outcomes with any individual biological drugs approved for IMIDs, based on statistical power calculation, a sample of the above mentioned adverse events with heterogenous background incidence rates (IRs) were selected: severe infections and SARS-CoV-2 infection, neoplasms, congestive heart failure, tuberculosis and optic neuritis.

Statistical analysis

Categorical variables of the study population were reported as absolute and relative frequencies (i.e. percentages). Continuous variables were reported as mean ± standard deviation.

Yearly prevalence of biological drugs use was computed as the number of drug users over the total population for each calendar year, overall and stratified per region. Prevalence was adjusted for age categories (<18 years, 18-44 years, 45-64 years, ≥ 65 years) using standardized direct method based on calendar year-specific Italian population. Yearly age-adjusted prevalence of biological drug users was graphically represented with a line chart for each region respectively.

For each biological drug user, the number of days of therapy, based on the DDD and the amount of dispensed drug, was calculated for every year, and the average number of Person Years (PYs) of exposure was computed in the study population. Cumulative time of exposure over the years to biological drugs was measured and stratified by region and molecule. Distribution of number and percentages of biological drug users (overall and within subgroups) were graphically described with bar plots or stacked bar plots as appropriate. Yearly cumulative number of biological drug users and PYs were graphically illustrated as stacked area plot.

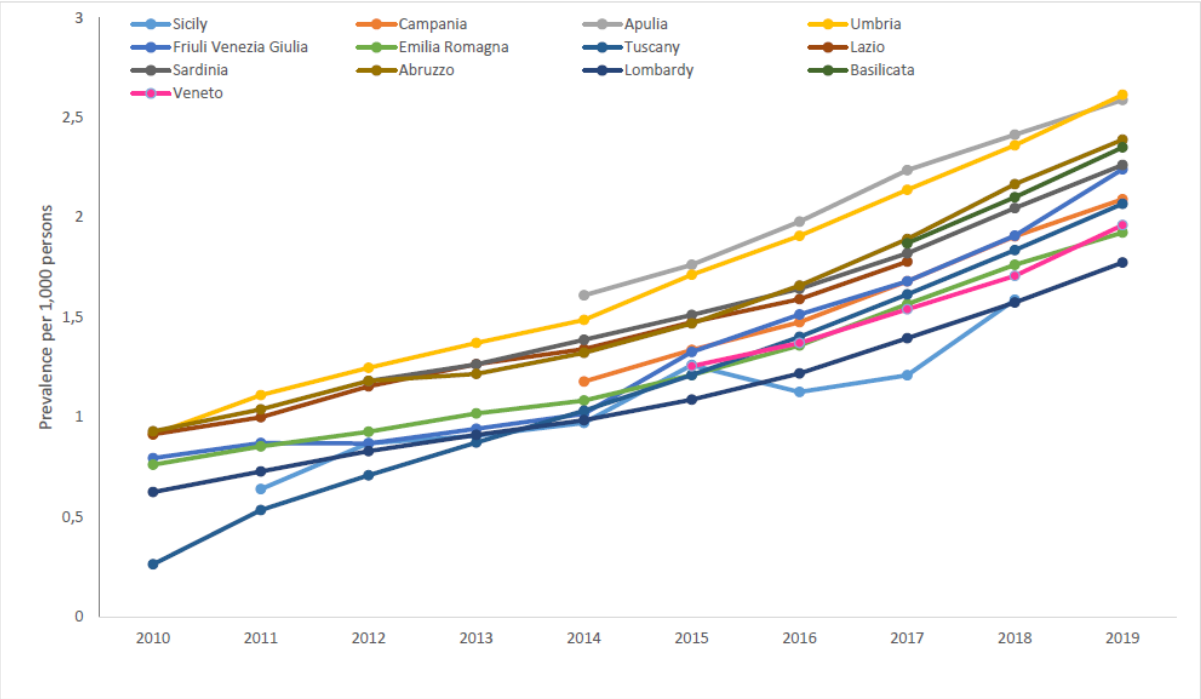
The required amount of PYs of exposure to individual biological drugs, considering adverse events having various background IR and different strength of association, assessed using Incident Rate Ratio (IRR), was graphically represented as approximate power curves [27].
The IRs of the safety outcomes in users of IMID-approved biological drugs were retrieved from the literature [28-31]. The total amount of PYs of exposure that would be required to detect an association between any biological drugs approved for IMIDs and the events of interest, was computed over varying magnitudes of IRR (1.5, 2, 4, and 6), using one-sided significance level $\alpha = 0.05$ and a power of 80% ($\beta = 0.2$), based on the formula described by Beaumont JJ et al [27]. The proportion of individual biological drugs, among the ones included in the study, for which there would be sufficient data for the investigation of different safety outcomes was consequently determined. All statistical analyses were performed using R version 4.0 (The R Foundation for Statistical Computing, Vienna, Austria).

Results

From a total underlying population of almost 50 million of inhabitants (83.3% of the total Italian population) from 13 Italian regions during the years 2010-2019 [mean age ranging from 42.1 to 47.1 years old with female to male ratio (F/M ratio) = 1.1] (see ***Online Resource 1***), 143,602 (0.3%) biological drug users were overall identified. Mean age (±standard deviation) of biological drug users was 49.3 (±16.3) with a F/M ratio equal to 1.2. Age-adjusted yearly prevalence of biological drug users increased three-fold from 0.7 per 1,000 inhabitants in 2010 to 2.1 per 1,000 inhabitants in 2019 (**Fig. 2**). Apulia and Umbria regions showed the highest prevalence of biological drug users (2.6 per 1,000 inhabitants for both regions in 2019). Cumulative exposure was 507,745 PYs during the entire follow-up. On average, each user had 3.5 PYs of exposure (**Fig. 3**).
Looking at drug classes, the largest number of users was reported for TNF-alpha inhibitors [N=118,276 (82.4%); PYs= 395,709 (77.9%)], followed by interleukin inhibitors [N=36,942 (25.7%); 83,704 PYs (16.5%)] and selective immunosuppressants [N=16,918 (11.8%); 25,300 PYs (5.0%)]. Regarding individual compounds, the largest number of users was observed for adalimumab [N=61,748 (43.0%); 121,363 PYs (23.9%)], etanercept [N=46,946 (32.7%); 106,948 PYs (21.0%)] and infliximab [N=25,127 (17.5%); 123,136 PYs (24.2%)]. Among interleukin inhibitors, the largest number of users was observed for ustekinumab [N=12,648 (8.8% of total biological drug users); 44,309 PYs (8.7%)], followed by secukinumab [N=12,564 (8.7%); 14,467 PYs (2.8%)]. Sarilumab and brodalumab, which were introduced into the market at the end of the study period, showed the lowest cumulative number of users [N=722 (0.5%); 263 PYs (<0.1%); and 132 (0.1%); 35 PYs (<0.1%), respectively] (**Fig. 4**).
As regards specific age groups, 10,457 (7.3%) biological drug users were younger than 18 years old and 46,479 (32.4%) were older than 65 years. Among elderly patients, 8,886 (6.2% of total biological users) were older than 80 years (data not shown).
Overall, 40,996 (almost 30% of total users) users of biosimilar of TNF-alpha inhibitors (i.e. etanercept, adalimumab and infliximab) were identified in the years 2015-2019 (**Fig. 5 (D)**). The proportion of biosimilar users for these biological drugs increased in all the Italian regions over time (**Fig. 5 (A-C)).** Of these, 46% (N=18,845) of etanercept, adalimumab and infliximab users switched between originator and biosimilars, or viceversa, at least once during the years 2015-2019.

As regards to safety outcomes, the IR of some adverse events of interest in cohorts of biological drug users were identified from the literature [27-30] as reported below (from the highest to the lowest IR): 4,312 for 100,000 PYs for severe infections; 382 for 100,000 PYs for neoplasms; 175 for 100,000 PYs for congestive heart failure; 164 for 100,000 PYs for SARS-CoV-2 infection; 95 for 100,000 PYs for tuberculosis; and 10.4 for 100,000 PYs for optic neuritis.
The amount of drug exposure in terms of PYs required to allow detection of a weak (IRR=1.5), moderate (IRR=2), strong (IRR=4) and very strong (IRR=6) association of individual biological drug and each of the five adverse events of interest is shown in **Fig. 6**. Particularly, for SARS-CoV-2 infection, 12,439 PYs of exposure to any biological drug would be required to detect a weak association, which allows to investigate 9 out of 15 individual study drugs. For optic neuritis and severe infections (events with lowest and highest background incidence rate), 43,311 PYs and 104 PYs of drug exposure would be necessary to detect a 'moderate' association (i.e. IRR = 2), which allows to investigate respectively 4 and 14 out of 15 study drugs (**Fig. 6**).
Based on women biologic drug users with at least one delivery after ID, the number of pregnant women exposed to biological drug in the VALORE project network was 794 (available data from 11/13 Regions). Considering the same sample size for non-exposed group, the minimum statistically significant relative risk (RR) detectable by event rate is shown in **Fig. 7**. Particularly, assuming an event rate of 7% for the outcome of interest, such as preterm delivery or low birth weight, it will be possible to detect associations with a RR=1.45.

Fig. 2 Age-adjusted yearly prevalence of use (per 1000 people) of biological drugs approved for immune-mediated inflammatory diseases, stratified by region in the period 2010–2019.



Age adjustment was performed using standardized direct method, based on calendar year-specific Italian population for the following age categories: < 18, 18–44, 45–64, and ≥ 65 years.

Fig. 3 Cumulated number of biological drug users (left) and person-years (PYs) of biological drug exposure (right) during the study period 2010–2019, stratified by regions.

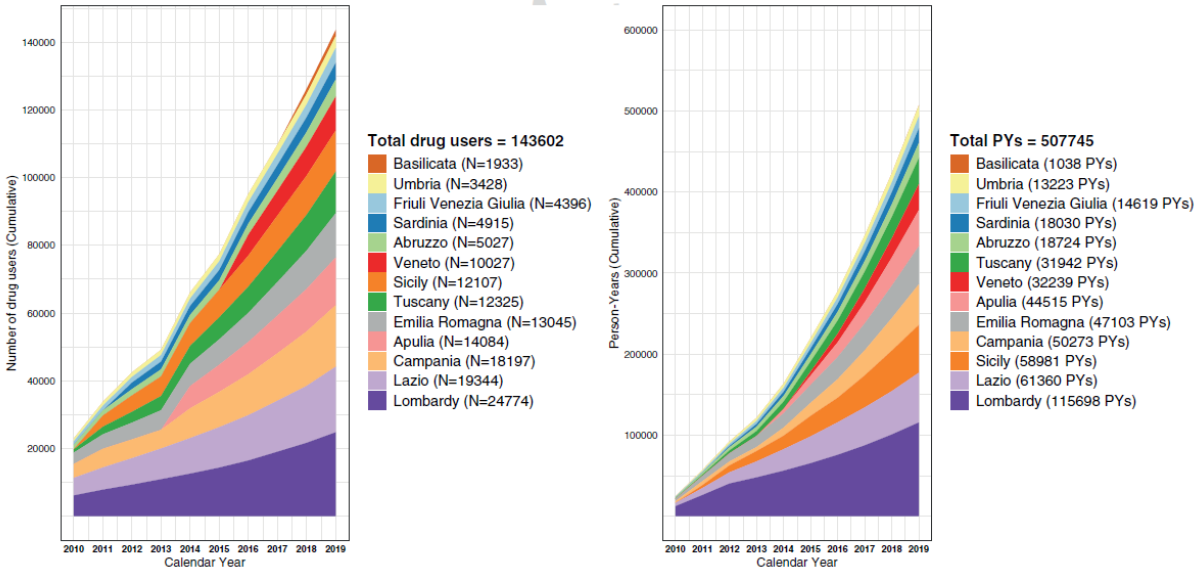


Fig. 4 Cumulated number of biological drug users (left) and person-years (PYs) of biological drug exposure (right) during the study period 2010–2019, stratified by single molecule.

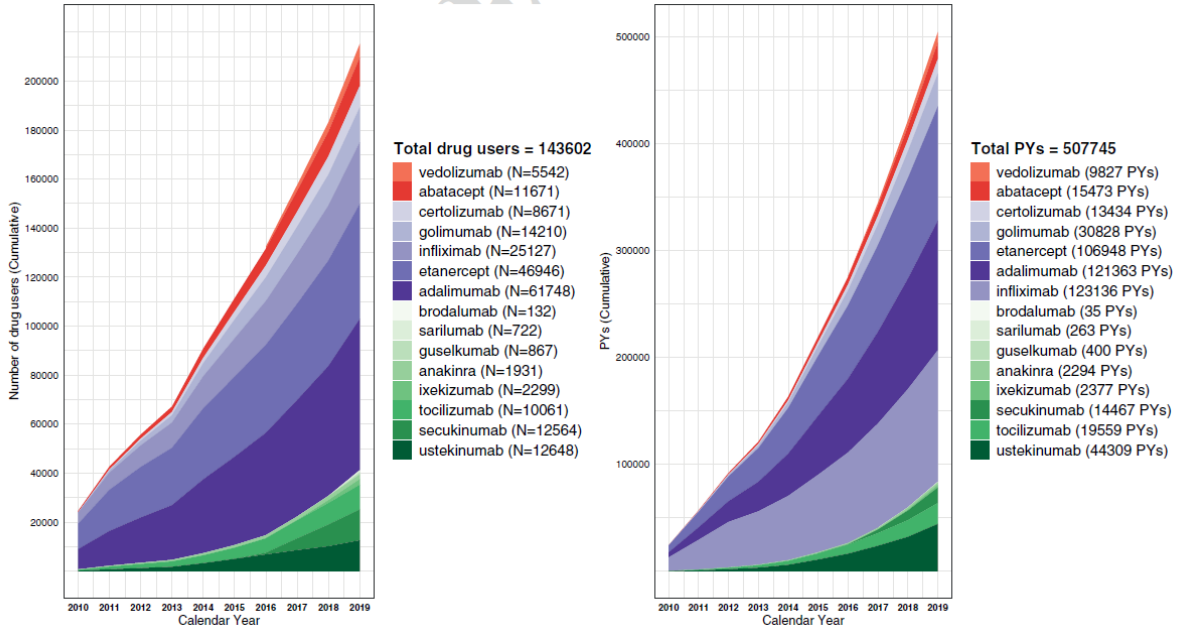
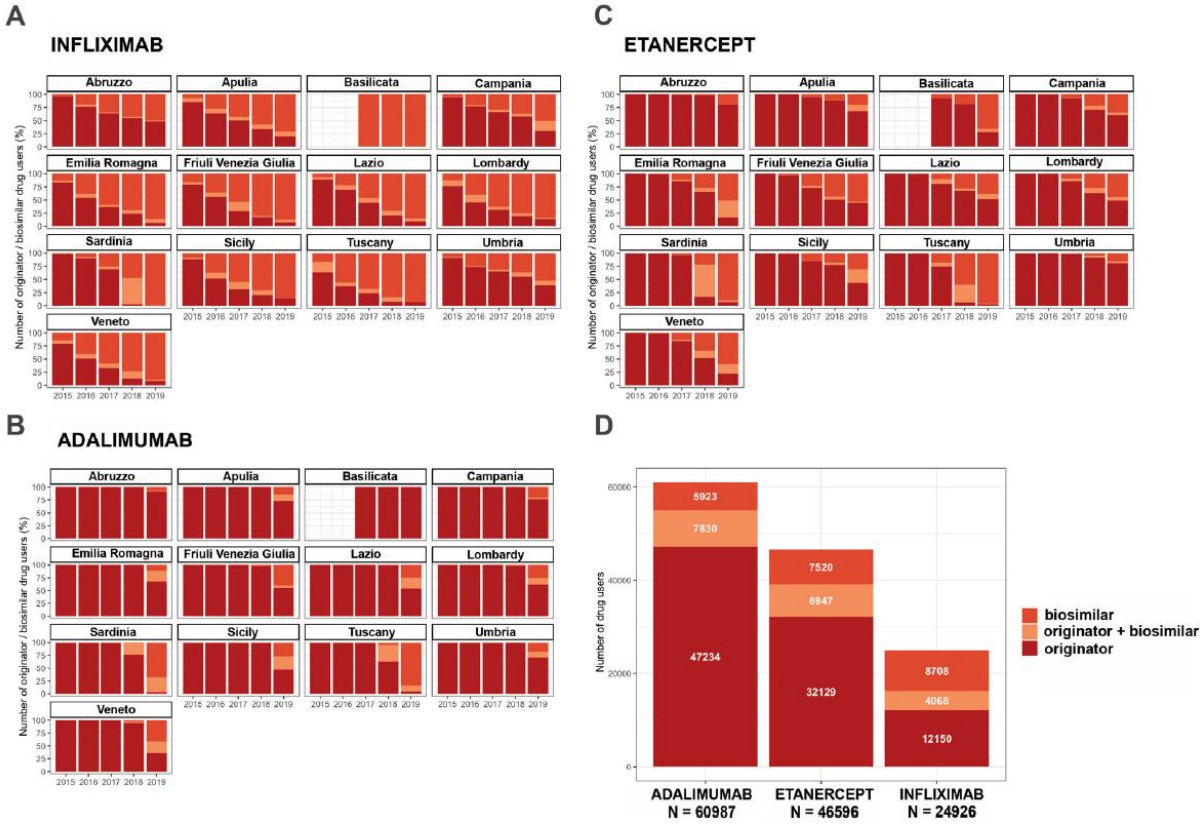
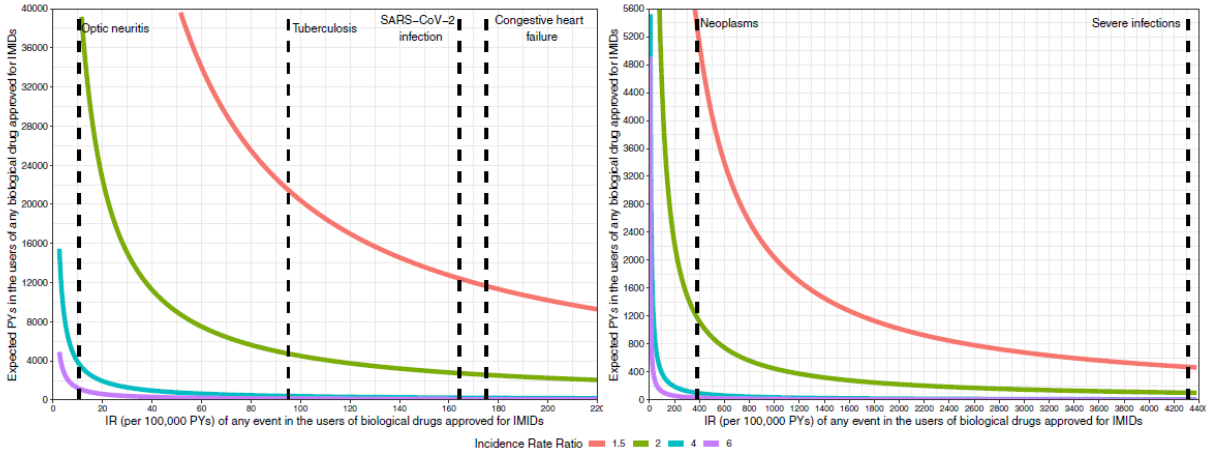


Fig. 5 Distribution of infliximab (**A**), adalimumab (**B**), and etanercept (**C**) originator/biosimilar use in the years 2015–2019, stratified by region and calendar year, and total number of users of those individual biological drugs, stratified by originator/biosimilar use (**D**).



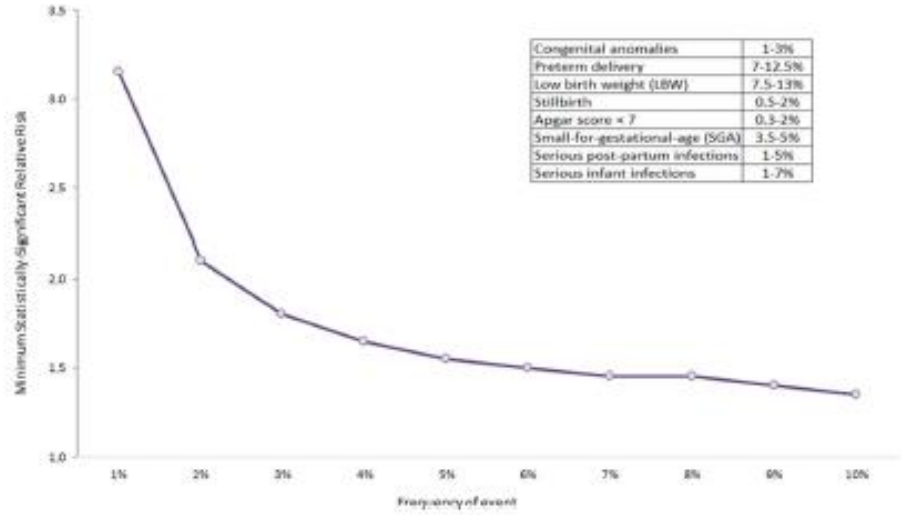
Biosimilar users: one or more dispensing of biosimilar only; *Originator users:* one or more dispensing of originator only; O*riginator + biosimilar users:* one or more dispensing of biosimilar and one or more dispensing of originator.

Fig. 6 Approximate power curves to estimate the required amount of drug exposure (PYs) to detect a statistically significant ratio of 1.5 (weak association), 2 (moderate association), 4 (strong association), and 6 (very strong association) between the IR of a given safety outcome in users of biological drugs approved for IMIDs vs. the general population, using one-sided significant level $\alpha = 0.05$ and a power of 80% ($\beta = 0.2$).



Note: The following background IRs were considered based on scientific literature: 175 for 100,000 PYs for congestive heart failure, 95 for 100,000 PYs for tuberculosis, 10.4 for 100,000 PYs for optic neuritis, 382 for 100,000 PYs for neoplasms, 164.1 for 100,000 PYs for SARS-CoV-2 infection, 4312 for 100,000 PYs for severe infections. IMID immune-mediated inflammatory diseases, IR incidence rate, PYs person-years, SARS-CoV-2 severe acute respiratory syndrome coronavirus 2.

Fig. 7 Minimum detectable relative risk for important pregnancy-related adverse events associated to biological drug users in pregnant women.



Discussion

This is the first large-scale multi-database network (13 Italian regions covering an underlying population of almost 50 million of inhabitants with ten-year follow-up) that has been specifically set up in Italy for post-marketing surveillance of biological drugs approved for IMIDs. Likewise, Biologic and Biosimilar Collective Intelligence Consortium has been established in the United States in 2015 to carry out observational studies of biological drugs using a distributed research

network of claims data for almost 95 million patients in USA. In Europe (especially Northern Europe), a number of well consolidated disease registries, like DANBIO, have been set up also for post-marketing surveillance of biological drugs in IMIDs; they include electronic data of treatments with biological drugs collected during periodic visits by specialists or other health-care professionals (e.g. nurses) and clinical information recorded by patients [19]. Instead, the VALORE-project network collects all routinely provided healthcare services to biological drug users using several claims databases, which can be further supplemented with clinical data from linkable regional disease registries, whenever available.

Yearly prevalence of biological drug users increased overall on average from 0.7 per 1,000 in 2010 to 2.1 per 1,000 in 2019. Heterogeneity across regions has been documented. Availability of highly qualified specialist centers, regional drug policies and characteristics of underlying population may all account for differences in biological drug access across geographic areas.

Several biological drug utilization studies from other European Countries have been previously published. Fassmer et al. investigated the frequency of biological drug use in a cross-sectional study, based on the claims data of a large German health insurance database. Consistently with our results, although the study period was more outdated, prevalence of biological drug use increased steadily from 2004 to 2011 (from 0.35 per 1,000 inhabitants in 2004 to 1.54 per 1,000 inhabitants in 2011) [32]. The VALORE project network currently covers 143,602 individual biological drug users and cumulated 507,745 PYs of exposure. As compared to 2010, the total number of biological drug users was four-fold in 2019 (N= 92,744), in line with the increased use of several biological drugs over the years reported by the national reports on medicine use in Italy [33-36] and with the results from the previously described population-based study conducted in Germany [32]. Similarly, Mendelsohn et al., evaluated the incident use of biologic anti-inflammatory agents in BBCIC's Distributed Research from 2012 to 2019. They identified 160,866 (0.5%) incident users of TNF-alpha inhibitors and abatacept, anakinra, brodalumab, canakinumab, guselkumab [37]. The increasing trend in the yearly prevalence of use of biological drugs across all the regions during the study years could be related to multiple factors, such as the marketing of several biological drugs (e.g. secukinumab, vedolizumab), including biosimilars, in more recent years as well as the extensions of the approved indications for use for many frequently prescribed biological drugs (e.g. adalimumab), thus expanding the number of patients eligible to the biological treatments.

The large scale population of biological drug users collected from VALORE project networks is essential to investigate the association of several clinically relevant outcomes and individual biological drugs, as pivotal trials of marketed biological drugs recruited in general a too small number of patients to investigate accurately the safety profile of those drugs. As an example the pivotal clinical trial of ustekinumab included a little more than 700 patients with psoriasis in PHOENIX 1 and around 1,200 psoriatic patients in PHOENIX 2 pivotal trials, while for adalimumab 1,368 patients overall were treated with this drug in pivotal phase III clinical trials [38, 39]. As regard to drug classes, we observed a progressively increasing use of interleukin inhibitors, especially in the last four observation years (2016-2019), with more than 40,000 users overall captured by the network in these years. Only for brodalumab, sarilumab and guselkumab very low number of users were identified, since they were introduced in the market at the end of the observation period and in some regions the access to the market of those biological drugs was further delayed due to the evaluation procedure for inclusion into the Regional Drug Formulary,

thus generating possible inequality in quality of care across Italian regions [40]. TNF-alpha inhibitors were the most frequently dispensed biological drugs (395,709 PYs of exposure related to 118,276 biological drug users), which is due to the observation period under study. As compared to chemically synthetized small molecules, more uncertainties about safety of biological drugs at the time of approval may exist [41]. Considering that clinical trials are not able to detect adverse outcomes occurring rarely or with a long latency, safety profile of biological drugs should be always intensively monitored in the real-world setting.

Using data from eight European healthcare databases, a previous large-scale retrospective study estimated the number of drugs (not restricted to biological drugs) that could be monitored for surveillance of a range of safety outcomes with different background incidence rates (acute myocardial infarction, upper gastrointestinal bleeding, acute renal failure, anaphylactic shock, bullous eruptions and rhabdomyolysis) using electronic healthcare databases [42].

Likewise, the VALORE-project database network showed enough statistical power to adequately detect even weak association of individual biological drugs approved for IMIDs and specific safety outcomes of interest. It has been reported that reliance on a single database could reduce statistical power [43], while combining multiple databases offers the ability to assess exposures to a larger variety of biological drugs within a wider range of patients and with heterogeneous pattern of use. Furthermore, given the different safety profile of individual biological drugs and drug classes, the gained statistical power of this network may allow conducting comparative safety studies for almost all individual IMID-approved biological drugs. The number of PYs of exposure (12,439 PYs) to any biological drugs approved for IMIDs that would be necessary to detect a weak association (IR=1.5) with SARS-CoV-2 infection was also identified. The SARS-CoV-2 infection pandemic raised concerns also about the management of patients with IMIDs. In general, the relationship between risk of SARS-COV-2 infection/COVID-19 prognosis and use of IMID-approved biological drugs is still debated [8, 9]. Although it has been reported that use of TNF-alpha inhibitors and interleukin 12/23 inhibitors in patients with inflammatory bowel disease or psoriasis did not worsen the clinical course of COVID-19 [44,45], there are still scarce data to draw firm conclusions about the association of individual biological compound and COVID-19. Through the linkage of COVID-19 regional registries and claims data, the VALORE project distributed database network may properly investigate this important safety outcome in large cohorts of biological drug users. This approach has already been adopted for investigating the relationship of COVID-19 prognosis and angiotensin converting enzyme inhibitors (ACEIs)/angiotensin receptor blockers (ARBs) or hydroxychloroquine/chloroquine and other conventional disease-modifying anti-rheumatic drugs (cDMARDs) in rheumatic patients, as well as to measure the survival rate of hospitalized COVID-19 patients [14, 25, 26]. Another aspect of interest concerns the use of biosimilars. There are different positions of international regulatory authorities about the interchangeability of originator and biosimilars [16, 20]. In VALORE project network we captured data on 40,996 biosimilar users of infliximab, adalimumab and etanercept during the years 2015-2019. The use of those biosimilars has been increasing significantly over the recent years, even if with heterogeneity across Italian regions, as documented in the national reports on medicine use in Italy [33-36] and previous Italian real-world studies [46,47]. This finding is probably due to the implementation of different regional health policies for promoting biosimilar use [48].

Interestingly, 46% of etanercept, adalimumab and infliximab biosimilar users switched between originator and biosimilar (or viceversa) during the follow-up, thus highlighting the potential of such a database network for investigating the interchangeability of originator and biosimilar in real-world setting. As it is unrealistic that randomized clinical trials may be systematically carried out to explore all potential switches of originator and related multiple biosimilars, intensified post-marketing surveillance, in addition to evidence of biosimilarity, has been suggested as optimal approach for ensuring interchangeability of biosimilars and originators [15].

Strengths and limitations

The main strength of this population-based study is the large size of the data source and the almost nationwide coverage (almost 50 million Italian persons over a total population of more than 60 million persons) for a period of 10 years, which can be further extended, based on continuous accrual of more recent data and possibly other regions. The VALORE project network captured data from 13 Italian regions, including almost all densely populated ones (e.g. Lombardy, Campania, Lazio, Sicily, and Veneto regions). The underlying population from 13 Italian regions included in the VALORE project network registered a mean age ranging from 42.1 to 47.1 years old with F/M ratio=1.1, in line with the mean age (ranging from 43.3 to 48.5 years old) and sex distribution (F/M ratio= 1.1) observed in the underlying population of the other eight Italian regions as proof of the representativeness of the population of VALORE project network [22]. As one third of biological drugs approved for IMIDs have been marketed in Italy before 2016, the long-term assessment of the pattern of use as well as the comparative safety and effectiveness of different biological drugs, including biosimilars, using VALORE project database network is feasible. Since our study focused on 13 Italian regions from Northern, Central and Southern Italy and the trend of biological drug users over the years from these databases are consistent with the trend documented in the Italian national reports on drug consumption, these study findings may be considered representative of the whole Italian population. Moreover, this study reported data of specific subgroups of biological drug users such as pregnant women, for whom a lack of information from pivotal studies of biological drugs exists. An open-source R-based tool (TheShinISS), developed for distributed analyses within a CDM framework, allowed on a side, the involvement of a large and growing number of regions and on the other side, once customized, the opportunity to rapidly update data and analytical dataset, in line with data privacy regulations.

Some limitations of the study warrant caution. First, we did not perform analysis stratified by indication of use which may be more informative. As some regions provide also access to electronic therapeutic plans filled by specialists for prescribing biological drugs and including information on exact indication for use, validation studies of coding algorithms for identifying the main indication of use of biological drugs approved for IMIDs are ongoing. As regards specifically the power calculation which is irrespective of indications of use, it has to be noted that the risk of safety outcomes may vary across different indication of use; on the other hand, all the indications approved for the biological drugs under investigation are inflammatory and immune-mediated diseases. As such, it is unlikely that differences in risk (if any) of safety outcomes across various indications of use are substantial [49] and, as such, the risk assessment of safety outcomes associated to biological drugs approved for IMIDs is likely to be informative even if not stratified by indication of use. Second, some study drug dispensing might not have

been captured by the databases (e.g. biological drugs occasionally administered to inpatients during a hospitalization). However, it is unlikely that this limitation influenced somehow the study results. Moreover, some biological drugs such as tildrakizumab, risankizumab, brodalumab were fully reimbursed by Italian National Health System only starting from 2019 onwards, thus yielding a very low number (if not null in some Regions) of users, which, at the moment, prevents the conduct of any post-marketing assessment. Third, estimated power of the network may be reduced for safety outcomes assessment, when restricted to specific indication of use or patients' categories (e.g. children, very old patients, pregnant women); however, the network currently cumulates such a large number of biological drug users that analyses on major safety outcomes for the most frequently prescribed individual compounds will be possible. Fourth, the exposure to biological drugs was assessed on the basis of DDD, but clearly situations in which some patients have to intensify/reduce the dose regimen could occur, and therefore DDD could not reflect the exact doses actually used in clinical practice. However, this approach has been commonly used as one of the best accurate way to estimate dosing regimen using claims databases in pharmacoepidemiology and it is unlikely to influence substantially our results. Fifth, concerning interchangeability between reference biological product and biosimilar, the most accurate approach to investigate the potentially related immunogenicity is testing levels of anti-drug antibodies. However, it is known that anti-drug antibodies are not measured routinely in clinical practice and even if measured, generally claims database hardly capture information on laboratory findings. Nevertheless, the VALORE project claims database network may potentially explore safety outcomes related to immunogenicity in case of clinical manifestations such as serious hypersensitivity reactions leading to hospitalization or emergency department visits or lack of effectiveness, which may be measured using some composite outcomes as proxy, as done in previous claims database studies on biological drugs [50]. Sixth, safety outcomes (especially those with a long latency period, e.g. neoplasms) observed during the follow-up could not be associated with the biological drug dispensed at ID, but also with a biological drug other than index drug/small molecule after a switch, thus requiring proper methodological approach. Finally, clinically relevant information of IMIDs (e.g. disease severity) in the network of regional claims databases are missing. Nevertheless, one of the ambitious goals of VALORE project is to enrich claims data with clinically relevant information such as disease activity scores, exact indication of use and reasons for treatment discontinuation through linkage with population-based disease registries from the same catchment area, which are available in some Italian regions [51-53]. For this scope, exploratory analyses have been conducted in the last year to link regional claims data with the Sicilian registry of biological drug users with inflammatory bowel disease and will be conducted in the near future with Veneto registries of biological drugs users with dermatology, rheumatology or gastroenterology diseases.

Conclusions

During the period 2010-2019, the VALORE project multi-database network identified 143,602 biological drug users from 13 Italian regions. The gained statistical power of this large-scale distributed database network allows the post-marketing surveillance of individual biological drugs with respect to a broad range of clinically relevant safety outcomes including SARS-CoV-2 infection. VALORE project multi-database network can be on a side further powered by adding data from more recent calendar years of follow-up and from other regions and, on the other side,

enriched though linkage with population-based clinical registries. Such a network has a great potential to generate real-world evidence on comparative benefit-risk assessment of individual biological drugs in patients with autoimmune disease as well as on the interchangeability of originators and related biosimilars.

References

1. European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP): guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-similar-biological-medicinal-products-containing-monoclonal-antibodies-non-clinical_en.pdf. Accessed 8 Mar 2021.
2. Cutroneo PM, Isgrò V, Russo A, Ientile V, Sottosanti L, Pimpinella G, Conforti A, Moretti U, Caputi AP, Trifirò G. Safety profile of biological medicines as compared with non-biologicals: an analysis of the italian spontaneous reporting system database. Drug Saf. 2014 Nov;37(11):961-70.
3. Sharma B. Immunogenicity of therapeutic proteins. Part 3: impact of manufacturing changes. Biotechnol Adv. 2007 May-Jun;25(3):325-31.
4. Giezen TJ, Mantel-Teeuwisse AK, Leufkens HG. Pharmacovigilance of biopharmaceuticals: challenges remain. Drug Saf. 2009;32(10):811-7.
5. Downing NS, Shah ND, Aminawung JA, Pease AM, Zeitoun JD, Krumholz HM, Ross JS. Postmarket Safety Events Among Novel Therapeutics Approved by the US Food and Drug Administration Between 2001 and 2010. JAMA. 2017 May 9;317(18):1854-1863.
6. Burke KE, Kochar B, Allegretti JR, Winter RW, Lochhead P, Khalili H, Colizzo FP, Hamilton MJ, Chan WW, Ananthakrishnan AN. Immunosuppressive Therapy and Risk of COVID-19 Infection in Patients With Inflammatory Bowel Diseases. Inflamm Bowel Dis. 2021 Jan 19;27(2):155-161.
7. Damiani G, Pacifico A, Bragazzi NL, Malagoli P. Biologics increase the risk of SARS-CoV-2 infection and hospitalization, but not ICU admission and death: Real-life data from a large cohort during red-zone declaration. Dermatol Ther. 2020 Sep;33(5):e13475.
8. Lebwohl M, Rivera-Oyola R, Murrell DF. Should biologics for psoriasis be interrupted in the era of COVID-19? J Am Acad Dermatol. 2020 May;82(5):1217-1218.
9. Bashyam AM, Feldman SR. Should patients stop their biologic treatment during the COVID-19 pandemic. J Dermatolog Treat. 2020 Jun;31(4):317-318.
10. Mikuls TR, Johnson SR, Fraenkel L, Arasaratnam RJ, Baden LR, Bermas BL, Chatham W, Cohen S, Costenbader K, Gravallese EM, Kalil AC, Weinblatt ME, Winthrop K, Mudano AS, Turner A, Saag KG. American College of Rheumatology Guidance for the Management of Rheumatic Disease in Adult Patients During the COVID-19 Pandemic: Version 3. Arthritis Rheumatol. 2021 Feb;73(2):e1-e12.
11. Crisafulli S, Isgrò V, La Corte L, Atzeni F, Trifirò G. Potential Role of Anti-interleukin (IL)-6 Drugs in the Treatment of COVID-19: Rationale, Clinical Evidence and Risks. BioDrugs. 2020 Aug;34(4):415-422.
12. Sultana J, Crisafulli S, Gabbay F, Lynn E, Shakir S, Trifirò G. Challenges for Drug Repurposing in the COVID-19 Pandemic Era. Front Pharmacol. 2020 Nov 6;11:588654.

13. Convertino I, Tuccori M, Ferraro S, Valdiserra G, Cappello E, Focosi D, Blandizzi C. Exploring pharmacological approaches for managing cytokine storm associated with pneumonia and acute respiratory distress syndrome in COVID-19 patients. Crit Care. 2020 Jun 11;24(1):331.
14. Trifirò G, Massari M, Da Cas R, Menniti Ippolito F, Sultana J, Crisafulli S, Giorgi Rossi P, Marino M, Zorzi M, Bovo E, Leoni O, Ludergnani M, Spila Alegiani S; ITA-COVID-19: RAAS inhibitor group. Renin-Angiotensin-Aldosterone System Inhibitors and Risk of Death in Patients Hospitalised with COVID-19: A Retrospective Italian Cohort Study of 43,000 Patients. Drug Saf. 2020 Dec;43(12):1297-1308.
15. Kurki P, van Aerts L, Wolff-Holz E, Giezen T, Skibeli V, Weise M. Interchangeability of Biosimilars: A European Perspective. BioDrugs. 2017 Apr;31(2):83-91.
16. Trifirò G, Marcianò I, Ingrasciotta Y. Interchangeability of biosimilar and biological reference product: updated regulatory positions and pre- and post-marketing evidence. Expert Opin Biol Ther. 2018 Mar;18(3):309-315.
17. Elkayam O, Pavelka K. Biologic registries in rheumatology: lessons learned and expectations for the future. Autoimmun Rev. 2012 Dec;12(2):329-36.
18. Amin M, Lee EB, Bhutani T, Wu JJ. Review of European registries for psoriasis. J Dermatolog Treat. 2019 May;30(3):227-236.
19. Hetland ML. DANBIO: a nationwide registry of biological therapies in Denmark. Clin Exp Rheumatol. 2005 Sep-Oct;23(5 Suppl 39):S205-7.
20. Ingrasciotta Y, Sultana J, Kirchmayer U, Trifirò G. Challenges in Post-marketing Studies of Biological Drugs in the Era of Biosimilars: A Report of the International Society for Pharmacoepidemiology 2019 Mid-Year Meeting in Rome, Italy. BioDrugs. 2019 Aug;33(4):345-352.
21. Trifirò G, Sultana J, Bate A. From Big Data to Smart Data for Pharmacovigilance: The Role of Healthcare Databases and Other Emerging Sources. Drug Saf. 2018 Feb;41(2):143-149.
22. Italian statistical institute. Population data. Available from: http://dati.istat.it/Index.aspx?QueryId=18462.
23. Gini R, Sturkenboom MCJ, Sultana J, Cave A, Landi A, Pacurariu A, Roberto G, Schink T, Candore G, Slattery J, Trifirò G; Working Group 3 of ENCePP (Inventory of EU data sources and methodological approaches for multisource studies). Different Strategies to Execute Multi-Database Studies for Medicines Surveillance in Real-World Setting: A Reflection on the European Model. Clin Pharmacol Ther. 2020 Aug;108(2):228-235.
24. Massari M, Spila Alegiani S, Da Cas R, Menniti Ippolito F. "The ShinISS": an open-source tool for conducting distributed analyses within pharmacoepidemiological multi-database studies. Boll Epidemiol Naz. 2020;1:39–45.
25. Ferroni E, Giorgi Rossi P, Spila Alegiani S, Trifirò G, Pitter G, Leoni O, Cereda D, Marino M, Pellizzari M, Fabiani M, Riccardo F, Sultana J, Massari M; ITA-COVID Working Group. Survival of Hospitalized COVID-19 Patients in Northern Italy: A Population-Based Cohort Study by the ITA-COVID-19 Network. Clin Epidemiol. 2020 Dec 8;12:1337-1346.
26. Alegiani SS, Crisafulli S, Rossi PG, Mancuso P, Salvarani C, Atzeni F, Gini R, Kirchmayer U, Belleudi V, Kurotschka PK, Leoni O, Ludergnani M, Ferroni E, Baracco S, Massari M, Trifirò G; ITA-COVID-19 Network. Risk of COVID-19 hospitalization and mortality in rheumatic patients treated with hydroxychloroquine or other conventional DMARDs in Italy. Rheumatology (Oxford). 2021 Apr 15:keab348.

27. Beaumont JJ, Breslow NE. Power considerations in epidemiologic studies of vinyl chloride workers. Am J Epidemiol. 1981 Nov;114(5):725-34.
28. Dixon WG, Hyrich KL, Watson KD, Lunt M, Galloway J, Ustianowski A; B S R B R Control Centre Consortium, Symmons DP; BSR Biologics Register. Drug-specific risk of tuberculosis in patients with rheumatoid arthritis treated with anti-TNF therapy: results from the British Society for Rheumatology Biologics Register (BSRBR). Ann Rheum Dis. 2010 Mar;69(3):522-8.
29. Carmona L, Descalzo MA, Perez-Pampin E, Ruiz-Montesinos D, Erra A, Cobo T, Gómez-Reino JJ; BIOBADASER and EMECAR Groups. All-cause and cause-specific mortality in rheumatoid arthritis are not greater than expected when treated with tumour necrosis factor antagonists. Ann Rheum Dis. 2007 Jul;66(7):880-5.
30. Khan N, Patel D, Xie D, Lewis J, Trivedi C, Yang YX. Impact of Anti-Tumor Necrosis Factor and Thiopurine Medications on the Development of COVID-19 in Patients With Inflammatory Bowel Disease: A Nationwide Veterans Administration Cohort Study. Gastroenterology. 2020 Oct;159(4):1545-1546.e1.
31. Winthrop KL, Chen L, Fraunfelder FW, Ku JH, Varley CD, Suhler E, Hills WL, Gattey D, Baddley JW, Liu L, Grijalva CG, Delzell E, Beukelman T, Patkar NM, Xie F, Herrinton LJ, Fraunfelder FT, Saag KG, Lewis JD, Solomon DH, Curtis JR. Initiation of anti-TNF therapy and the risk of optic neuritis: from the safety assessment of biologic ThERapy (SABER) Study. Am J Ophthalmol. 2013 Jan;155(1):183-189.e1.
32. Fassmer AM, Garbe E, Schmedt N. Frequency and trends of disease-modifying antirheumatic drug (DMARD) use in Germany. Pharmacol Res Perspect. 2016 Sep 27;4(5):e00254.
33. Agenzia Italiana del Farmaco (AIFA). L'uso dei farmaci in Italia—rapporto OsMed 2016. Available from: https://www.aifa.gov.it/documents/20142/241052/Rapporto_OsMed_2016_AIFA-acc.pdf/b44a6258-6a84-4293-0cdb-1d6f7c4be629.
34. Agenzia Italiana del Farmaco (AIFA). L'uso dei farmaci in Italia—rapporto OsMed 2017. Available from: http://www.agenziafarmaco.gov.it/sites/default/files/Rapporto_OsMed_2017_AIFA.pdf.
35. Agenzia Italiana del Farmaco (AIFA). L'uso dei farmaci in Italia—rapporto OsMed 2018. Available from: https://www.aifa.gov.it/documents/20142/0/Rapporto_OsMed_2018.pdf/c9eb79f9-b791-2759-4a9e-e56e1348a976.
36. Agenzia Italiana del Farmaco (AIFA). L'uso dei farmaci in Italia—rapporto OsMed 2019. Available from: https://www.aifa.gov.it/documents/20142/1205984/rapporto-osmed-2019.pdf/f41e53a4-710a-7f75-4257-404647d0fe1e.
37. Mendelsohn AB, Nam YH, Marshall J, McDermott CL, Kochar B, Kappelman MD, Brown JS, Lockhart CM. Utilization patterns and characteristics of users of biologic anti-inflammatory agents in a large, US commercially insured population. Pharmacol Res Perspect. 2021 Feb;9(1):e00708.
38. European Medicines Agency. Humira EPAR scientific discussion. Available from: https://www.ema.europa.eu/en/documents/scientific-discussion/humira-epar-scientific-discussion_en.pdf. Accessed on 4 July 2021.

39. European Medicines Agency. Stelara EPAR public assessment report. Available from: https://www.ema.europa.eu/en/documents/assessment-report/stelara-epar-public-assessment-report_en.pdf. Accessed on 4 July 2021.
40. Pizzimenti V, Formica D, Sultana J, Lucchesi S, Aiello A, Ientile V, Trifirò G. Access of medicines to the market: three years' experience of Sicily's regional drug formulary. Gazzetta Medica Italiana - Archivio per le Scienze Mediche 2020 May;179(5):317-25.
41. Vermeer NS, Duijnhoven RG, Straus SM, Mantel-Teeuwisse AK, Arlett PR, Egberts AC, Leufkens HG, De Bruin ML. Risk management plans as a tool for proactive pharmacovigilance: a cohort study of newly approved drugs in Europe. Clin Pharmacol Ther. 2014 Dec;96(6):723-31.
42. Coloma PM, Trifirò G, Schuemie MJ, Gini R, Herings R, Hippisley-Cox J, Mazzaglia G, Picelli G, Corrao G, Pedersen L, van der Lei J, Sturkenboom M; EU-ADR Consortium. Electronic healthcare databases for active drug safety surveillance: is there enough leverage? Pharmacoepidemiol Drug Saf. 2012 Jun;21(6):611-21.
43. Hammond IW, Gibbs TG, Seifert HA, Rich DS. Database size and power to detect safety signals in pharmacovigilance. Expert Opin Drug Saf. 2007 Nov;6(6):713-21.
44. Piaserico S, Gisondi P, Cazzaniga S, Naldi L. Lack of Evidence for an Increased Risk of Severe COVID-19 in Psoriasis Patients on Biologics: A Cohort Study from Northeast Italy. Am J Clin Dermatol. 2020 Oct;21(5):749-751.
45. Brenner EJ, Ungaro RC, Colombel JF, Kappelman MD. SECUREIBD database public data update. 2020. Available from: https ://covid ibd.org. Accessed 15 March 2021.
46. Marcianò I, Ingrasciotta Y, Giorgianni F, Bolcato J, Chinellato A, Pirolo R, Di Giorgio A, Manna S, Ientile V, Gini R, Santarpia M, Genazzani AA, Uomo I, Pastorello M, Pollina Addario SW, Scondotto S, Cananzi P, Da Cas R, Traversa G, Rossi M, Sottosanti L, Caputi AP, Trifirò G. How did the Introduction of Biosimilar Filgrastim Influence the Prescribing Pattern of Granulocyte Colony-Stimulating Factors? Results from a Multicentre, Population-Based Study, from Five Italian Centres in the Years 2009-2014. BioDrugs. 2016 Aug;30(4):295-306.
47. Ingrasciotta Y, Giorgianni F, Bolcato J, Chinellato A, Pirolo R, Tari DU, Troncone C, Fontana A, Ientile V, Gini R, Santoro D, Santarpia M, Genazzani A, Uomo I, Pastorello M, Addario WS, Scondotto S, Cananzi P, Caputi AP, Trifirò G. How Much Are Biosimilars Used in Clinical Practice? A Retrospective Italian Population-Based Study of Erythropoiesis-Stimulating Agents in the Years 2009-2013. BioDrugs. 2015 Aug;29(4):275-84.
48. Agenzia Italiana del Farmaco (AIFA). Medicinali biosimiari – analisi di sicurezza. Available from: https://www.aifa.gov.it/documents/20142/0/190712_MedBio19.pdf/05b20f88-0202-c0cb-3079-c6c2966e7006.
49. Kuek A, Hazleman BL, Ostör AJ. Immune-mediated inflammatory diseases (IMIDs) and biologic therapy: a medical revolution. Postgrad Med J. 2007 Apr;83(978):251-60.
50. Kirchgesner J, Desai RJ, Beaugerie L, Kim SC, Schneeweiss S. Calibrating Real-World Evidence Studies Against Randomized Trials: Treatment Effectiveness of Infliximab in Crohn's Disease. Clin Pharmacol Ther. 2021 May 24.
51. Viola A, Muscianisi M, Macaluso FS, Ventimiglia M, Cappello M, Privitera AC, Magnano A, Pluchino D, Magrì G, Ferracane C, Mocciaro F, Garufi S, Giuffrida E, Costantino G, Fiocco G, Grova M, Guida L, Alibrandi A, Orlando A, Fries W; "Sicilian Network for Inflammatory Bowel Disease (SN-IBD)". Ustekinumab in Crohn's disease: Real-world outcomes

from the Sicilian network for inflammatory bowel diseases. JGH Open. 2021 Feb 2;5(3):364-370.
52. Naldi L, Cazzaniga S, Di Mercurio M, Grossi E, Addis A; Psocare study centres. Inequalities in access to biological treatments for psoriasis: results from the Italian Psocare registry. Br J Dermatol. 2017 May;176(5):1331-1338.
53. Caporali R, Sarzi-Puttini P, Atzeni F, Gorla R, Filippini M, Marchesoni A, Favalli EG, Bobbio-Pallavicini F, Montecucco C. Switching TNF-alpha antagonists in rheumatoid arthritis: the experience of the LORHEN registry. Autoimmun Rev. 2010 Apr;9(6):465-9.

Online Resource 1. Demographic information of underlying population of the regions participating in the VALORE project network.

Regions	**Population**	**Mean age (±SD)**	**Sex distribution (F/M ratio)**
Abruzzo	1,300,645	45.7 (23.5)	1.05
Apulia	3,975,528	44.2 (23.3)	1.06
Basilicata	558,587	45.3 (23.3)	1.03
Campania	5,740,291	42.1 (22.9)	1.05
Emilia-Romagna	4,459,453	45.8 (23.7)	1.06
Friuli Venezia Giulia	1,210,414	47.1 (23.6)	1.06
Lazio	5,773,076	44.7 (23.2)	1.07
Lombardy	10,010,833	44.8 (23.5)	1.04
Sardinia	1,622,257	46.4 (22.8)	1.03
Sicily	4,908,548	43.5 (23.3)	1.06
Tuscany	3,701,343	46.6 (23.7)	1.07
Umbria	873,744	46.5 (23.8)	1.07
Veneto	4,884,590	45.2 (23.4)	1.04

*The demographic information are related to the year 2019.

Online resource 2. Biological drugs approved for the treatment of immune-mediated inflammatory diseases during the study period in Italy.

Mechanistic class	Active substance	ATC	NDC	Brand name	Originator/biosimilar	Date of reimbursement approval by NHS in Italy
Selective immunosuppressants	Abatacept	L04AA24	037989*	ORENCIA	Originator	22/11/2007
	Vedolizumab	L04AA33	043442019	ENTYVIO	Originator	15/04/2016
Tumor necrosis factor-alpha inhibitors	Etanercept	L04AB01	034675*	ENBREL	Originator	04/05/2001
			044691*	BENEPALI	Biosimilar	14/06/2016
			045451*	ERELZI		09/03/2018
	Infliximab	L04AB02	034528012	REMICADE	Originator	04/05/2001
			043010*	INFLECTRA	Biosimilar	15/11/2014
			044892*	FLIXABI		31/05/2017
			042942*	REMSIMA		01/01/2015
			046635*	ZESSLY		10/03/2019
	Adalimumab	L04AB04	035946*	HUMIRA	Originator	02/07/2004
			047088*	HULIO	Biosimilar	09/02/2019
			045616*	IMRALDI		19/09/2018
			047805*	IDACIO		04/02/2020
			046889*	HYRIMOZ		10/02/2019
			046888*	HALIMATOZ		12/02/2020
			045317*	AMGEVITA		08/08/2018
			046887*	HEFIYA		09/02/2020
	Certolizumab pegol	L04AB05	039539*	CIMZIA	Originator	16/10/2010
	Golimumab	L04AB06	039541*	SIMPONI	Originator	31/08/2010
Interleukin inhibitors	Anakinra	L04AC03	035607*	KINERET	Originator	02/03/2003
	Ustekinumab	L04AC05	038936*	STELARA	Originator	31/08/2010
	Secukinumab	L04AC10	043873*	COSENTYX	Originator	12/11/2016
	Ixekizumab	L04AC13	044863*	TALTZ	Originator	30/06/2017
	Brodalumab	L04AC12	045484*	KYNTHEUM	Originator	20/04/2019
	Guselkumab	L04AC16	045772*	TREMFYA	Originator	12/10/2018
	Sarilumab	L04AC14	045491*	KEVZARA	Originator	17/07/2018
	Tildrakizumab	L04AC17	047196*	ILUMETRI	Originator	12/02/2020
	Risankizumab	L04AC18	047821018	SKYRIZI	Originator	04/03/2020
	Tocilizumab	L04AC07	038937*	ROACTEMRA	Originator	20/03/2010

Legend: ATC= Anatomical Therapeutic Chemical classification system; NDC= National Drug Code; NHS= National Health Service

Online resource 3. Major safety outcomes reported for TNF-alpha inhibitors, as reported on SmPC and RMP.

Safety outcome	TNF-alpha inhibitors				
	Infliximab	**Adalimumab**	**Golimumab**	**Etanercept**	**Certolizumab**
Immune system disorders					
Hypersensitivity (incl. anaphylaxis or anaphylactoid reactions)[a,b]	•	•	•	•	•
Infections and infestations					
Tuberculosis [a,b]	•	•	•	•	•
Sepsis[a,b]	•	•	•	•	•
Pneumonia[a,b]	•	•	•		
Invasive fungal infections[a,b]	•	•	•	•	
Hepatitis B virus (HBV) reactivation[a,b]	•	•	•	•	•
Cardiac disorders					
Congestive heart failure[a,b]	•	•	•	•	•
Hepatobiliary disorders					
Worsening of hepatitis C[a]				•	
Autoimmune hepatitis[a]	•				
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)					
Lymphomas[a,b]	•	•	•	•	•
Leukaemia[a,b]	•	•	•	•	•
Melanoma[a,b]	•	•	•	•	•
Nonmelanoma skin cancer[a,b]		•	•	•	
Merkel cell carcinoma[a,b]	•	•	•	•	•
Colon cancer/dysplasia [a,c]	• α	• α	• α		
Cervical cancer[b]	•				
Lung Cancer[a]				•	
Breast Cancer[a]				•	
Blood and lymphatic system disorders					
Pancytopenia, leukopenia, neutropenia and thrombocytopenia[a,b]	•	•	•	•	•
Wegener's granulomatosis[a]				•	
Musculoskeletal and connective tissue disorders					
Lupus and lupus-like illness[a,b]	•	•	•	•	•
Nervous system disorders					

Guillain-Barré syndrome[a,b]	•	•		•	
Multiple Sclerosis[a,b]	•	•	•	•	•
Serious depression (including suicidality)[c]			•		
Optic neuritis[b]	•	•			
Progressive multifocal leukoencephalopathy (PML)[c]		•		•	
Reversible posterior leukoencephalopathy syndrome[c]		•			
Encephalitis/Leukoencephalomyelitis[c]				•	
Metabolism and nutrition disorders					
Hypoglycaemia[a]				•[β]	

α Patients treated for diabetes a Paragraph 4.4 Special warnings and precautions for use, Summary of product characteristics. b Risk Management Plan, Important identified risk c Risk Management Plan, Important potential risk

Legend: RMP=risk management plan; SmPC= summary of product characteristic; TNF-alpha inhibitors= Tumor Necrosis Factor alpha inhibitors.

Online resource 4. Major safety outcomes reported for selective immunosuppressants, as reported on SmPC and RMP.

Safety outcome	**Selective immunosuppressants**	
	Abatacept	**Vedolizumab**
Immune system disorders		
Hypersensitivity (incl. anaphylaxis or anaphylactoid reactions)[a,b]	•	•
Infections and infestations		
Tuberculosis [a,b]	•	
Sepsis[a]	•	
Pneumonia[a]	•	
Invasive fungal infection[b]	•	
Gastrointestinal infections[c]		•
Upper Respiratory Tract Infections[b]		•
Hepatitis B virus (HBV) reactivation[a]	•	
Nervous system disorders		
Progressive multifocal leukoencephalopathy (PML)[a,c]	•	•
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)		
Non-melanoma skin cancers[c]		•[α]
Colon cancer[c]		•[α]

α Patients with inflammatory bowel disease a Paragraph 4.4 Special warnings and precautions for use, Summary of product characteristics. b Risk Management Plan, Important identified risk c Risk Management Plan, Important potential risk **Legend**: RMP=risk management plan; SmPC= summary of product characteristics.

Online resource 5. Major safety outcomes reported for interleukin inhibitors, as reported on SmPC and RMP.

Safety outcome	Interleukin inhibitors									
	Ustekinumab	Secukinumab	Tocilizumab	Anakinra	Brodalumab	Ixekizumab	Risankizumab	Tildrakizumab	Guselkumab	Sarilumab
General disorders and administration site conditions										
Hypersensitivity (incl. anaphylaxis or anaphylactoid reactions)[a,b,c]	•	•	•	•	•	•	•	•	•	•
Infections and infestations										
Tuberculosis[a,b,c]	•		•	•			•	•	•	•
Hepatitis B virus (HBV) reactivation[a,c]		•	•							
Diverticulitis aggravated[a,b]			•							
Upper Respiratory Tract Infections[a,b]						•				
Conjunctivitis[a,b]						•				
Fungal infections[a,b]						•				
Cardiac disorders										
Hyperlipidaemia[a]			•							
Major Adverse Cardiac Events (MACE)[c]	•	•	•			•	•	• [α]	• [α]	•
Blood and lymphatic system disorders										
Pancytopenia, leukopenia, neutropenia and thrombocytopenia[a,b]		•	•	•						•
Gastrointestinal disorders										
Inflammatory bowel disease (including Crohn's disease and ulcerative colitis)[a,b,c]		•			•	•		•		
Gastrointestinal perforation[b]										•
Investigations										
Transaminase elevations[a]			•	•					•	•

Increases in lipid parameters[a,c]			•							•
Metabolism and nutrition disorders										
Hyperlipidaemia[a]										•
Respiratory, thoracic and mediastinal disorders										
Eosinophilic pneumonia[a]	•									
Pulmonary alveolar proteinosis[a,c]				• β						
Pulmonary hypertension[a,c]				• β						
Interstitial lung disease[a,c]				• β						
Skin and subcutaneous tissue disorders										
Exfoliative dermatitis[a]	•									
Psoriasis[b]	•									
Nervous system disorders										
Facial palsy[b]	•									
Serious depression (incl. suicidality)[a,c]	•	•			•			• α		
Reversible posterior leukoencephalopathy syndrome [c]	•									
Vascular disorders										
Venous thromboembolism[c]	• γ									
Hepatobiliary disorders										
Acute liver failure[b,c]			•	• β						
Hepatitis[b,c]			•	• β						
Jaundice[a]			•							
Immuno system disorders										
Macrophage activation syndrome (MAS)[a,c]				• β						
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)										
Lymphoma[a,c]				•			• α			
Non-melanoma skin cancer[c]		•					• α			
Lung cancer[c]							• α			

α Patients with psoriasis β Patients with Still's disease γ Patients with inflammatory bowel disease a Paragraph 4.4 Special warnings and precautions for use, Summary of product characteristics.
b Risk Management Plan, Important identified risk c Risk Management Plan, Important potential risk **Legend**: RMP=risk management plan; SmPC= summary of product characteristics.

3.4. In search of potential predictors of erythropoiesis-stimulating agents (ESAs) hyporesponsiveness: a population-based study

Adapted from:

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Abstract

Background: Evidences show that around 20% of biosimilar or originator erythropoiesis-stimulating agents (ESAs) users are hyporesponsive. Controversial post-marketing data exist on the predictors of ESA hyporesponsiveness. The aim of this study was to identify predictors of ESA hyporesponsiveness in patients with chronic kidney disease (CKD) or cancer in clinical practice.

Methods: During the years 2009–2015, a multi-center, population-based, cohort study was conducted using claims databases of Treviso and Caserta Local Health Units (LHUs). All incident ESA users were characterized at baseline and the differences between the baseline hemoglobin (Hb) value, that is the Hb registered within 30 days prior to the first ESA dispensing (index date, ID) and each outcome Hb value (registered between 30 and 180 days after ID) were calculated and defined as delta Hb (ΔHb). Incident ESA users were defined as hyporesponsive if, during follow-up, they registered at least one $\Delta Hb < 0$ g/dL. Including all potential predictors of ESA hyporesponsiveness and stratifying by indication for use, univariate and multivariate binary logistic regression models and Receiver Operating Characteristic (ROC) curves were carried out.

Results: In general, 1080 incident ESA users (CKD: 57.0%; cancer: 43.0%) were identified. In CKD, predictors of ESA hyporesponsiveness were C-reactive protein (OR = 1.2, 95% CI: 1.0–1.5; P-value = 0.060) and high levels of baseline Hb (OR = 1.7, 95% CI: 1.2–2.2; P-value< 0,001), the latter being also predictor of ESA hyporesponsiveness in cancer (OR = 1.7, 95% CI: 1.1–2.4; P-value = 0.007). Both in CKD and in cancer, the type of ESA, biosimilar or originator, was not a predictor of ESA hyporesponsiveness. In CKD, concomitant use of iron preparations (OR = 0.3, 95% CI: 0.2–0.7; P-value = 0.002) and of high dosage of angiotensin-converting enzyme inhibitors/angiotensin II-receptor blockers (OR = 0.5, 95% CI: 0.3–0.9; P-value = 0.022) were protective factors against ESA hyporesponsiveness.

Conclusions: The study confirmed traditional potential predictors of hyporesponsiveness to ESA. The use of biosimilar or originator ESA was not a predictor of hyporesponsiveness in an outpatient setting from two large Italian areas. A better knowledge of the predictors of ESA response would allow a better anemia management to improve patients' quality of life.

Introduction

Erythropoiesis-stimulating agents (ESAs) are biological products, analogues of human erythropoietin, produced by cell lines using the recombinant DNA technology. ESAs are approved for the treatment of anaemia related to chronic kidney disease (CKD) or chemotherapy-induced in cancer patients. According to the Italian Medicines Agency, ESAs are indicated when hemoglobin (Hb) levels are lower than 11 g/dl in CKD patients and lower than 10 g/dl in cancer patients. In Italy, for both indications, haemoglobinemia has to range between 11 and 12 g/dl [1], avoiding a rise in Hb values greater than 2 g/dl over a four-week period.

Generally, the term "ESA hyporesponsive" refers to patients who need high doses of ESAs (25–100% higher doses than what recommended) to increase and/or maintain their Hb levels within the acceptable range [2]. More specifically, the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines define patients as ESA hyporesponsive if they do not experience an increase in Hb levels within the first month of ESA treatment, using an appropriate weight-based dosing (not graded) [3].

ESA hyporesponsiveness could be acute or chronic, but, to date, there is neither consensus nor shared position on the definition of the chronic condition in particular [3]. Based on the definition gave by Sibbel et al., "*4 months of continuous ESA hyporesponsiveness [defined considering both Hb concentrations and ESAs doses] can be used to differentiate acute from chronic hyporesponsiveness*" [4].

A previously published population-based study, conducted on Italian administrative healthcare databases, evaluated the comparative effectiveness of both biosimilar and originator ESAs in CKD and cancer patients. Results highlighted that, in clinical practice, around 20% of ESA users were non-responders, defined as subjects experiencing no variations or a reduction in Hb levels within the first 3months of ESA treatment. Furthermore, no differences were observed between different type of ESAs (i.e., biosimilars or originators), in terms of ESA responsiveness [5].

In patients with conservative end-stage renal disease, as well as in dialysis patients, ESA hyporesponsiveness and Hb level variability may lead to cardiovascular complications, increasing the risk of all-cause mortality, due to the required higher doses of ESA [6–8].

In both CKD and cancer patients, several factors may contribute to ESA hyporesponsiveness, such as iron deficiency, inflammation and malnutrition status, while chronic hyperparathyroidism may affect ESA response in CKD patients, specifically [9, 10].

Debate is still on-going regarding the potential effects of renin-angiotensin system inhibitors, such as angiotensinconverting enzyme (ACE) inhibitors or angiotensin IIreceptor antagonists (ARBs), on the development of anaemia in patients with renal disease [11].

This naturalistic population-based study was aimed atidentifying factors could be associated to ESA hyporesponsiveness in anaemic patients with CKD or cancer, in the general population of two Italian Local Health Units (LHUs).

Methods

Data source

A population-based, retrospective, cohort study was conducted. As data source, claims databases of Treviso and Caserta LHUs, covering a total population of more than 1.5 million people during the years 2009–2015 (data were available till 2014 in Treviso LHU), were considered. Each prescription of ESA requires a specific therapeutic plan to be filled in by specialists, specifying

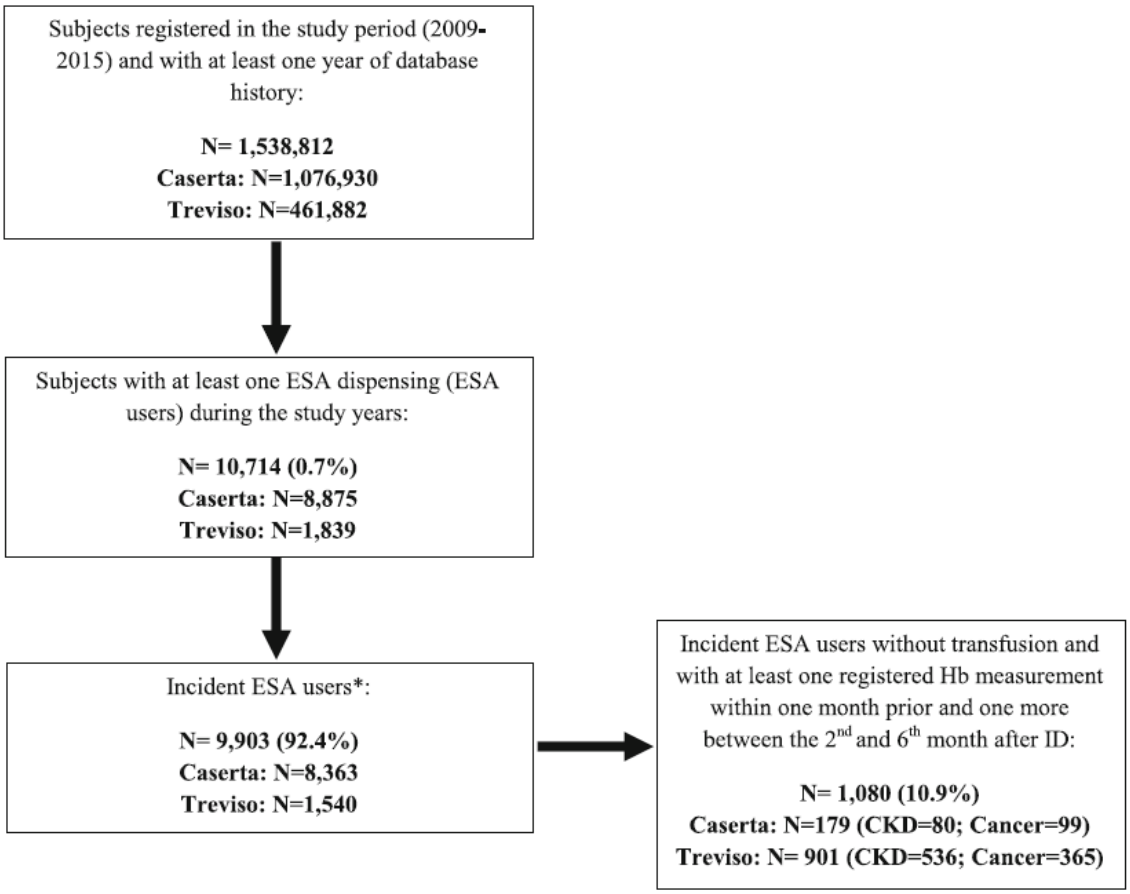
the exact drug name, number of dispensed packages, dosing regimen and indication for use of the drug. These data can be linked, through anonymized patient unique identifier, to other claims databases including information onhospital discharge diagnoses, healthcare service payment exemptions, drug dispensing, outpatient diagnostic tests, results of laboratory tests (in Caserta LHU, these data are available only for a random sample of around 15% of the general population), etc. ICD-9-CM diagnosis codes were used to identify hospital discharge diagnoses and indications for use, while Anatomical Therapeutic Chemical (ATC) classification system codes and Italian marketing authorization (AIC) codes, which distinguish reference products from biosimilars and other ESAs still covered by patent, were used to identify drug dispensing. Additional details about data source can be found elsewhere [12].

Study population

All the residents in Treviso or Caserta LHUs catchment areas in the years 2009–2015 were included in the study, if they had at least 1 year of database history, at least one ESA dispensing during the study period, with no ESAs dispensing within the previous 6 months (i.e. incident ESA users with 6-month washout period), at least one Hb measurement within 1 month prior to the date of the first ESA dispensing during the study period (i.e. Index Date, ID), defined as baseline Hb value, and at least another one between the 2nd and the 6th month after ID, defined as outcome Hb value (**Fig. 1**).

The included subjects were observed from the month prior to the ID to the first 6 months after the ID. Patients were excluded in case they received at least one blood transfusion from 1 month prior to the ID to the last observed outcome Hb value.

Fig. 1 Flow-chart of study population.



* no treatment within 6 months prior to Index Date (ID, i.e. date of ESA treatment start). ESA = erythropoiesis-stimulating agents; Hb = hemoglobin; CKD = chronic kidney disease.

Study drugs

All the available ESAs in Italy during the study period were included in the study: epoetin alfa (ATC: B03XA01; Eprex®, Abseamed®, Binocrit®), epoetin beta (ATC: B03XA01; Neorecormon®), epoetin zeta (B03XA01; Retacrit ®), darbepoetin alfa (ATC: B03XA02; Aranesp®), and methoxypolyethyleneglycol-epoetin beta (ATC: B03XA03; Mircera®). Binocrit®, Abseamed® and Retacrit® are biosimilars of the reference product (Eprex®), while all other ESAs are ESAs still covered by the patent.

Data analysis

ESA users were categorized as CKD or cancer patients, according to indication for use recorded in the electronic therapeutic plan. In case of non-availability of electronic therapeutic plans, an algorithm described elsewhere was used to identify indication for use [12]. All incident ESA users were characterized at baseline, in terms of demographics, clinical parameters (e.g. hemoglobinemia and hematic level of creatinine, albumin, ferritin, folate, potassium, sideremia, parathyroid hormone, vitamin B12, C-reactive protein (CRP), and transferrin saturation), comorbidities including arrhythmia, ischemic heart diseases, diabetes mellitus, heart failure and hypertension, and concomitant use of iron preparations, folic acid, vitamin B12 and ACE inhibitors/ARBs.

During follow-up, the distribution of mean Hb values among incident ESA users was calculated. The differences between the baseline Hb and each outcome Hb value were calculated and defined as delta Hb (ΔHb). Incident ESA users were classified as ESA hyporesponsive if, during follow-up, they registered at least one $\Delta Hb < 0$ g/dL. Only incident ESA users having a baseline Hb value lower than 11 g/dL were included in these analyses. All analyses were stratified by indication for use.

Sensitivity analysis

Due to the lack of a shared position on the description of ESA hyporesponsiveness, the definition of ESA hyporesponsiveness was modified in the sensitivity analyses. Incident ESA users with at least two consecutive outcome Hb values ≥11 g/dL, were classified as ESA responders, irrespective of ΔHb. Elsewhere, they were considered as ESA hyporesponsive patients.

Statistical analysis

Depending on the distribution for quantitative variables ,results were presented as mean ± standard deviation (SD) or median with interquartile range (IQR), and by absolute frequencies and percentages for categorical variables.

Univariate and multivariate binary logistic regression models were performed to identify predictors of ESA hyporesponsiveness, stratifying by indication for use (CKD and cancer). The dependent variable of the model was the hyporesponsiveness to ESA treatment, that is at least once $\Delta Hb < 0$ g/dL.

As covariates, all the potential predictors of ESA responsiveness identified from the database, including sex, age, baseline Hb value, ESA dosage at ID, type of ESA dispensed at ID (biosimilar, reference product or other ESAs still covered by patent), LHU, type of hospital discharge diagnosis (categorized into cardiovascular, non-cardiovascular or both cardiovascular and non-cardiovascular hospitalizations) within 1 year prior to ID, comorbidities (arrhythmia, ischemic heart disease, diabetes mellitus, heart failure, hypertension and dialysis, only for CKD patients), CKD stage or type of tumor (i.e. solid malignant, non-solid malignant, both solid and non-solid malignant, or not classified), concomitant drug use (e.g. iron preparations, vitamin B12, folic acid, high dosage of ACE inhibitor/ARBs) and laboratory values (e. g. hematic levels of creatinine, albumin, ferritin, folate, potassium, sideremia, parathyroid hormone, vitamin B12, C-reactive protein [CRP], transferrin saturation, acidosis) were included in the model. By restricting potential predictors to all those factors identified from the database, reduce the likelihood of an overstatement.

In the multivariate model, we included all the covariates, which were significantly associated to the outcome at the univariate analysis. For each model, a Receiver Operating Characteristic (ROC) curve was performed to predict the discriminatory power of the variables included in the model.

For each covariate tested as possible predictor of ESA hyporesponsiveness, the corresponding odds ratio (OR) were reported along with 95% confidence interval (95% CI). All statistical analyses were performed using SAS 9.3 (SAS Institute, Cary, NC) and SPSS/PC, Version 21 (SPSS Inc., Chicago, Illinois, USA). The significance level for all statistical tests was set at p-value < 0.05.

Results

On a total population of 1,538,812 subjects registered in Treviso and Caserta LHUs, 10,714 (0.7%) received at least one ESA dispensing during the years 2009–2015; of these, 1080 (10.1%) incident ESA users were included inthe study, based on the above-mentioned inclusion criteria [CKD = 616 (57.0%); cancer = 464 (43.0%)] (**Fig. 1**). As shown in **Table 1**, ESAs were in general more frequently used by males among CKD patients, and by females among cancer patients. Regarding age distribution, incident ESA users with CKD appeared to be on average older (mean age ± SD: 72.6 ± 14.7) than patients with cancer (66.9 ± 12.2). Although most of ESA users started ESA treatment having baseline Hb values within the range recommended by the Italian guidelines (Hb < 10 g/dL in cancer and Hb < 11 g/dL in CKD), 18.5% (N = 114) of CKD patients and 10.3% (N = 48) of cancer patients started ESA treatment with baseline Hb values ≥11 g/dL. Around 45% of incident ESA users received a biosimilar ESA at ID, irrespective of indication of use. In general, CKD patients were more likely to be hospitalized than cancer patients (66.2% vs. 56.2%), especially due to noncardiovascular diseases. As compared to cancer patients, CKD patients were more likely to be affected by chronic comorbidities, such as hypertension (93.2% vs. 66.8%) and diabetes mellitus (41.9% of vs. 25.0%). Among ESA users with CKD, 410 (66.5%) were affected by stage IV-V CKD or were on dialysis. Instead, more than one third of cancer patients were affected by solid malignant neoplasms, although for most of cancer patients the type of tumor was not known (N = 208; 44.8%). CKD patients were more likely to be treated with iron preparations (CKD: 18.3%; cancer: 8.4%) or anti-hypertensive drugs (ACE inhibitor or ARBs) (CKD: 43.0%; cancer: 30.8%) than cancer patients. Considering laboratory parameters, no differences were found among cancer and CKD patients.

The target Hb value, as recommended by the Italian Medicines Agency, was reached on average between 45 and 60 days after ID and was thereafter stable during follow-up (**Fig. 2**).

Excluding incident ESA users with baseline Hb values higher than recommended (i.e., ≥11 g/dL), we observed that most of subjects included in the study cohort reached, at least once, the target Hb values (11 ≤ Hb levels≤12 g/dL), according to recommendations from Italian guidelines, despite 664 (61.5%) incident ESA users reached Hb levels> 13.0 g/dL, at least once during follow-up (**Online Resource 1**).

Table 2 showed that, for each cohort, the proportion of ESA hyporesponsive patients was similar using the two approaches of ESA hyporesponsiveness. According to the given definition of ESA hyporesponsiveness, the multivariate binary logistic regression showed that the type of dispensed ESA (biosimilar or originator) was not a predictor of ESA response in CKD.

Moreover, high baseline Hb values (OR = 1.7, 95% CI: 1.2–2.2; P-value<0.001) and CRP hematic levels (OR = 1.2, 95% CI: 1.0–1.5; P-value = 0.060) were associated to ESA hyporesponsiveness in CKD (**Table 3**), while high baseline Hb values (OR = 1.7, 95% CI: 1.1–2.4; P-value = 0.007) and prior ischemic heart disease diagnosis (OR = 2.7, 95% CI: 0.9–7.9; P-value = 0.072) were predictors of ESA hyporesponsiveness in cancer patients (**Table 4**). On the contrary, ESA hyporesponsiveness was decreased by concomitant use of iron preparations (OR = 0.3, 95% CI: 0.2–0.7; P-value = 0.002) and high dosage of ACE inhibitors/ARBs (OR = 0.5, 95% CI: 0.3–0.9; P-value = 0.022) in CKD patients and by higher levels of albumin and potassium in cancer patients, although not significantly (P-values> 0.005).

The discriminatory power of the predictive response of the variables included into the models was good, as confirmed by the ROC curves (**Figs. 3-4**).

By modifying the ESA hyporesponsiveness definition in the sensitivity analysis, high baseline Hb value was a positive predictor of responsiveness both in CKD (OR = 0.7, 95% CI: 0.5–1.0; P-value = 0.053) and in cancer patients (OR = 0.5, 95% CI: 0.3–0.8; P-value = 0.003); that is, patients with high baseline Hb values had more chance to reach the target Hb values rather than patients starting ESA treatment with low baseline Hb values (**Online Resources 2-5**). In addition, concomitant use of iron preparations and acidosis condition increased ESA response in CKD patients, with a good predictive power (AUC = 0.6969 ± 0.03; P-value< 0.001). Moreover, males with CKD (OR = 0.5, 95% CI: 0.3–0.9; P-value: 0.011) seemed to be more responsive than females.

Table 1. Characterization of incident ESA users at baseline.

	Cancer patients N= 464	**CKD patients N= 616**
Sex – N (%)		
Males	217 (46.8)	356 (57.8)
Females	247 (53.2)	260 (42.2)
Age – year[a]	66.9±12.2	72.6±14.7
Age category – N (%)		
<45	22 (4.7)	38 (6.1)
45-64	154 (33.2)	126 (20.5)
65-79	227 (48.9)	234 (38.0)
≥80	61 (13.2)	218 (35.4)
Baseline Hb - g/dL[a]	9.7±1.1	10.1±1.1
Baseline Hb ≥11 g/dL - N (%)	48 (10.3)	114 (18.5)
Days of ESA exposure[a]	101.8±40.5	119.4±41.0
ESA dosage during the follow-up[a]		
IU	34,994.1±9,308.1	8,564.6±4,835.4
Mcg	204.7±132.1	49.9±30.0
Catchment area –N (%)		
Caserta	99 (21.3)	80 (13.0)
Treviso	365 (78.7)	536 (87.0)
Type of ESA – N (%)		
Reference product	129 (27.8)	126 (20.5)
Biosimilar	209 (45.0)	284 (46.1)
Other ESAs covered by patent	126 (27.2)	206 (33.4)
Hospitalizations/PS visits – N(%)[b]		
No	203 (43.8)	208 (33.8)
Cardiovascular hosp.	6 (1.3)	44 (7.1)
Non cardiovascular hosp.	244 (52.6)	283 (45.9)

Both cardiovascular and non-cardiovascular hosp.	11 (2.4)	81 (13.1)
Comorbidities – N (%)[c]		
Arrhythmia	30 (6.5)	139 (22.6)
Ischemic heart disease	23 (5.0)	106 (17.2)
Diabetes mellitus	116 (25.0)	258 (41.9)
Heart failure	28 (6.0)	193 (31.3)
Hypertension	310 (66.8)	574 (93.2)
Dialysis	-	90 (14.6)
Stage of CKD – N(%)		
1 (GFR ≥ 90)	-	2 (0.3)
2 (90 > GFR ≥ 60)	-	11 (1.8)
3 (60 > GFR ≥ 30)	-	188 (30.5)
4 (30 > GFR ≥ 15)	-	230 (37.3)
5 and dialysis (GFR < 15 (or dialysis code))	-	180 (29.2)
Not classified		5 (0.8)
Type of tumor – N(%)		
Benign	4 (0.9)	-
Solid malignant	161 (34.7)	-
Non solid malignant	72 (15.5)	-
Both solid and non-solid malignant	19 (4.1)	-
Non classified	208 (44.8)	-
Concomitant drugs – N (%)[d]		
Iron preparations	39 (8.4)	113 (18.3)
Vitamin B_{12}	7 (1.5)	12 (1.9)
Folic acid	37 (8.0)	59 (9.6)
ACE Inhibitors/ARBs	143 (30.8)	265 (43.0)
Laboratory values		
Albumin (g/dL; normal range: 3.5-5.5)[a]	3.6±0.6	3.7±0.6
Creatinine (mg/dL; normal range: M=0.7-1.2; F=0.6-1.2)[e]	0.9 (0.7-1.1)	2.5 (1.7-4.0)
Potassium (mEq/L; normal range: 3.6-5.0)[a]	4.4±0.6	4.7±0.7
Transferrin saturation (%)[a]	20.7±14.3	22.3±14.1
Sideremia (mcg/dL; normal range: M=75-160; F=60-150)[e]	56.0 (37.0-83.7)	50.0 (33.0-71.0)
Ferritin (mcg/L; normal range: M=60-300; F=30-150)[e]	278.4 (112.0-583.6)	150.6 (59.5-329.3)
Parathyroid hormone (pg/ml; normal range: 10-60)[e]	47.0 (27.0-79.0)	160.0 (85.0-300.3)
Vitamin B_{12} (ng/ml; normal range:300–900)[a]	491.6±224.3	506.9±248.4
Folate (ng/ml; normal range: 2.7-17)[e]	6.0 (3.9-8.8)	5.2 (3.5-7.6)
CRP (mg/dL; normal value: <0.5)[e]	0.9 (0.3-4.4)	0.9 (0.3-3.1)

Legend: CKD: Chronic kidney disease; GFR: Glomerular filtration rate; ACE: angiotensin converting enzyme; ARBs: Angiotensin II receptor antagonists; CRP: C-reactive protein; SD: Standard deviation; IQR: Interquartile range; IU: International Unit; Mcg: Microgram

[a] Data are expressed as mean±SD

[b] Evaluated within the year prior to ID
[c] Evaluated any time prior to ID
[d] Evaluated within three months prior to ID
[e] Data are expressed as median and IQR

Fig. 2 Mean Hb variation during the follow-up, stratified by indication for use.

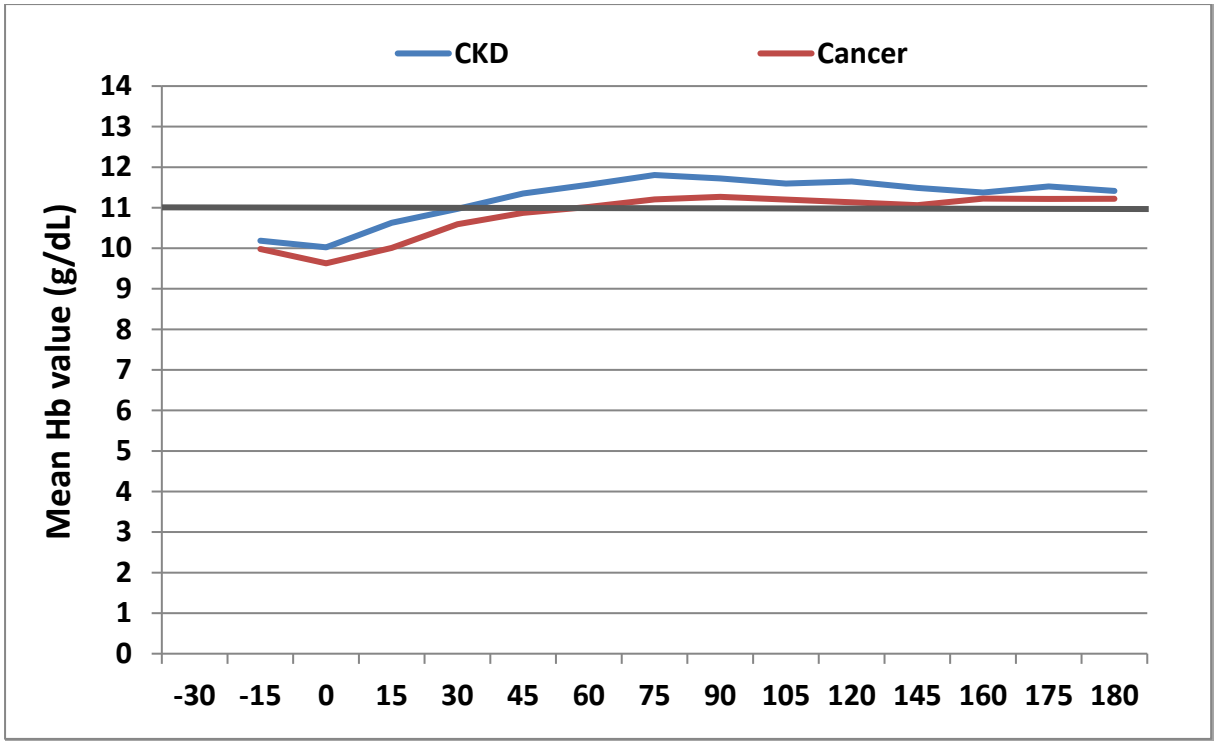


Table 2. Frequency of incident ESA hyporesponders.

	Cancer **N= 416 (%)**	**CKD** **N= 502 (%)**
Non responsiveness		
ΔHb<0g/dL[a]	146 (35.1)	152 (30.3)
Hb<11g/dL[b]	135 (32.4)	147 (29.3)

[a] Incident ESA users with at least one ΔHb<0g/dL.
[b] Incident ESA users with Hb values <11 g/dL or with only one Hb value ≥11 g/dL registered between the 2nd and the 6th month after ID.
Only incident ESA users having a baseline Hb value lower than 11 g/dL were included in these analyses.

Table 3. Multivariate binary logistic regression to evaluate non responsiveness to ESAs between the 2nd and the 6th month after ID in CKD patients.

	Non responsiveness ΔHb<0g/dL (at least once)	
	OR (95% CI)	**P-value**
Baseline Hb (g/dL)	**1.7 (1.2-2.2)**	**<0.001**
Comorbidities		
Hypertension	0.8 (0.3-1.7)	0.513
Concomitant drugs		
Iron preparations	**0.3 (0.2-0.7)**	**0.002**
Folic acid	0.5 (0.2-1.1)	0.100
High dosage ACE inhibitors/ARBs	**0.5 (0.3-0.9)**	**0.022**
Laboratory Values		
CRP	**1.2 (1.0-1.5)**	**0.060**

Legend: ACE: angiotensin converting enzyme; CRP: C-reactive protein
Transferrin saturation covariate was excluded because of the high proportion of missing values (>50%)
CKD ESA users starting the treatment at baseline Hb≥11 g/dL were excluded.

Table 4. Multivariate binary logistic regression to evaluate non responsiveness to ESAs between the 2nd and the 6th month after ID in cancer patients.

	Non responsiveness ΔHb<0g/dL (at least once)	
	OR (95% CI)	**P-value**
Baseline Hb (g/dL)	**1.7 (1.1 -2.4)**	**0.007**
Comorbidities		
Ischemic heart disease	2.7 (0.9-7.9)	0.072
Laboratory Values		
Albumin (g/dL)	0.7 (0.5 -1.1)	0.091
Potassium (mEq/L)	0.7 (0.4-1.0)	0.063
CRP (mg/dL)	1.1 (0.9-1.3)	0.537

Legend: Covariates as ferritin and vitamin B_{12} levels were excluded because of the high proportion of missing values (>40%)
Cancer ESA users starting the treatment at baseline Hb≥11 g/dL were excluded

Fig. 3 ROC curve to predict the discriminant power of non-responsiveness in CKD.

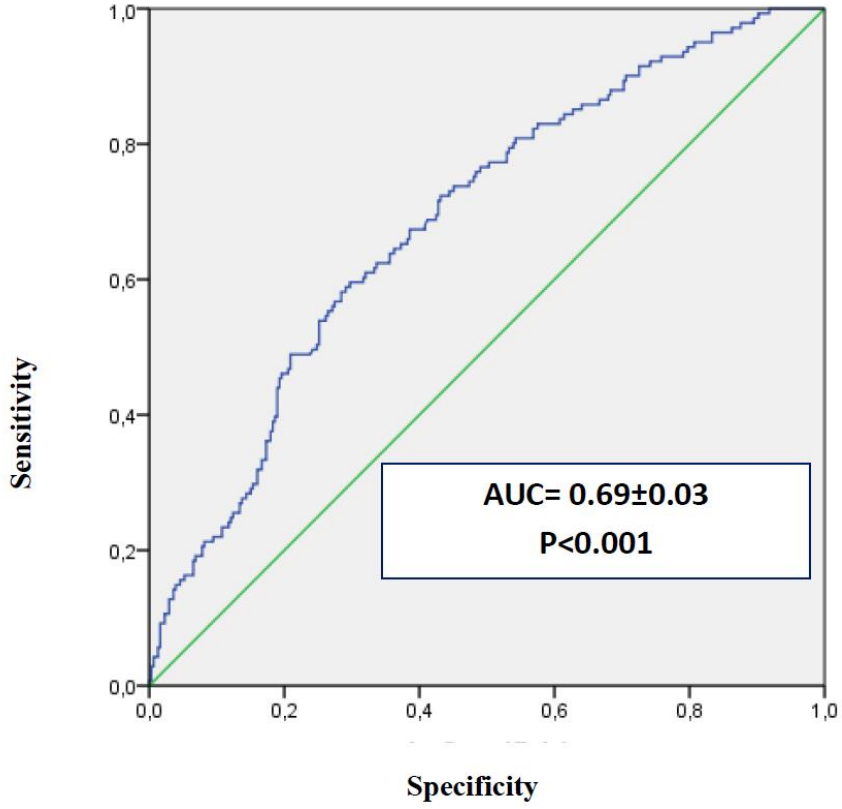
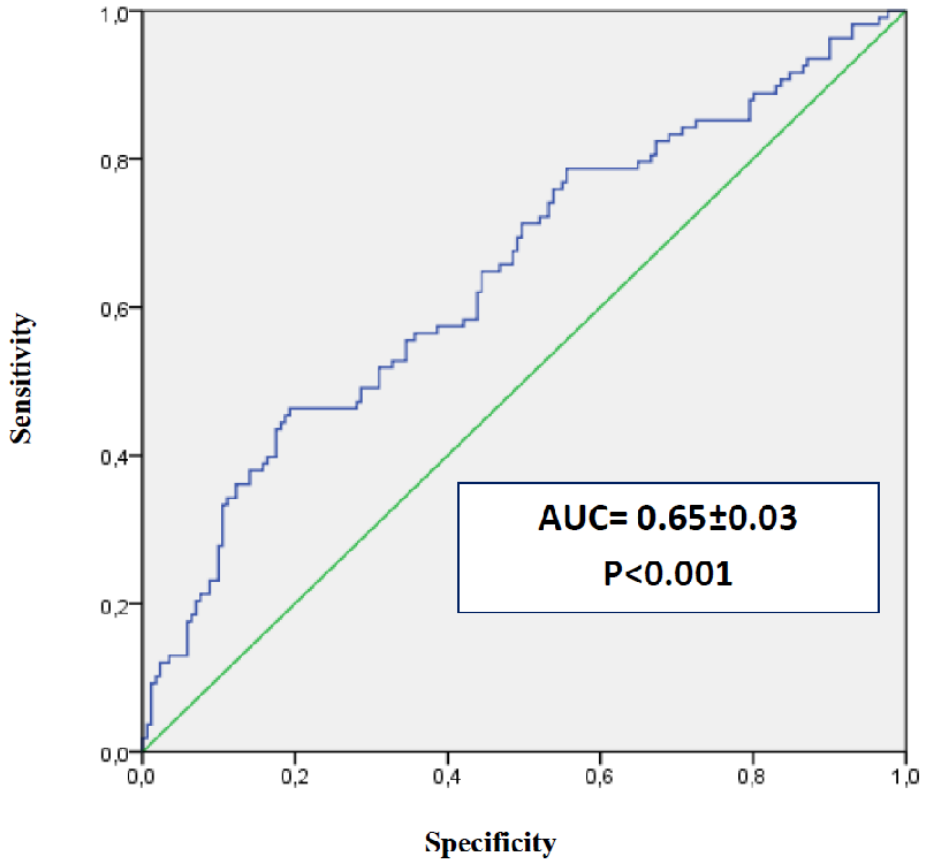


Fig. 4 ROC curve to predict the discriminant power of non-responsiveness in cancer.



Discussion

Anaemia is a common complication in both cancer and CKD patients and it could contribute to a poor prognosis. ESA therapy represents the main treatment to increase Hb levels in such groups of patients, leading to improvement of quality of life and reducing the risk of cardio- and cerebrovascular complications, as well as the requirement of blood transfusions. However, ESA therapy must be carefully handled due to the increased risk of stroke in older patients having Hb levels above the target range. Indeed, due to the occurrence of ESA resistance, the need for higher doses of ESA may increase the risk of developing cardiovascular diseases and, ultimately, death [13].

Moreover, Minutolo et al. demonstrated that ESA hyporesponsiveness increased the risk of end stage renal disease by 2.5-fold in CKD patients [14]. Our data confirmed that the inflammatory condition and the iron intake affect ESA response. Inflammatory cytokines may affect the development of anemia through suppression of bone marrow erythropoiesis, suppression of erythropoietin production, or interfering with the iron status [15]. Several published studies demonstrated that high levels of CRP in hemodialysis patients were associated with ESA hyporesponsiveness, leading to an increased risk of death [16–18]. Although the prevalence of ESA hyporesponsiveness in hemodialysis patients is similar to that found in non-dialysis patients, limited studies on the predictors of ESA hyporesponsiveness have been conducted in the latter population [14].

Regarding the iron intake, our results highlighted that the use of iron preparations was a predictive factor of ESA response, whilst serum iron and ferritin were not independently associated to responsiveness to ESA treatment. Although previous studies on hemodialysis patients demonstrated that an altered iron status (in terms of low transferrin saturation levels and/or low ferritin levels), is a common factor inducing ESA hyporesponsiveness [19], there is no general consensus regarding the role of iron status as a predictor of ESA response. A recent study examined the relationship between iron markers, such as transferrin saturation and ferritin levels, and ESA responsiveness. Finding from the study highlighted that transferrin saturation, but not ferritin, was statistically associated to ESA hyporesponsiveness [20]. On the hand, in our study, transferrin saturation covariate was excluded from the analysis, due to the high proportion of missing values (> 50%).

Minutolo et al. studied for the first time the risk of endstage renal disease in CKD patients, who were hyporesponsive to ESA treatment. The study findings demonstrated that ESA hyporesponsiveness correlated to an increased risk of end-stage renal disease and the authors suggested that high ESA doses, together with the persistence of anemia, could lead to hypoxia, tubular atrophy and interstitial fibrosis, thus causing the progression of the renal damage. On the other hand, no correlation between the iron markers, CRP levels, serum parathyroid hormone, body mass index and ESA response was found [14].

The influence of gender on ESA response is still controversial. Female gender was associated with ESA hyporesponsiveness in our study cohort. This result is in line with previous studies [19, 21], and may be related to the underlying differences in iron release from reticuloendothelial cells between the two genders [22]. Conversely, other studies demonstrated that males were more likely to be ESA hyporesponsive, in comparison to women [23, 24].

In our study, high doses of ACE inhibitor and/or ARBs were related to ESA responsiveness. This data has been controversially discussed in previous papers. Several studies showing that ACE

inhibitors and ARBs are associated to an increase of ESA hyporesponsiveness [23, 25] hypothesized that these anti-hypertensive drugs may interfere with erythropoiesis. It is known that the activation of reninangiotensin system enhances the erythropoietin productions [26], while its inhibition due to ACE inhibitors may exacerbate anaemia [27]. Moreover, it has been demonstrated that ACE inhibitors may cause an increase in serum N-acetyl-seryl-aspartyl-lysyl-proline (Ac-SDKP) levels, which inhibit the recruitment of pluripotent erythroid cells in bone marrow [28]. Other potential mechanisms by which the considered anti-hypertensive drugs may cause anemia are the serum reduction of specific cytokines, such as interleukin-12, and/or of insulin-like growth factor-1, which physiologically stimulate erythropoiesis [11].
Our results also demonstrated that ESA users with metabolic acidosis (pH < 7.38 and serum $HCO3^{-}$ < 22 mmol/l) had a good ESA response. Due to the lack of evidence explaining such potential association between metabolic acidosis and ESA hyporesponsiveness, further investigations on this potential predictive factor are needed.
Considering cancer patients, we found that higher baseline Hb values were associated with ESA hyporesponsiveness (p-value = 0.007), together with the history of ischemic heart disease, although this correlation is close to be significant (p-value = 0.072). The role of cardiovascular diseases as predictors of ESA hyporesponsiveness has been previously studied [18, 29] in CKD patients and the most liable mechanism is related to an increased production of inflammatory cytokines, such as interleukins 1 and 6, Tumor Necrosis Factor and interferon, which induce apoptosis in erythroid progenitor cells and decrease the iron availability by stimulating hepcidin production [30]. Further analyses are, on the other hand, required to confirm the role of cardiovascular diseases as predictors of ESA hyporesponsiveness in cancer setting.

Strengths and limitations
This study has several strengths. Firstly, we may explore data on ESA dispensing from two large Italian LHUs over a 7-year observation period. Secondly, thanks to the electronic therapeutic plans, information on the exact brand name, number of dispensed packages, and indication for use were available. Moreover, we could explore variations in Hb values as a result of ESA treatment, using real-world data from more than 1000 ESA users. Most of the previous randomized clinical trials were conducted considering CKD patients only, while our study explored the potential predictors of ESA hyporesponsiveness both CKD and cancer patients. However, some limitations warrant caution. The high frequency of missing values for some variables considered into the study (namely: transferrin saturation for CKD, as well as ferritin and vitamin B12 for cancer) precluded the possibility to test the independent effect of these risk factors on the study outcome. Thus such an issue remains to be investigated in a specifically designed future cohort study. Furthermore, although we tested into the models a series of laboratory risk factors assessed proximally to the Hb measurement, the possibility of residual time dependent confounding due to unmeasured confounders cannot be excluded. Some ESA as well as concomitant drugs (i.e. iron preparations) dispensing might not have been fully captured by the LHUs databases, as these drugsmay be initially dispensed directly by the public hospitals or purchased by patients as out of pocket, thus not being traced using the study data sources. However, it is unlikely that this limitation affected the study results, as the potential selection bias is expected to be minimal and non-differential between ESAs responders and hyporesponders.

Finally, since the exact body weight of each ESA user was not available and we could not evaluate the exact ESA dosing regimen, we defined ESA hyporesponsiveness as a decrease in Hb levels and, in the sensitivity analysis, as the failure in achieving Hb values ≥11 g/dL, as reported by Suttorp et al. in a multi-center, prospective study [7].

Conclusions

This study tries to identify some potential predictive factors associated with ESA hyporesponsiveness. Covariates as serum CRP or high levels of baseline Hb were confirmed to be associated with poor response to ESA. A better knowledge of the factors associated with ESA response may help avoiding the use of higher ESA doses, and allow a better anaemia management in order to improve the patients' quality of life and reduce morbidity and mortality of both CKD and cancer patients.

References

1. Determinazione AIFA. Aggiornamento del Piano terapeutico AIFA per prescrizione SSN di Eritropoietine (ex Nota 12). http://www.agenziafarmaco.gov.it/sites/default/files/2010-07-29_determina_aggiornamento_template_nota_12_g.u._75_del_31-03-2009.pdf. Accessed 12 June 2018.

2. Khankin EV, Mutter WP, Tamez H, Yuan HT, Karumanchi SA, Thadhani R. Soluble erythropoietin receptor contributes to erythropoietin resistance in end-stage renal disease. PLoS One. 2012;5:e9246.

3. International Society of Nephrology. KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease. Kidney In Suppl. 2012;2(Issue 4. Chapter 3):299–310.

4. Sibbel SP, Koro CE, Brunelli SM, Cobitz AR. Characterization of chronic and acute ESA hyporesponse: a retrospective cohort study of hemodialysis patients. BMC Nephrol. 2015;16:144.

5. Ingrasciotta Y, Giorgianni F, Marcianò I, Bolcato J, Pirolo R, Chinellato A, Ientile V, Santoro D, Genazzani AA, Alibrandi A, Fontana A, Caputi AP, Trifirò G. Comparative effectiveness of biosimilar, reference product and other erythropoiesis-stimulating agents (ESAs) still covered by patent in chronic kidney disease and cancer patients: an Italian population-based study. PLoS One. 2016;11(5):e0155805.

6. Szczech LA, Barnhart HX, Inrig JK, Reddan DN, Sapp S, Califf RM, Patel UD, Singh AK. Secondary analysis of the CHOIR trial epoetin-alpha dose and achieved haemoglobin outcomes. Kidney Int. 2008;74:791–8.

7. Suttorp MM, Hoekstra T, Rotmans JI, Ott I, Mittelman M, Krediet RT, Dekker FW. Erythropoiesis-stimulating agent resistance and mortality in hemodialysis and peritoneal dialysis patients. BMC Nephrol. 2013;25(14):200.

8. Gilbertson DT, Ebben JP, Foley RN, Weinhandl ED, Bradbury BD. Hemoglobin level variability: associations with mortality. Clin J Am Soc Nephrol. 2008;3:133–8.

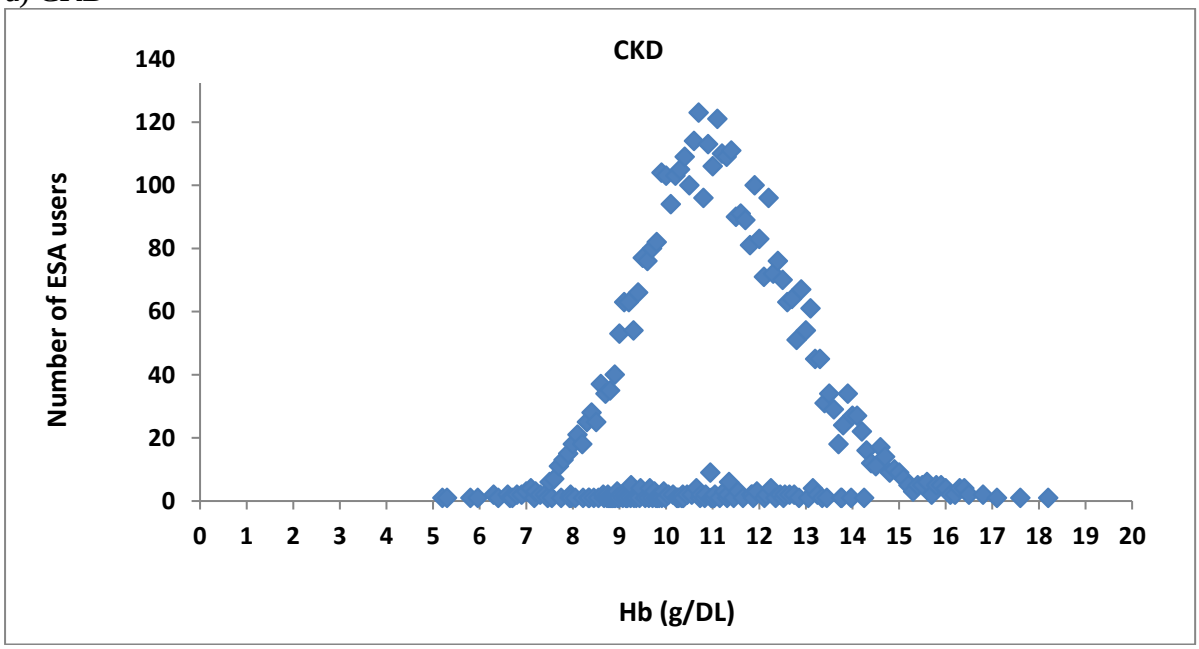
9. Locatelli F, Andrulli S, Memoli B, Maffei C, Del Vecchio L, Aterini S, De Simone W, Mandalari A, Brunori G, Amato M, Cianciaruso B, Zoccali C. Nutritional-inflammation status and resistance to erythropoietin therapy in haemodialysis patients. Nephrol Dial Transplant. 2006;21:991–8.

10. KDOQI. National Kidney Foundation. KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Anemia in Chronic Kidney Disease. Am J Kidney Dis. 2006;47(5 Suppl 3):S11–145.
11. Macdougall IC. The role of ACE inhibitors and angiotensin II receptor blockers in the response to epoetin. Nephrol Dial Transplant. 1999;14(8):1836–41.
12. Ingrasciotta Y, Giorgianni F, Bolcato J, Chinellato A, Pirolo R, Tari DU, Troncone C, Fontana A, Ientile V, Gini R, Santoro D, Santarpia M, Gennazzani A, Uomo I, Pastorello M, Pollina Addario WS, Scondotto S, Cananzi P, Caputi AP, Trifirò G. How much are biosimilars used in clinical practice? A retrospective Italian population-based study of erythropoiesis-stimulating agents in the years 2009-2013. BioDrugs. 2015;29(4):275–84.
13. Solomon SD, Uno H, Lewis EF, Eckardt KU, Lin J, Burdmann EA, de Zwwuw D, Ivanovich P, Levey AS, Parfrey P, Remuzzi G, Singh AK, Toto R, Huang F, Rossert J, McMurray JJ, Pfeffer MA. Erythropoietic response and outcomes in kidney disease and type 2 diabetes. N Engl J Med. 2010;363:1146–55.
14. Minutolo R, Conte G, Cianciaruso B, Bellizzi V, Camocardi A, De Paola L, De Nicola L. Hyporesponsiveness to erythropoiesis-stimulating agents and renal survival in non-dialysis CKD patients. Nephrol Dial Transplant. 2012;27(7):2880–6.
15. De Francisco ALM, Stenvinkel P, Vaulont S. Inflammation and its impact on anaemia in chronic kidney disease: from haemoglobin variability to hyporesponsiveness. NDT Plus. 2009;2 [Suppl 1:i18–26. https://doi.org/10.1093/ndtplus/sfn176.
16. Kalantar-Zadeh K, McAllister CJ, Lehn RS, Lee GH, Nissenson AR, Kopple JD. Effect of malnutrition-inflammation complex syndrome on EPO hyporesponsiveness in maintenance hemodialysis patients. Am J Kidney Dis. 2003;42:761–73.
17. Kimachi M, Fukuma S, Yamazaki S, Yamamoto Y, Akizawa T, Akiba T, Saito A, Fukuhara S. Minor elevation in C-reactive protein levels predicts incidence of erythropoiesis-stimulating agent hyporesponsiveness among hemodialysis. Patients Nephron. 2015;131(2):123–30.
18. López-Gómez J, Portolés J, Aljama P. Factors that condition the response to erythropoietin in patients on hemodialysis and their relation to mortality. Kidney Int. 2008;74(Suppl 111):S75–81.
19. Kalantar-Zadeh K, Lee GH, Miller JE, Streja E, Jing J, Robertson JA, Kovesdy CP. Predictors of hyporesponsiveness to erythropoiesis stimulating agents in hemodialysis patients. Am J Kidney Dis. 2009;53:823–34.
20. Kuragano T, Kitamura K, Matsumura O, Matsuda A, Hara T, Kiyomoto H, Murata T, Fujimoto S, Hase H, Joki N, Fukatsu A, Inoue T, Itakura Y, Nakanishi T. ESA hyporesponsiveness is associated with adverse events in maintenance hemodialysis (MHD) patients, but not with iron storage. PLoS One. 2016;11(3):e0147328.
21. Mallick S, Rafiroiu A, Kanthety R, Iqbal S, Malik R, Rahman M. Factors predicting erythropoietin resistance among maintenance hemodialysis patients. Blood Purif. 2012;33:238–44.
22. Uchida T, Akitsuki T, Kimura H, Tanaka T, Matsuda S, Kariyone S. Relationship among plasma iron, plasma iron turnover, and reticuloendothelial iron release. Blood. 1983;61:799–802.
23. Rossert J, Gassmann-Mayer C, Frei D, McClellan W. Prevalence and predictors of epoetin hyporesponsiveness in chronic kidney disease patients. Nephrol Dial Transplant. 2007;22(3):794–800.

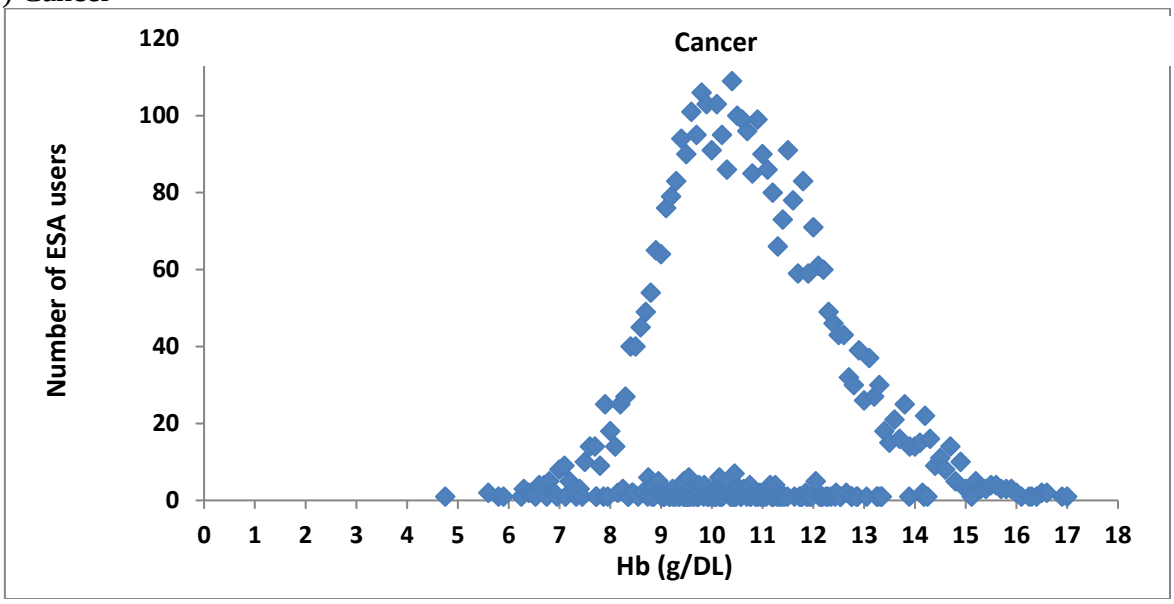
24. Gilbertson DT, Peng Y, Arneson TJ, Dunning S, Collins AJ. Comparison of methodologies to define hemodialysis patients hyporesponsive to epoetin and impact on counts and characteristics. BMC Nephrol. 2013;14:44.
25. Erturk S, Ates K, Duman N, Karatan O, Erbay B, Ertug E. Unresponsiveness to recombinant human erythropoietin in haemodialysis patients: possible implications of angiotensin-converting enzyme inhibitors. Nephrol Dial Transplant. 1996;11:396–7.
26. Vlahakos DV, Balodimos C, Papachristopoulos V, Vassilakos P, Hinari E, Vlachojannis JG. Renin-angiotensin system stimulates erythropoietin secretion in chronic hemodialysis patients. Clin Nephrol. 1995;43(1):53–9.
27. Vlahakos DV, Canzanello VJ, Madaio MP, Madias NE. Enalapril-associated anemia in renal transplant recipients treated for hypertension. Am J Kidney Dis. 1991;17(2):199–205.
28. Azizi M, Rousseau A, Ezan E, Guyene TT, Michelet S, Grognet JM, Lenfant M, Corvol P, Ménard J. Acute angiotensin-converting enzyme inhibition increases the plasma level of the natural stem cell regulator N-acetyl-serylaspartyl-lysyl-proline. J Clin Invest. 1996;97(3):839–44.
29. Guerrero-Riscos MÁ, Montes-Delgado R, Seda-Guzmán M, Praena-Fernàndez JM. Erythropoietin resistance and survival in non-dialysis patients with stage 4–5 chronic kidney disease and heart disease. Nefrologia. 2012;32(3):343–52.
30. Van der Putten K, Braam B, Jie KE, Gaillard CA. Mechanisms of disease: erythropoietin resistance in patients with both heart and kidney failure. Nat Clin Pract Nephrol. 2008;4(1):47–57.
31. Ministero della Salute, Agenzia Italiana del Farmaco (AIFA). Circolare AIFA del 3agosto 2007. Linee guida per la classificazione e conduzione degli studi osservazionali sui farmaci. http://xoomer.virgilio.it/pgiuff/osservazionali.pdf. Accessed 9 Sept 2019.

Online Resource 1. Distribution of Hb values during the follow-up among incident ESA users, stratified by indication for use: a) CKD; b) Cancer

a) CKD



b) Cancer



Incident ESA users starting the treatment at baseline Hb≥11 g/dL were excluded

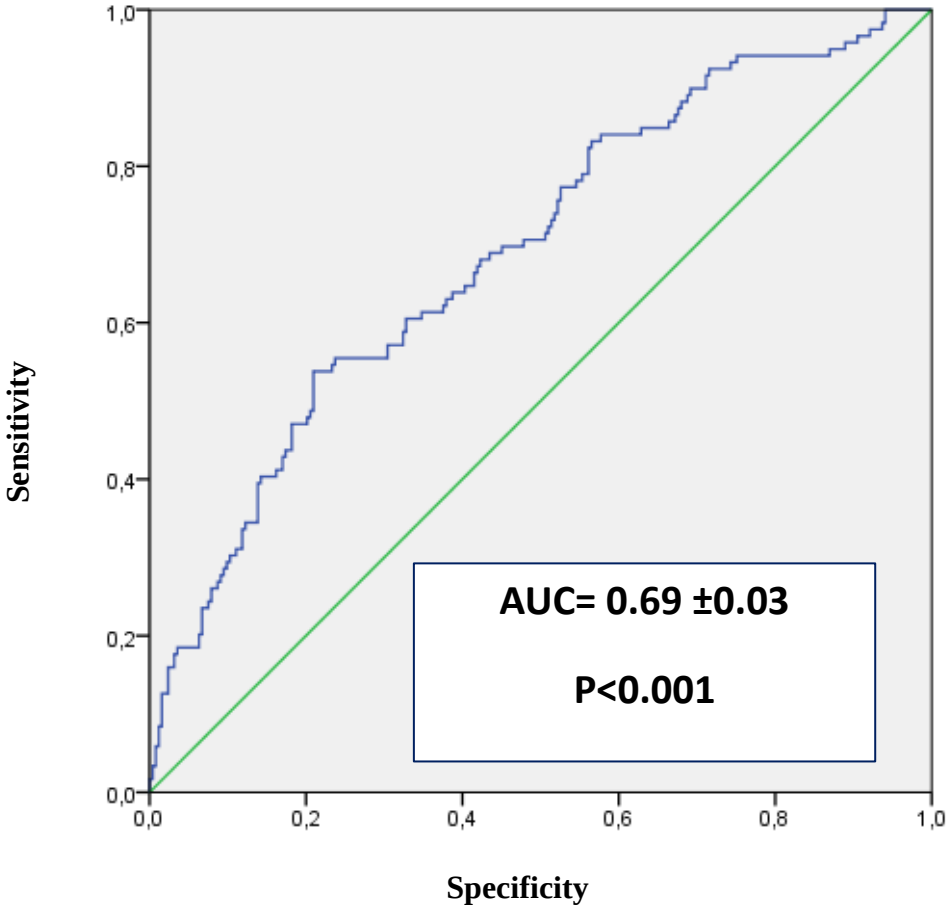
Online Resource 2. Multivariate binary logistic regression to evaluate non responsiveness to ESAs between the 2nd and the 6th month after ID in CKD patients.

	Non responsiveness (Hb<11g/dL) N=147	
	HR (95% CI)	**P-value**
Age (1 year)	1.0 (1.0-1.1)	0.161
Sex (Males)	**0.5 (0.3-0.9)**	**0.011**
Baseline Hb - g/dL	**0.7 (0.5-1.0)**	**0.053**
ESA type		
Reference product	**Reference**	
Biosimilar	1.7 (0.8-3.5)	0.142
Other ESAs covered by patent	1.4 (0.7-2.8)	0.392
Comorbidities		
Diabetes mellitus	1.4 (0.8-2.2)	0.188
Heart failure	1.4 (0.8-2.4)	0.236
Concomitant drugs		
Iron preparations	**0.4 (0.2-0.8)**	**0.008**
High dosage ACE inhibitors/ARBs	1.0 (0.6-1.8)	0.931
Laboratory values		
Albumin (g/dL)	0.9 (0.6-1.3)	0.503

Creatinine (mg/dL)	1.0 (0.9-1.1)	0.783
Acidosis	**0.6 (0.3-0.9)**	**0.037**

CKD ESA users with at least two consecutive Hb values ≥11 g/dL registered between the 2nd and the 6th month after ID were considered ESA responders

Online Resource 3. ROC curve to predict the discriminant power of non-responsiveness in CKD



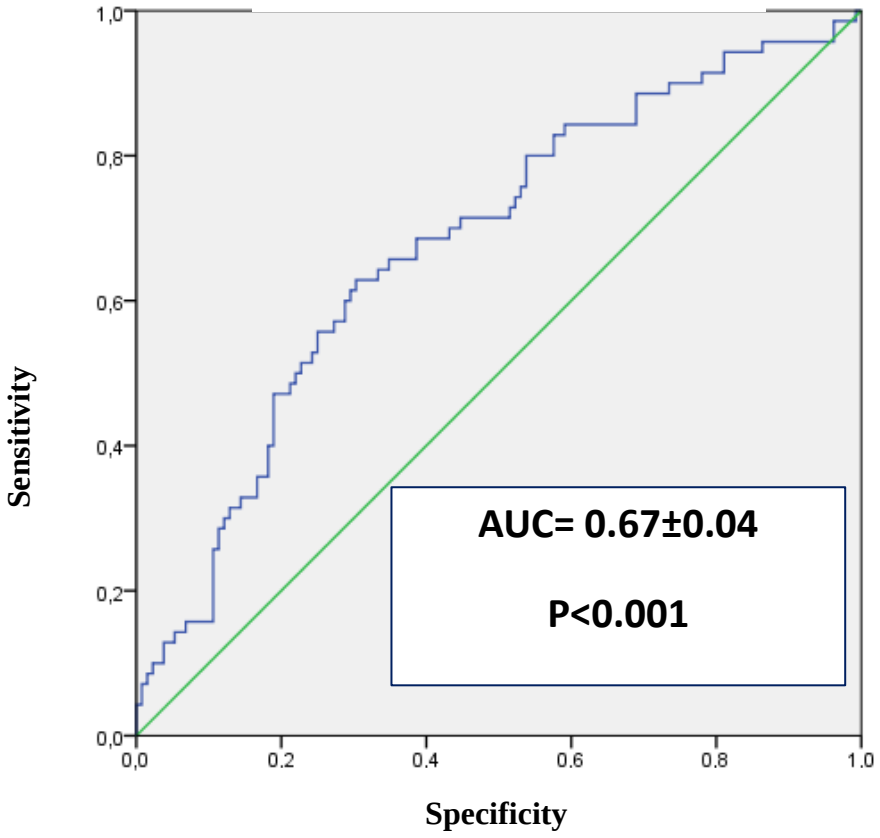
Online Resource 4. Multivariate binary logistic regression to evaluate non responsiveness to ESAs between the 2nd and the 6th month after ID in cancer patients

	Non responsiveness (Hb<11g/dL) N=135	
	OR (95% CI)	**P-value**
Baseline Hb - g/dL	**0.5 (0.3-0.8)**	**0.003**
Acidosis	0.6 (0.3-1.1)	0.109
Concomitant drugs		
High dosage ACE inhibitors/ARBs	1.6 (0.5-5.0)	0.391
Laboratory values		
Albumin (g/dL)	1.0 (0.6-1.6)	0.907
Ferritin (mcg/L)	1.0 (1.0-1.1)	0.233

Cancer ESA users with at least two consecutive Hb values ≥11 g/dL registered between the 2nd and the 6th month after ID were considered ESA responders

Vitamin B_{12} covariates were excluded because of the high proportion of missing values (>70%)

Online Resource 5. ROC curve to predict the discriminant power of non-responsiveness in Cancer



CHAPTER 4.

INTERCHANGEABILITY AND SWITCHING PRACTICES OF BIOLOGICS ORIGINATORS AND BIOSIMILARS

4.1. Interchangeability of biosimilar and biological reference product

Adapted from:

Gianluca Trifirò[1,2], Ilaria Marcianò[1], Ylenia Ingrasciotta[2]. **Interchangeability of biosimilar and biological reference product: updated regulatory positions and pre- and post-marketing evidence.** Expert Opin Biol Ther. 2018 Mar;18(3):309-315. doi: 10.1080/14712598.2018.1410134. Epub 2017 Nov 29. PMID: 29186988.

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Abstract

Introduction: Since 2006, biosimilars have been available in several countries worldwide, thus allowing for potential savings in pharmaceutical expenditure. However, there have been numerous debates about the interchangeability of biosimilars and reference products based on concerns of immunogenicity by switching between biological products, which may cause lack of effect and toxicity.

Areas covered: The authors provide the reader with an overview of the different positions of regulatory authorities on the interchangeability and automatic substitution of biosimilars and reference products. Presently, the FDA allows automatic substitution without prescriber intervention if the biosimilar is interchangeable with reference products, while the European Medicines Agency delegate to each single EU member state.

Expert opinion: Different approaches in defining interchangeability and automatic substitution call for harmonization to increase confidence of healthcare professionals and patients about the clinical impact of switching. Networks of electronic healthcare records and administrative databases, potentially linkable to clinical charts and registries may rapidly assess frequency and benefit-risk profile of different switching patterns in routine care at different levels, thus integrating and strengthening pre-marketing evidence.

Introduction

In recent years, marketing of highly innovative and costly biologicals improved dramatically the management of highburden diseases such as autoimmune diseases (e.g. TNF-alfa antagonists), cancers (e.g. rituximab, trastuzumab), or chronic renal failure (e.g. epoetins). In most therapeutic areas, it is expected a continuously growing marketing of innovative biotechnological therapies in future years. On the other hand, several widely prescribed biological drugs have recently lost or will shortly lose their patent, thus opening the avenues to the marketing of a growing number of biosimilars worldwide. As an example, 36 biosimilars have been already approved by European Medicines Agency (EMA) and additional 18 biosimilars, including anticancer biological drugs, are under evaluation [1].

Biosimilars are granted the marketing authorization on the basis of comparability exercise which has to demonstrate that no clinically significant differences exist between biosimilars and reference product in terms of quality characteristics, biological activity, efficacy, and safety. Biosimilars in general provide a 20–30% purchase cost reduction in comparison to the reference product, despite such a price discount may be substantially greater in some countries and under special circumstances, as observed for infliximab biosimilar in Norway [2].

These drugs therefore represent a valid cost containing strategy, which may favor sustainability of National Health Systems and patients' access to innovative therapies. Biosimilars can be prescribed in patients who are naïve to biological therapy.

The term 'naïve' may refer to both nevertreated patients (i.e. primary naïve), and to patients having stopped a previous biological therapy for a time period (washout period) that, in clinicians' judgment, is long enough to consider those further exposed to biological drugs as newly treated patients (i.e. secondary naïve). While the definition of primary naïve is quite clear, that of secondary naïve may be subject to several interpretations [3]. The variables to take into account to define the washout period and identify secondary naïve patients may be related to:

– The type of biological drug and its pharmacological properties. For instance, considering monoclonal antibodies targeted to cell surface molecules (i.e. rituximab), studies on patients affected by non-Hodgkin lymphoma demonstrated a sustained but reversible depletion of CD20-positive B cells up to 6 months after the end of the treatment [4], thus suggesting a washout period of more than 6 months would be suitable to take into account the pharmacological effect of the drug [3]. On the other hand, biological drugs targeting soluble mediators, such as cytokines, have a different pharmacodynamics. A randomized clinical trial (RCT) concerning antitumor necrosis factor inhibitors used a washout period of 8 weeks for subcutaneous adalimumab and etanercept, and 12 weeks for intravenous infliximab [5].

– The biological drug immunogenicity. Even in case of fully humanized monoclonal antibodies, biological drugs are immunogenic molecules, which can be recognized as nonself-antigens and trigger the production of antidrug antibodies (ADAs), which are antigen-specific but are not crossreacting even with molecules displaying comparable pharmacological activity [6,7]. Furthermore, the potentially induced immunological memory is almost lifelong and can lead to an immunogenic response in presence of the same antigen [3].

The identification of 'secondary naïve' patients is not well defined and can be subjected to different interpretations. It is therefore necessary to clarify the definition of naïve patients to

biosimilars to support the therapeutic strategy of the prescribing physicians, to whom the choice between biosimilars and originators is entrusted.
Besides naïve patients, also patients with chronic diseases who are successfully treated with biological therapy may theoretically receive biosimilars as a switch from reference product to contain costs, whether reference product and related biosimilar are judged as interchangeable.
Based on EMA definition [8], interchangeability refers to the property of a medicine to be exchanged with another one, which is expected to have the same clinical effects. This may mean replacing a reference product with a biosimilar or vice versa or replacing one biosimilar with another. Such replacing may be done by:

● Switching, if the prescriber decides to exchange one medicine for another one with the same therapeutic intent;

● Automatic substitution, which is the practice of dispensing one medicine instead of another equivalent and interchangeable one at pharmacy level, without previously consulting the prescriber.

Positions of regulatory authorities on interchangeability and automatic substitution of biosimilars and reference products are rather heterogeneous worldwide. In Latin America, a biological drug is defined interchangeable with another one if the two show similar safety and
effectiveness. In this case, the substitution is acceptable, otherwise only the physician can allow it [9]. While in India the biosimilar substitution is automatic as soon as the drug is approved, it is not allowed in other countries such as Japan, Australia and Canada and it is still a not addressed issue in South Korea [10,11].
Based on the US FDA definition, the term ‘interchangeable’ means that ‘the biological product may be substituted for the reference product without the intervention of the healthcare provider who prescribed the reference product’ [12]. In addition to the studies demonstrating biosimilarity, FDA requests the drug companies to conduct premarketing studies on multiple and reverse switching of biosimilar and reference products to grant the biosimilar with interchangeable status [13]. Specifically, the FDA draft guidance for industries contains detailed requests for the demonstration of interchangeability between biosimilars and reference products. This draft requires the evaluation of at least three switches between reference product and biosimilar (back and forward). Upon review of a submitted application, FDA will define the biological product interchangeable with the reference product if submitted data are sufficient to demonstrate that for a biological product that is administered more than once, the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch. FDA allows automatic substitution without prescriber intervention if the biosimilar is interchangeable with reference products, based on the evidence from the abovementioned studies. However, several US states restricted automatic substitution [14].
On the contrary, EMA does not include any recommendation on interchangeability and automatic substitution of biosimilars and reference product [8]. The decision on whether to grant interchangeability status and allow substitution of the reference product and the biosimilar is taken at national level, being in charge to each single EU member state [15].

Different positions are taken by various European countries about automatic substitution. Spain and Italy adopted a nosubstitution policy for all biologics [16,17], while France allowed substitution of biosimilars for naïve patients (but never implemented a corresponding decree), allowing interchangeability as long as transparency, monitoring, and traceability of biosimilars can be guaranteed [18]. In the UK, pharmacists are not allowed to dispense biosimilars in place of reference products and clinicians are required to prescribe biologics by brand name and not by International Nonproprietary Names [19]. One of the main concerns about interchangeability is the potential immunogenicity triggered by the switch between different biological drugs/biosimilars, which may be associated to lack of efficacy as well as toxicity.

The current EMA guidelines on the immunogenicity assessment of biological drugs/biosimilars recommend exploring immunogenicity in the preapproval phase through validated methods able to measure incidence, neutralizing capacity, persistence of ADAs and their effects on drug exposure, safety, and efficacy outcomes. Due to the limited number of enrolled patients in the preapproval studies, EMA recommends in addition to further evaluate the immunogenicity in post-marketing setting [20].

Due to the still ongoing debate about interchangeability of biosimilar and biological reference product, this review aims to provide an overview of the pharmacological aspects as well as data from RCT and real-world–based evidence on switching between reference product and biosimilars are reported.

Pharmacological considerations

It is well known that all biological drugs, even fully humanized monoclonal antibodies, may be recognized as non-self-antigens by the host and may trigger immunogenicity. The immune response may depend, on a side, on even minor differences in the formulation, purity or packaging of the drug and, on the other side, on the characteristics of individual patients. Different factors related to patients (e.g. age, genetic factors modulating the immune response or related to a gene defect), disease, and concomitant use of immunomodulatory therapies may influence the development of an immune response against a therapeutic protein [21]. Most of the clinically meaningful effects of immunogenicity are due to the production of ADAs, which are specific for the molecule that triggered their production and do not cross-react, even with molecules having comparable pharmacological activity. This means that, for instance, ADAs induced by a given antitumor necrosis factor (anti-TNF) agent do not recognize other anti-TNF agent [7].

ADAs may lower bioavailability of the biological drug, acting as neutralizing antibodies that block the active site of the drug, or may favor the formation of immune-complexes that eventually accelerate the clearance of the complexed molecules (ADA plus the drug), thus potentially reducing or even eliminating the therapeutic effect [6,22,23]. ADAs may alsoworsen the patient's clinical conditions by neutralizing the endogenous target of the biological drug [24].

Effects of ADAs production range from asymptomatic responses to serious adverse reactions [24], even if ADAs do not necessarily determine a lack or loss of efficacy. The degree of immunogenicity is not the same for all biological drugs. A recent systematic literature review explored the immunogenicity of 10 biological drugs, including biosimilar infliximab, approved for the treatment of inflammatory diseases, ranging from dermatology to gastroenterology and rheumatology. Up to 394 studies, both RCTs and longitudinal observational studies were

included in the review. Although the number of patients who developed ADAs varied widely across different biological drugs, infliximab reference product, adalimumab, and infliximab biosimilar were associated with the highest rates of ADA formation (respectively, 0–83%, 0–54%, and 21–52%) [21].

Switch is not expected to trigger immunogenicity, unless the biological drug to which the patient is switched is qualitatively inferior compared to that previously administered, i.e. is not truly comparable [25]. Based on the complexity of their structure, the risk of switch-induced immunogenicity is therefore theoretically displayed by all biological drugs, as they typically undergo manufacturing changes [26] leading to potentially different versions of the same drug. One example of how sensitive the immune system is, that even a subtle change in the manufacturing process may trigger the immunogenicity, is that of the anti-epoetin antibody-induced Pure Red Cell Aplasia (PRCA), which occurred in patients with chronic kidney disease (CKD) who were switched from a previous to a new version of reference product epoetin alfa, after a change in both the product formulation and the route of administration [27].

Similarly, switching treatment from intravenous to subcutaneous formulations may be considered risky. A study investigated switching from intravenous to subcutaneous trastuzumab and vice versa in patients with breast cancer. The switch was associated with an increased incidence of ADAs in the switching cohort from intravenous to subcutaneous formulation, but not adverse events [28].

The above-mentioned examples highlight that switchinduced immunogenicity is not a biosimilar-related issue, but concerns any potential switch between biological drugs, even different formulations or administration routes.

Evidence from RCT

A retrospective analysis has been conducted on published data fromthree multicenter phase 3 clinical trials (two 24-week randomized, double-blind studies and a 56-week, open-label, follow-on study) involving adult patients with CKD, maintained on hemodialysis, and receiving epoetin alfa or epoetin zeta. The study aimed at evaluating the impact of switching patients from epoetin alfa to epoetin zeta, or vice versa. Results confirmed that epoetin alfa and
epoetin zeta therapy can be interchanged without any clinically significant alteration in efficacy, safety, or epoetin dose, in patients with CKD on dialysis receiving stable epoetin maintenance therapy. Furthermore, none of the 481 patients developed antiepoetin antibodies or PRCA [29].

In addition, three phase 3 clinical trials compared the efficacy and safety of somatropin (rGH) in children receiving continuous biosimilar rGH therapy (lyophilized powder for solution or ready-to-use solution) for up to 60 months vs. children who received 9-month treatment with reference product rGH followed by a switch to biosimilar solution rGH.

Immunogenicity was uncommon and no relevant increased risk of anti-rGH antibodies emerged after the switch from reference product to biosimilar rGH. The authors concluded that switching from reference product to biosimilar rGH has no impact on efficacy or safety in children with growth hormone deficiency, and the different rGH formulations are well tolerated [30].

In the extension of PLANETAS and PLANETRA studies, which explored the efficacy and safety of switching to biosimilar infliximab in patients previously treated with reference product infliximab for the treatment of ankylosing spondylitis and rheumatoid arthritis, respectively, ADAs incidence as well as response rate were comparable between maintenance and switch

infliximab groups [31,32]. Similarly, another clinical trial investigated safety and immunogenicity of switching from reference product to biosimilar infliximab in patients affected by inflammatory bowel diseases. Results demonstrated that switching did not result in a significant change in disease activity scores and had no impact on the incidence of ADAs [33]. Such results have been confirmed by preliminary data on pediatric patients affected by inflammatory bowel diseases [34].

The NOR-SWITCH study is a randomized, non-inferiority, double-blind, phase 4 trial, including 482 patients with rheumatoid arthritis, spondyloarthritis, psoriatic arthritis, ulcerative colitis, Crohn's disease, and chronic plaque psoriasis [2]. The study showed the non-inferiority of the switching from infliximab originator to the biosimilar vs. the continuity of the treatment with the originator drug, according to a prespecified non-inferiority margin of 15%. On the other hand, the study was not powered to demonstrate the non-inferiority within each individual disease group, due to the low number on patients eligible to treatment with reference product in Norway. In addition, the 15%margin was chosen based on the PLANETRA trial as well as discussions with the Norwegian Medicines Agency. Although this margin may be considered too wide based on the FDA requirements and may therefore include clinically important differences, it has been defined as sufficient by the EMA in the biosimilar infliximab assessment report. In order to allow further assessment of immunogenicity and disease activity
during a longer follow-up period (12 months), an extension of the NOR-SWITCH study is currently ongoing [2].

Other clinical studies have been conducted to compare the efficacy and safety of the switch from reference product to biosimilar etanercept and rituximab, both highlighting comparable efficacy, safety, and immunogenicity between the groups [35,36].

Real-world experience

To date, more than 10-years' experience of real-world use of biosimilars has been cumulated in Europe and lo lesser extent in other countries worldwide, thus offering the opportunity to evaluate data from post-marketing setting about clinical effects of switching between reference product and biosimilars.

Switching between biological drugs for the treatment of chronic diseases is very frequent in clinical practice (e.g. 15–20% for epoetins [37,38] and 20% for filgrastim [39] during the first year of therapy) and may occur between reference products to biosimilars or vice versa as well as between different originators.

Flodmark et al. [40] evaluated the impact of switching from reference product to biosimilar rGH, in terms of treatment efficacy and costs in 98 children in routine care. Results demonstrated that the switch had no impact on growth velocity and trajectory and highlighted that substantial savingsmay be achieved by switching from reference product to biosimilar rGH (approximately, an annual saving of 650,000 euros). No serious or unexpected adverse events were reported following the switch. Similar results were described by Rashid et al. [41] and in a review of the available safety data on the switch from originators to biosimilar rGH [42].

A population-based analysis on patients with renal anemia demonstrated that epoetins consumption and treatment persistence were not affected following a switch from the reference product to a biosimilar [43]. These results are in contrast with those from Minutolo et al. showing that the switch from originator to biosimilar epoetins may require 40% higher doses to maintain

anemia control in clinical practice [44]. However, this retrospective matched case-control study show major limitations; in particular, reasons for switching were not clearly explained and may have induced dosing penalty irrespective of the administered epoetins.

A recent observational study from the Danish DANBIO registry evaluated the impact of a nationwide nonmedical switch from originator to biosimilar infliximab in patients with rheumatoid arthritis, psoriatic arthritis, and axial spondyloarthritis, and compared disease activity before vs. after switching. Results showed that disease activity and flare rates were unchanged with no statistically meaningful differences during the 3-month period pre- vs. post-switch [45], in line with other studies [46,47]. In addition, a review on interchangeability of biosimilar monoclonal antibodies and fusion proteins in rheumatology, gastroenterology, and dermatology demonstrated that data on switch from reference product to biosimilars confirmed the maintenance of safety and efficacy [48].

In conclusion, 'the concern of switching to biosimilars is overhyped and preventing patients on biologic medicines from switching to biosimilars due to anticipated risks seems to be disproportional compared to the expected cost savings and/or improved patient access', as stated by Inotai et al. [49].

Given the high frequency of switching between different biological products including biosimilars in routine care, if the hypothesized risk of immunogenicity would have held true, it would have been likely captured through routine pharmacovigilance activities. Ebbers et al. [50] reviewed both data from clinical trials conducted worldwide and from the EudraVigilance database, which includes suspected serious adverse drug reactions reported to the regulatory authorities in the EU, in Norway, and Iceland, and found no evidence that the switching practice may lead to safety concerns. The lack of safety signals provides further reassurance about the safety of switching between reference products and biosimilars [25].

Conclusion

Animated debates are still ongoing about the interchangeability of biosimilars and reference products and about the clinical impact of switching in routine care. All biological drugs, even fully humanized monoclonal antibodies, may be recognized as non-self-antigens by the host and may trigger immunogenicity. However, data from both clinical trials and post-marketing setting show that switching from reference product to biosimilar is not expected to trigger or enhance immunogenicity.

Expert opinion

In chronic diseases, switching from highly costly biological reference products to corresponding lower cost biosimilars may be a valid cost containing strategy, provided that not only biosimilarity but also interchangeability have been previously demonstrated. In lack of evidence data on interchangeability, the automatic substitution is not recommended.

Some regulatory agencies, such as FDA, recommend a twostep approach to obtain the interchangeable biologic designation, first gaining approval as a biosimilar and then submitting supplemental data to support interchangeability on the basis of the transition studies (i.e. one-time transition for patients who are on the reference product to be switched to the biosimilar to show that there are no increases safety issues between the pre- and post-switch population).

Transitions studies requested by FDA should consider at least three switches (back and forward). This request is in line with common practice, where multiple and reverse switching occur frequently. On the other hand, residual uncertainty still remains as switching practice can be even more complex and should be addressed in post-marketing setting. Several decades of common switching practice of biological drugs are rather reassuring about effectiveness and safety of switching in clinical practice. In addition, RCTs and observational studies did not demonstrate a potential negative impact of the switch between reference product and biosimilars and therefore healthcare professionals' concerns about such safety issues regarding biosimilars are not supported. These results have been recently confirmed by a review on interchangeability of biosimilar monoclonal antibodies and fusion proteins [48]. Yet, the positions about interchangeability and automatic substitution of reference product and biosimilars among different regulatory agencies in Asia, the USA, and Europe are rather heterogeneous, differing also at country and regional level. This fragmented context leads to different national and locoregional approaches, which call for harmonization across different regulatory agencies to increase confidence of healthcare professionals and patients about clinical effects of switching of reference product and biosimilars. In general, lowest income countries are more favorable to automatic substitution toward lower cost biologicals (e.g. in general, biosimilars) as cost-containing strategies. Instead, Western countries have more cautious positions regarding replacing automatically biological drugs with corresponding lower cost biosimilars, despite growing body of evidence coming from both pre- and post-marketing settings.

Several published observational studies highlighted that the switching practice is very frequent in routine care, even during the first year of treatment, occurring not only from a reference product to the biosimilar but also between different originators [37–39,51]. In the next years, switching practice may become even more complex, as a large number of biosimilars for the same reference product will be available and a growing number of modified version of reference products will be newly marketed (e.g. subcutaneous vs. intravenous formulation of rituximab), thus expanding the options of switching scenarios. To date, all the data available for infliximab refer to only one infliximab biosimilar, but we believe there is no reason why results should be different for others infliximab biosimilars, given the pre-marketing demonstrated biosimilarity to the reference product. Otherwise, same potential concerns should be raised regarding the switch between different batches of the same biological drug which undergoes major change production requiring comparability exercise before marketing. FDA requirements for granting biosimilars with interchangeable status based on premarketing studies may only partly address the uncertainty about the switching between different biosimilars and originators. Given the limitations of pre-marketing RCTs (e.g. small samples, short-term follow-up, etc.), post-marketing monitoring is necessary to address residual uncertainty regarding a demonstration of interchangeability and the safety of the switch. Large-scale, observational studies based on registries or claims databases using real-world data may complement and strengthen pre-marketing evidence.

Another issue is that multiple switches make the detection of potential pharmacovigilance signals more challenging, due to the difficulty in attributing the reported adverse reactions to a specific biological drug, which is difficult to address. Different active post-marketing surveillance strategies may be implemented in order to detect potential switch-related adverse reactions. Networks of electronic healthcare records and administrative databases which may also be linked

to clinical charts and registries may rapidly assess frequency and benefit–risk profile of different switching patterns in routine care at international, national and loco-regional level, thus integrating and strengthening pre-marketing evidence. Funding from European Committee and other public funding bodies and other stakeholders worldwide to build data infrastructure for systematic post-marketing monitoring of biologics including biosimilar in clinical practice is desirable.

References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. European Medicines Agency. European public assessment reports - biosimilars [Internet]. cited 2017 Sep 28. Available from: https://www.ema.europa.eu/en/medicines/search_api_aggregation_ema_medicine_types/field_ema_med_biosimilar

2. Jørgensen KK, Olsen IC, Goll GL, et al. Switching from originator infliximab to biosimilar CT-P13 compared with maintained treatment with originator infliximab (NOR-SWITCH): a 52-week, randomised, double-blind, non-inferiority trial. Lancet. 2017 Jun 10;389(10086):2304–2316.

•• A milestone randomized, non-inferiority, double-blind, phase 4 clinical trial on non-inferiority of switching from infliximab reference product to biosimilar vs. continued treatment with infliximab reference product.

3. Biggioggero M, Danova M, Genovese U, et al. The challenging definition of naïve patient for biological drug use. Autoimmun Rev. 2015;14:543–546.

4. McLaughlin P, Grillo-López AJ, Link BK, et al. Rituximab chimeric anti-CD20 monoclonal antibody therapy for relapsed indolent lymphoma: half of patients respond to a four-dose treatment program. J Clin Oncol. 1998 Aug;16(8):2825–2833.

5. Smolen JS, Kay J, Doyle MK, et al. Golimumab in patients with active rheumatoid arthritis after treatment with tumour necrosis factor α inhibitors (GO-AFTER study): a multicentre, randomised, double-blind, placebo-controlled, phase III trial. Lancet. 2009;374 (9685):210–221.

6. Vincent FB, Morand EF, Murphy K, et al. Antidrug antibodies (ADAb) to tumour necrosis factor (TNF)-specific neutralising agents in chronic inflammatory diseases: a real issue, a clinical perspective. Ann Rheum Dis. 2013;72(2):165–178.

7. Bendtzen K, Ainsworth M, Steenholdt C, et al. Individual medicine in inflammatory bowel disease: monitoring bioavailability, pharmacokinetics and immunogenicity of anti-tumour necrosis factor-alpha antibodies. Scand J Gastroenterol. 2009;44(7):774–781.

8. European Medicines Agency; European Commission. Biosimilars in the EU - Information guide for health care professionals [Internet]. 2017. cited 2017 Sep 28. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Leaflet/2017/05/WC500226648.pdf

9. Pineda C, Caballero-Uribe CV, de Oliveira MG, et al. Recommendations on how to ensure the safety and effectiveness of biosimilars in Latin America: a point of view. Clin Rheumatol. 2015;34(4):635–640.

10. Nagai S, Yanagihara R, Kishioka Y. Japanese regulatory authority's perspective on biosimilars. Lancet Oncol. 2015 Mar;16(3):e101.

11. Bennett CL, Chen B, Wyatt MD, et al. Regulatory and clinical considerations for biosimilar oncology drugs. Lancet Oncol. 2014;15 (13):e594–605.
12. Food and Drug Administration. Public Health Service Act. Title III - General Powers and Duties of Public Health Service. USA. Section 351(i)(3) [Internet]. 2013. cited 2017 Sep 28. Available from: http://legcounsel.house.gov/Comps/PHSA_CMD.pdf
13. Food and Drug Administration. Considerations in demonstrating interchangeability with a reference product - guidance for industry [Internet]. 2017. cited 2017 Sep 28. Available from: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM537135.pdf
14. Indiana State. Senate enrolled act. Bill number 262 [Internet]. 2014. [Cited 2017 Nov 26]. Available from: http://iga.in.gov/staticdocuments/b/3/b/f/b3bf9b4c/SB0262.04.ENRS.pdf
15. European Medicines Agency. Guideline on similar biological medicinal products [Internet]. 2014. cited 2017 Sep 28. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/10/WC500176768.pdf
16. GABI Journal. Biosimilar policies in Spain [Internet]. 2013. Cited 2017 Sep 28. Available from: http://gabi-journal.net/news/biosimilar-policies-in-spain
17. Italian Medicines Agency. Position Paper sui Farmaci Biosimilari [Internet]. 2013. cited 2016 Aug 4. Available from: http://www.agenziafarmaco.gov.it/sites/default/files/AIFA_POSITION_PAPER_FARMACI_BIOSIMILARI.pdf
18. GABI Journal. France to allow biosimilars substitution [Internet]. 2014. cited 2017 Sep 28. Available from: www.gabionline.net/Policies-Legislation/France-to-allow-biosimilars-substitution
19. FederSanitàAnci. Per creare cultura su un approccio corretto dei farmaci biosimilari. Position Paper [Internet]. 2015. cited 2017 Sep 28. Available from: http://www.federsanita.it/
20. European Medicines Agency. Guideline on immunogenicity assessment of biotechnology-derived therapeutic proteins [Internet]. 2007. cited 2017 May 12. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003946.pdf
21. Strand V, Balsa A, Al-Saleh J, et al. Immunogenicity of biologics in chronic inflammatory diseases: a systematic review. Bio Drugs. 2017;31(4):299–316.
22. Descotes J, Gouraud A. Clinical immunotoxicity of therapeutic proteins. Expert Opin Drug Metab Toxicol. 2008;4(12):1537–1549.
23. Aarden L, Ruuls SR, Wolbink G. Immunogenicity of anti-tumor necrosis factor antibodies-toward improved methods of anti-antibody measurement. Curr Opin Immunol. 2008;20(4):431–435.
24. Cai X-Y, Thomas J, Cullen C, et al. Challenges of developing and validating immunogenicity assays to support comparability studies for biosimilar drug development. Bioanalysis. 2012 Sep;4(17):2169–2177.
25. Kurki P, Van Aerts L, Wolff-Holz E, et al. Interchangeability of biosimilars: a European perspective. Bio Drugs. 2017;83–91.
•• A milestone paper exploring the theoretical basis of the potential risks of switching between biosimilar and reference products and the available data on switches.

26. Vezér B, Buzás Z, Sebeszta M, et al. Authorized manufacturing changes for therapeutic monoclonal antibodies (mAbs) in European Public Assessment Report (EPAR) documents. Curr Med Res Opin. 2016;32(5):829–834.
27. Boven K, Stryker S, Knight J, et al. The increased incidence of pure red cell aplasia with an Eprex formulation in uncoated rubber stopper syringes. Kidney Int. 2005 Jun;67(6):2346–2353.
28. Pivot X, Gligorov J, Müller V, et al. Patients' preferences for subcutaneous trastuzumab versus conventional intravenous infusion for the adjuvant treatment of HER2-positive early breast cancer: final analysis of 488 patients in the international, randomized, twocohort PrefHer study. Ann Oncol Off J Eur Soc Med Oncol. 2014 Oct;25(10):1979–1987.
29. Więcek A, Ahmed I, Scigalla P, et al. Switching epoetin alfa and epoetin zeta in patients with renal anemia on dialysis: posthoc analysis. Adv Ther. 2010;27(12):941–952.
30. Romer T, Zabransky M, Walczak M, et al. Effect of switching recombinant human growth hormone: comparative analysis of phase 3 clinical data. Biol Ther. 2011;1:5.
31. Park W, Yoo DH, Miranda P, et al. Efficacy and safety of switching from reference infliximab to CT-P13 compared with maintenance of CT-P13 in ankylosing spondylitis: 102-week data from the PLANETAS extension study. Ann Rheum Dis. 2017;76(2):346–354.
32. Yoo DH, Prodanovic N, Jaworski J, et al. Efficacy and safety of CT-P13 (biosimilar infliximab) in patients with rheumatoid arthritis: comparison between switching from reference infliximab to CT-P13 and continuing CT-P13 in the PLANETRA extension study. Ann Rheum Dis. 2017;76(2):355–363.
33. Buer LCT, Moum BA, Cvancarova M, et al. Switching from Remicade® to Remsima® is well tolerated and feasible: a prospective, open-label study. J Crohn's Colitis. 2017;11(3):297–304.
34. Sieczkowska J, Jarzębicka D, Banaszkiewicz A, et al. Switching between infliximab originator and biosimilar in paediatric patients with inflammatory bowel disease. Preliminary observations. J Crohns Colitis. 2016;10(2):127–132.
35. Griffiths CEM, Thaçi D, Gerdes S, et al. The EGALITY study: a confirmatory, randomized, double-blind study comparing the efficacy, safety and immunogenicity of GP2015, a proposed etanercept biosimilar, vs. the originator product in patients with moderate-to-severe chronic plaque-type psoriasis. Br J Dermatol. 2017;176(4):928–938.
36. Park W, Suh CH, Shim SC, et al. Efficacy and safety of switching from innovator rituximab to biosimilar CT-P10 compared with continued treatment with CT-P10: results of a 56-week open-label study in patients with rheumatoid arthritis. Bio Drugs. 2017;31 (4):369–377.
37. Ingrasciotta Y, Giorgianni F, Bolcato J, et al. How much are biosimilars used in clinical practice? A retrospective Italian population-based study of erythropoiesis-stimulating agents in the years 2009-2013. Bio Drugs. 2015;29(4):275–284.
• A population-based study on Italian administrative healthcare databases on the pattern of use and switching pattern of epoetins in routine care.
38. D'Amore C, Da Cas R, Rossi M, et al. Switching between epoetins: a practice in support of biosimilar use. Bio Drugs. 2016;30 (1):27–32.
• An observational, population-based study on Italian regional administrative healthcare database on the switching pattern of epoetins in routine care.
39. Marcianò I, Ingrasciotta Y, Giorgianni F, et al. How did the introduction of biosimilar filgrastim influence the prescribing pattern of granulocyte colony-stimulating factors? Results

from a multicentre, population-based study, from five Italian centres in the years 2009-2014. Bio Drugs. 2016;30(4):295–306.
• An important drug-utilization study on the pattern of use and the switching pattern of granulocyte colony-stimulating factors in Italy, using administrative healthcare databases.
40. Flodmark C-E, Lilja K, Woehling H, et al. Switching from originator to biosimilar human growth hormone using dialogue teamwork: single-center experience From Sweden. Biol Ther. 2013;3:35–43.
41. Rashid N, Saenger P, Wu Y-L, et al. Switching to Omnitrope (registered trademark) from other recombinant human growth hormone therapies: a retrospective study in an integrated healthcare system. Biol Ther. 2014;4(1–2):27–39.
42. Borras Perez MV, Kristrom B, Romer T, et al. Ten years of clinical experience with biosimilar human growth hormone: a review of safety data. Drug Des Devel Ther. 2017;11:1497–1503.
43. Hörbrand F, Bramlage P, Fischaleck J, et al. A population-based study comparing biosimilar versus originator erythropoiesis-stimulating agent consumption in 6,117 patients with renal anaemia. Eur J Clin Pharmacol. 2013;69(4):929–936.
44. Minutolo R, Bolasco P, Chiodini P, et al. Effectiveness of switch to Erythropoiesis-Stimulating Agent (ESA) biosimilars versus maintenance of ESA originators in the real-life setting: matched-control study in hemodialysis patients. Clin Drug Investig. 2017;37(10):1–9.
45. Glintborg B, Sørensen IJ, Loft AG, et al. A nationwide non-medical switch from originator infliximab to biosimilar CT-P13 in 802 patients with inflammatory arthritis: 1-year clinical outcomes from the DANBIO registry. Ann Rheum Dis. 2017;76(8):1426–1431.
46. Nikiphorou E, Kautiainen H, Hannonen P, et al. Clinical effectiveness of CT-P13 (Infliximab biosimilar) used as a switch from Remicade (infliximab) in patients with established rheumatic disease. Report of clinical experience based on prospective observational data. Expert Opin Biol Ther. 2015;15 (12):1677–1683.
47. Becciolini A, Raimondo MG, Crotti C, et al. A review of the literature analyzing benefits and concerns of infliximab biosimilar CT-P13 for the treatment of rheumatologic diseases: focus on interchangeability. Drug Des Devel Ther. 2017;11:1969–1978.
48. Moots R, Azevedo V, Coindreau JL, et al. Switching between reference biologics and biosimilars for the treatment of rheumatology, gastroenterology, and dermatology inflammatory conditions: considerations for the clinician. Curr Rheumatol Rep. 2017;19(6).
49. Inotai A, Prins CPJ, Csanádi M, et al. Is there a reason for concern or is it just hype?–A systematic literature review of the clinical consequences of switching from originator biologics to biosimilars. Expert Opin Biol Ther. 2017;17(8):915–926.
50. Ebbers HC, Muenzberg M, Schellekens H. The safety of switching between therapeutic proteins. Expert Opin Biol Ther. 2012;12 (11):1473–1485.
•• Amilestone review of data from clinical trials and EudraVigilance database and on the frequency and safety concerns of switching between biological drugs of these products.
51. Loiacono C, Sgroi C, Coppolino S, et al. How much are biosimilars used in southern Italy?: A retrospective analysis of epoetin utilization in the local health unit of Messina in the years 20102011. Bio Drugs. 2012;26(2):113–120.

4.2. In search of predictors of switching between erythropoiesis-stimulating agents in clinical practice

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Abstract

Background and objectives: Switching between different erythropoiesis-stimulating agents (ESAs) during the first year of therapy is frequent (15–20%), much more so toward reference products than biosimilars. The objectives of this study were to investigate the frequency and identify the potential predictors of switching between biosimilar and originator ESAs during the first year of treatment in patients with chronic kidney disease (CKD), or chemotherapy-related anemia from six large Italian geographic areas in the years 2009–2015.

Methods: A retrospective cohort study was conducted using six Italian regional claims databases (≥ 13 million inhabitants) during 2009–2015. Among incident epoetin users, the frequency of single, multiple, and backward switch during the first year of treatment was evaluated. Using frailty Cox models, potential predictors of first switch were identified. All analyses were stratified by the main indications for use.

Results: Among 102,240 incident epoetin users, 15,853 (15.5%) switched to another epoetin during the first year of therapy; only 18% of these switched to biosimilars. Single switch was more common (62.2% of the switchers) than multiple (23.5%) or backward switch (14.3%). In cancer, the cumulative number of transfusions and iron preparations dispensed, as well as hyperparathyroidism, were predictors of switching. In CKD, the cumulative number of transfusions, number of vitamin A/D preparations dispensed, and CKD severity increased the probability of switching.

Conclusions: Switching between ESAs was frequent in both CKD and cancer patients. The number of cumulative transfusions and severity of disease seemed to affect the switch.

Introduction

Erythropoiesis-stimulating agents (ESAs) play a major role in the management of anemia in several therapeutic settings. In particular, the benefits with these drugs for the treatment of anemia induced by chemotherapy or associated with chronic kidney disease (CKD) are well-documented [1–3]. In Europe, the biosimilar version of epoetin alfa has been available since 2007, following approval by the European Medicines Agency (EMA) [4]. In general, the uptake of biosimilars is heterogeneous across countries and therapeutic areas, highlighting differences in clinicians' confidence in prescribing those biologics [5], despite biosimilars representing a great opportunity for the sustainability of national health services (NHSs) [6–10].

In 2017, biosimilars accounted for 51% of overall ESA consumption in Italy [11], which was strongly influenced by the implementation of specific regional healthcare policies [12]. The Italian national report on drug expenditure showed an increase of 65.1% in consumption of biosimilars of epoetin alfa as compared to 2016, with an overall reduction of 8.0% of the total ESA per capita expenditure.

Besides naïve patients, patients with chronic diseases who are successfully treated with biological therapy may theoretically receive biosimilars as a switch from reference product to contain costs, if the reference product and related biosimilar are judged to be interchangeable [8]. However, the positions of individual national regulatory agencies on interchangeability and automatic substitution of biosimilars and reference products are heterogeneous worldwide. According to the EMA, interchangeability refers to the ability of a medicine to be exchanged with another one that is expected to have the same clinical effects [9]. Such replacement may be performed by switching, if the prescriber decides to exchange one medicine for another one with the same therapeutic intent, or automatic substitution, which is the practice of dispensing one medicine instead of another judged to be interchangeable at a pharmacy level, without previous consultation of the prescriber [8].

The US Food and Drug Administration (FDA) requests that drug companies conduct pre-approval studies on multiple and reverse switching of biosimilar and reference products in order to grant the biosimilar interchangeable status [13]. Specifically, the FDA draft guidance requires the evaluation

of at least three switches between reference product and biosimilar (backward and forward). The FDA allows automatic substitution without prescriber intervention if the biosimilar is interchangeable with reference product, based on the evidence from the abovementioned studies. However, to date, no biosimilars have received an FDA interchangeable status. In contrast, the EMA does not provide any recommendation on interchangeability and automatic substitution of biosimilars and reference product [9]. The decision on whether to grant interchangeability status and allow substitution of the reference product and the biosimilar is made at a national level by each single European Union (EU) member state [14].

Providing a picture of switching patterns of biologics from a real-world setting may help discussion about interchangeability. Recent population-based studies have documented that almost 20% of patients switched between different ESAs during the first year of treatment, and this was more frequent towards originators than biosimilars in Italy [12, 15, 16]. Hyporesponsiveness can be a reason for switching from one ESA to another. In both CKD and cancer patients, several factors may contribute to ESA hyporesponsiveness, such as iron

deficiency, inflammation, and malnutrition status, while chronic hyperparathyroidism may affect ESA response in CKD patients specifically [17, 18].

This retrospective cohort study aimed to investigate the frequency and identify potential predictors of switching between biosimilar and originator ESAs during the first year of treatment in patients with cancer, CKD, or chemotherapy-related anemia from six large Italian geographic areas in the
years 2009–2015.

Materials and Methods

Study Design and Data Source

This was an observational, record-linkage, multi-database, retrospective cohort study carried out in six Italian Regions, covering a total population of more than 13 million inhabitants from all over Italy during a period ranging from 2009 to 2015. Fully anonymized data were retrieved from administrative databases of the catchment area of each participating center: Caserta, Palermo, and Treviso local health units (LHUs) and Tuscany, Umbria, and Lazio Regions. Individual patient-level data on dispensed drugs reimbursed by the NHS, hospital discharges, emergency department visits, exemptions from co-payment to the healthcare service, and laboratory tests were retrieved. Drug information was coded using the Anatomical Therapeutic Chemical (ATC) classification system and the Italian marketing authorization code (AIC), which allows distinction among biosimilar and originator ESAs, while the International Classification of Disease, Clinical Modification, Ninth Revision (ICD9-CM) was used to code diseases.

Study Population

All subjects with at least 1 year of database history and one ESA dispensed between 1 January 2009 and 31 December 2015 were identified. Furthermore, the study cohort was restricted to subjects without any ESA dispensing within 6 months prior to the first ESA dispensing date (index date [ID]), defined as incident ESA users. ESA users could be included in the analysis multiple times if they restarted an ESA treatment after at least 6 months' withdrawal.

Exposure to Study Drugs

Use of the following ESAs during the study period was assessed: epoetin alfa (Eprex®, Abseamed®, Binocrit®, Globuren®), epoetin zeta (Retacrit®), epoetin beta (Neorecormon®), epoetin theta (Eporatio®), darbepoetin alfa (Aranesp®, Nespo®), and methoxypolyethyleneglycol–epoetin beta (Mircera®). Abseamed®, Binocrit®, and Retacrit® are biosimilars of the reference epoetin alfa (Eprex®), while the other ESAs are still covered by the patent. Three main groups of substances were defined for the analyses: (1) reference epoetin alfa (Eprex®); (2) biosimilars of epoetin alfa (Abseamed®, Binocrit®, and Retacrit®); and (3) other patented ESAs (Neorecormon®, Eporatio®, Aranesp®, Nespo®, Globuren®, and Mircera®).

Switching

Switching was defined as any transition from one ESA to another one in a series of two consecutive dispensings during follow-up. In general, ESA users with at least two dispensings

were classified as (1) switchers—patients who experienced at least one switch; or (2) non-switchers— patients who received the same ESA during follow-up.
The following switch groups were specifically considered:
1. From reference epoetin alfa to biosimilar of epoetin alfa.
2. From reference epoetin alfa to other patented ESA.
3. From biosimilar of epoetin alfa to reference epoetin alfa.
4. From biosimilar of epoetin alfa to another biosimilar of epoetin alfa.
5. From biosimilar of epoetin alfa to other patented ESA.
6. From other patented ESA to reference epoetin alfa.
7. From other patented ESA to biosimilar of epoetin alfa.
8. From other patented ESA to another patented ESA.

Data Analysis
Incident ESA users were classified according to the type of dispensed ESA (reference epoetin alfa, biosimilar of epoetin alfa, and other patented ESAs) at the ID. The indication for use was mutually exclusively categorized as CKD or cancer, as recorded in the electronic therapeutic plan. In centers
where this information was not available, the indication for use was derived from various claims databases according to the algorithm described elsewhere [12].
In each participating center, incident users of each ESA were characterized at baseline in terms of demographic and clinical characteristics (e.g., baseline hemoglobin levels, transferrin, ferritin, sideremia), co-morbidities (including arrhythmia, arterial and venous thrombosis, diabetes mellitus,
heart failure, hypertension, cerebrovascular disease, respiratory disease, and hyperparathyroidism), stage of CKD/type of tumor, concomitant use of granulocyte colony-stimulating factor (G-CSF), iron preparations, vitamin B12, folic acid, vitamin A/D, drugs for treatment of hyperkalemia and hyperphosphatemia, type of ESA dispensed at ID, center, number of previous hospitalizations or blood transfusions, hypersensitivity reactions.
The frequency of simple switch (i.e., one switch, from A to B), multiple switch (i.e., two switches of three or more different ESAs, from A to B to C), and switch-back (i.e., two or more switches including a switch back to the first ESA dispensed, from A to B to A) during the first year of treatment was evaluated.

Statistical Analysis
The characteristics of incident ESA users at baseline were reported as mean ± standard deviation (SD) or frequency and percentage for continuous and categorical variables, respectively. When the distribution of continuous variables was skewed (i.e., values were not normally distributed), mean ± SD was replaced with median and interquartile range (IQR; i.e., first–third quartiles). To identify potential independent predictors of the first ESA switch incidence (i.e., time-to-event outcome), two multivariable shared frailty Cox models [19] were separately performed, according to the ESA users' indication for use. To account for heterogeneity between clusters, each model incorporated the center identification as the random effect covariate. Patient-level covariates were selected following the stepwise variable selection criterion (significance level for entry into the model: $p = 0.10$; significance level for staying in the model: $p = 0.05$) among

the following baseline covariates: age, sex, type of ESA and stage of CKD at ID, all co-morbidities evaluated any time prior to ID (i.e., diabetes, hypertension, arrhythmia, heart failure, cerebrovascular disease, respiratory disease, hyperparathyroidism), type of tumor evaluated within 1 year prior to ID (i.e., malignant neoplasm of lip, oral cavity and pharynx, malignant neoplasm of digestive organs and peritoneum, malignant neoplasm of respiratory and intrathoracic organs, malignant neoplasm of bone, connective tissue, skin and breast, malignant neoplasm of genitourinary organs, malignant neoplasm of other and unspecified sites, malignant neoplasm of lymphatic and hematopoietic tissue, benign neoplasms), and among the following time-dependent covariates: presence of hypersensitivity reactions, number of previous of blood transfusions, cumulative number of ESAs dispensed and hospitalizations, history of arterial and venous thrombosis, number of iron preparations, G-CSF, vitamin B12, folic acid, drugs for treatment of hyperkalemia and hyperphosphatemia, vitamin A/D prescriptions, and laboratory values (e.g., hemoglobin, ferritin, transferrin, serum iron levels). For each selected covariate, the independent association with the time-to-event outcome was estimated by the corresponding regression coefficient (which corresponds to the log hazard ratio [HR]), and thus the HR was derived in a straightforward manner along with its 95% confidence interval (CI). A two-sided p value < 0.05 was considered for statistical significance. All statistical analyses were performed using SAS ® version 9.3 (SAS Institute, Cary, NC, USA) and SPSS®/PC version 15 (SPSS Inc., Chicago, IL, USA).

Results

During the study period, a total population of 13,338,676 subjects registered in the study centers; 102,240 (0.8%) were incident ESA users [CKD = 61,242 (59.9%); cancer = 40,998 (40.1%)] (**Fig. 1**). As shown in **Table 1**, the sex distribution (male/female = 1) was homogeneous in both cohorts of CKD and cancer patients, with CKD patients being older (mean age ± SD: 76.0 ± 13.4 vs. 69.3 ± 13.4 years). Both CKD and cancer patients more frequently started the treatment with an originator ESA (CKD: 87.8%; cancer: 81.6%) than with a biosimilar. Compared with cancer patients, CKD patients were more likely to be affected by diabetes, hypertension, arrhythmia, heart failure, or chronic obstructive pulmonary disease and to receive more concomitant drugs.

During the first year of ESA treatment, 15,853 (15.5%) incident ESA users switched to another ESA (**Fig. 2**). This percentage was higher in CKD patients [n = 11,122 (18.2%)] than in cancer patients [n = 4731 (11.5%)].

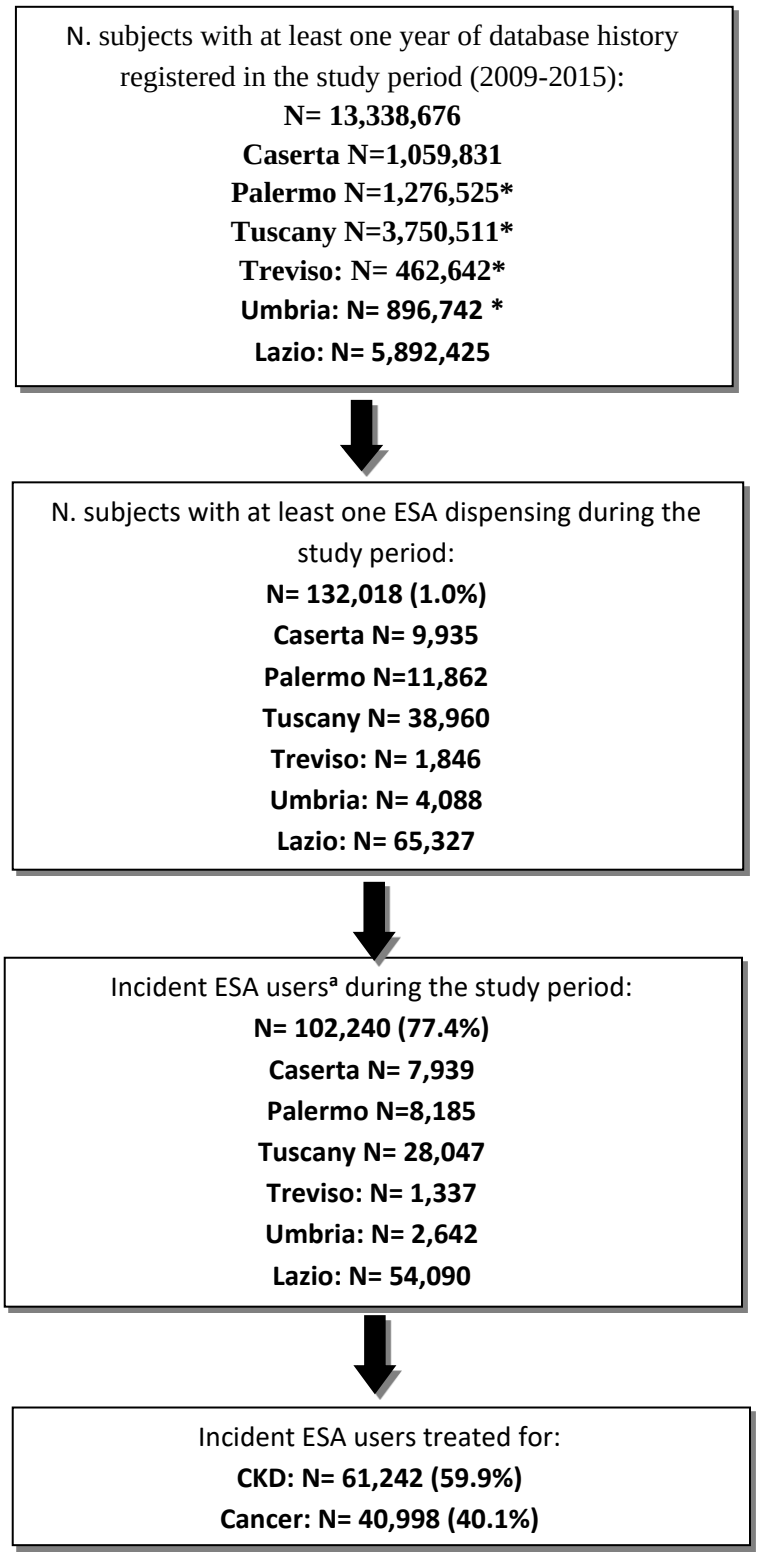
Among switchers, ESA users switched more frequently toward a patented ESA (82%) than toward a biosimilar (18%) (**Figs. 3, 4**). In cohorts of CKD and cancer patients, most patients starting with the reference epoetin alfa switched to other patented ESAs within the first year of treatment and 8.4% and 4.6% of incident users of other patented ESAs with CKD and cancer, respectively, switched to another patented ESA. Moreover, 3.1% and 3.7% of biosimilar users with CKD and cancer, respectively, made at least one switch to another biosimilar. Simple switch was more common (62.2% of the switchers) than multiple (23.5%) or backward switch (14.3%) (**Fig. 5**).

Compared with reference epoetin alfa, initiating biosimilars/other patented ESAs increased the probability of switching in cancer patients (biosimilar of epoetin alfa HR: 1.76, 95% CI 1.60–1.92; other patented ESAs HR: 1.56, 95% CI 1.45–1.68) and reduced it in CKD patients (biosimilar of epoetin alfa HR: 0.79, 95% CI 0.70–0.90; other patented ESAs HR: 0.56, 95% CI

0.52–0.61). In the CKD cohort, the cumulative number of transfusions and vitamin A/D prescriptions as well as CKD severity (stage V HR: 1.29, 95% CI 1.11–1.49; dialysis HR: 1.55, 95% CI: 1.43–1.69) increased the probability of switching (**Table 2**).

In the cancer group, the cumulative number of transfusions, iron preparations, as well as a history of hyperparathyroidism [odds ratio (OR) 2.07, 95% CI 1.15–3.75] or arterial and venous thrombosis (HR: 1.97, 95% CI 1.31–2.98) were predictors of switching (**Table 3**); a history of gastrointestinal tumors (HR: 0.71, 95% CI 0.61–0.83) and the cumulative number of antineoplastic agents (HR: 0.98, 95% CI 0.97–0.99) reduced the probability of switch.

Fig. 1 Identification of incident erythropoiesis-stimulating agent (ESA) users in the six participating centers.



*Data available for the years 2009–2014.

[a]ESA user without any ESAs dispensed in the 6 months prior to the index date. **CKD:** chronic kidney disease

Table 1. Characteristics at baseline of incident erythropoiesis-stimulating agent users, stratified by indication for use.

	CKD N= 61,242	**Cancer N= 40,998**
Sex [n (%)]		
M	30,135 (49.2)	20,866 (50.9)
F	31,107 (50.8)	20,132 (49.1)
Age (years) [mean ± SD]	76.0 ± 13.4	69.3 ± 13.2
Age category [n (%)]		
<45	2,217 (3.6)	2,199 (5.4)
45-64	8,207 (13.4)	10,971 (26.8)
65-79	19,799 (32.3)	17,889 (43.6)
≥80	31,019 (50.6)	9,939 (24.2)
Baseline Hb (g/dL) [mean± SD]	10.2 ± 1.1	9.8 ± 1.1
LHU [n (%)]		
Caserta	4,456 (7.3)	3,483 (8.5)
Palermo	5,274 (8.6)	2,911 (7.1)
Tuscany	16,188 (26.4)	11,859 (28.9)
Treviso	794 (1.3)	543 (1.3)
Umbria	2,001 (3.3)	641 (1.6)
Lazio	32,529 (53.1)	21,561 (52.6)
Type of ESA [n (%)]		
Reference epoetin alfa	11,709 (19.1)	14,950 (36.5)
Biosimilar of epoetin alfa	7,485 (12.2)	7,530 (18.4)
Other patented ESA	42,048 (68.7)	18,518 (45.2)
Hospitalizations[a] (n) [median (IQR)]	1 (0-2)	2 (1-3)
Previous blood transfusions[b] [n (%)]	5,842 (9.5)	6,678 (16.3)
Hypersensitivity reactions[c] [n (%)]	322 (0.5)	192 (0.5)
Comorbidities[d] [n (%)]		
Arrhythmia	22,405 (36.6)	7,627 (18.6)
Arterial and venous Thrombosis	996 (1.6)	678 (1.7)
Diabetes mellitus	27,004 (44.1)	10,933 (26.7)
Heart failure	14,438 (23.6)	2,435 (5.9)
Hypertension	35,147 (57.4)	13,114 (32)
Cerebrovascular Disease	10,713 (17.5)	2,845 (6.9)
Respiratory disease	8,684 (14.2)	3,050 (7.4)
Hyperparathyroidism	183 (0.3)	45 (0.1)
CKD stage [n (%)]		
1 (GFR ≥ 90)	1,308 (2.1)	159 (0.4)
2 (90 > GFR ≥ 60)	2,416 (3.9)	279 (0.7)
3 (60 > GFR ≥ 30)	7,611 (12.4)	562 (1.4)
4 (30 > GFR ≥ 15)	6,027 (9.9)	246 (0.6)
5 (GFR < 15)	4,143 (6.8)	133 (0.3)
Dialysis	9,321 (15.2)	369 (0.9)
Not classified	39,737 (64.9)	39,619 (96.6)
Type of tumor[a] [n (%)]		
Malignant Neoplasm of Lip, Oral Cavity, And Pharynx	5 (0.0)	182 (0.4)
Malignant Neoplasm of Digestive	160 (0.3)	2,974 (7.3)

Organs And Peritoneum		
Malignant Neoplasm of Respiratory And Intrathoracic Organs	65 (0.1)	2,934 (7.2)
Malignant Neoplasm of Bone, Connective Tissue, Skin, And Breast	40 (0.1)	1,409 (3.4)
Malignant Neoplasm of Genitourinary Organs	233 (0.4)	2,393 (5.8)
Malignant Neoplasm of Other And Unspecified Sites	373 (0.6)	9,136 (22.3)
Malignant Neoplasm of Lymphatic And Hematopoietic Tissue	58 (0.1)	526 (1.3)
Benign Neoplasms	58 (0.1)	310 (0.8)
Concomitant drugs[c] [n (%)]		
G-CSF	148 (0.2)	9,870 (24.1)
Iron preparations	23,394 (38.2)	10,524 (25.7)
Vitamin B_{12}	1,850 (3.0)	1,003 (2.4)
Folic acid	9,099 (14.9)	5,203 (12.7)
Vitamin A/D	14,122 (23.1)	3,366 (8.2)
Drugs for treatment of hyperkalemia and hyperphosphatemia	5,110 (8.3)	389 (0.9)
Laboratory values[a,e]		
Transferrin (mg/dL; normal range: 200-400) [mean ± SD]	209.3 ± 65	222.8 ± 63.8
Sideremia (mcg/dL; normal range: M=75-160; F=60-150) [mean ± SD]	58.4 ± 39.2	71.8 ± 49.5
Ferritin (mcg/L; normal range: M=60-300; F=30-150) [median (IQR)]	187.1 (80.2-375.3)	248.8 (114-579.7)

CKD: chronic kidney disease, ESA: erythropoiesis-stimulating agent, F: females, G-CSF: granulocyte colony-stimulating factor, Hb: hemoglobin, ID: index date, IQR: interquartile range, LHU: local health units, M: males, SD: standard deviation

[a] Evaluated within 1 year prior to ID

[b] Evaluated within 6 months prior to ID

[c] Evaluated within 3 months prior to ID

[d] Evaluated any time prior to ID

[e] Available only for Treviso, Caserta, and Lazio centers

Fig. 2 Frequency of switching among incident erythropoiesisstimulating agent users during the first year of treatment, stratified by center.

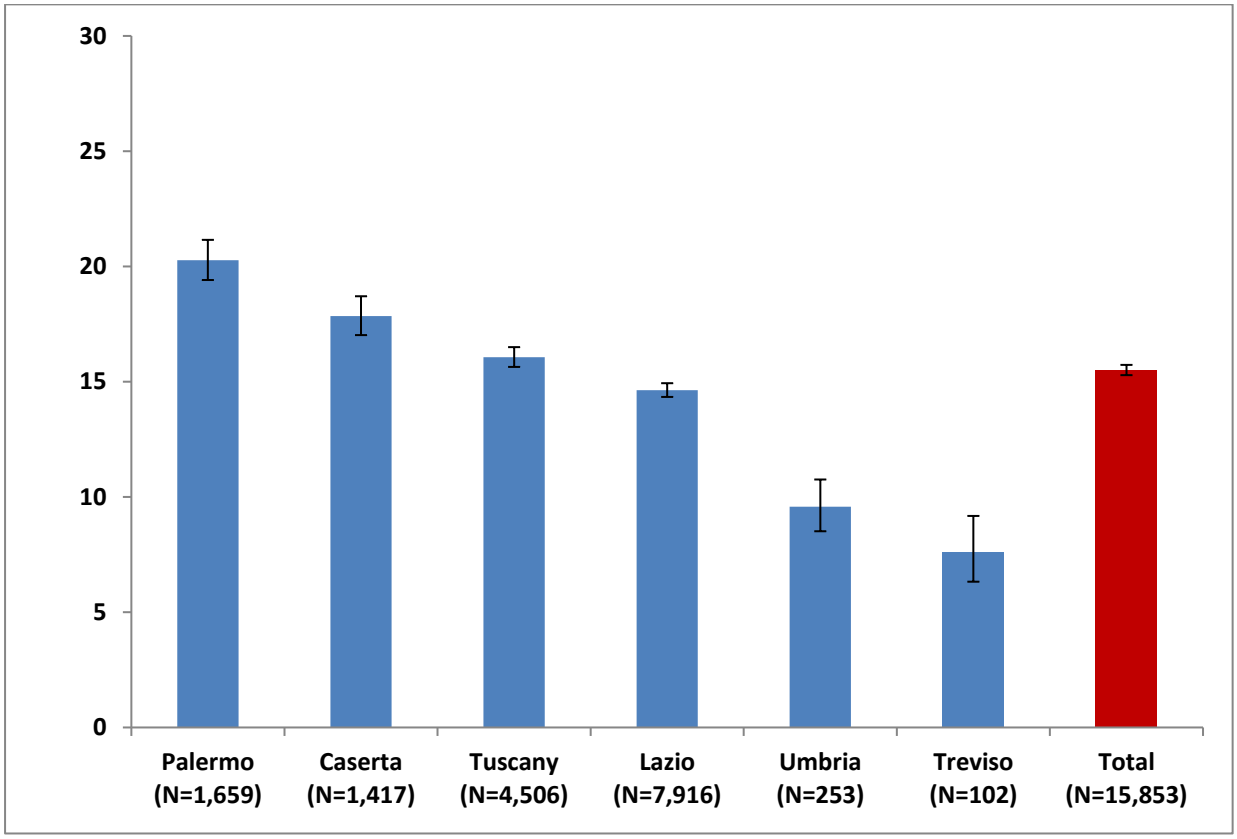
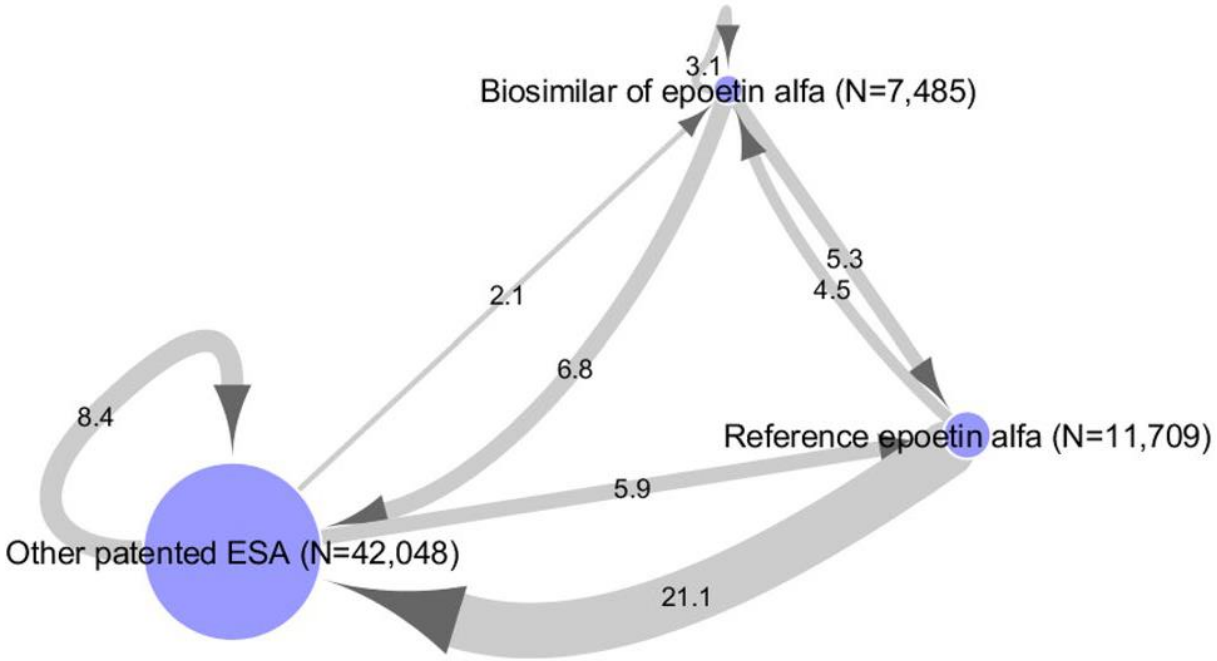
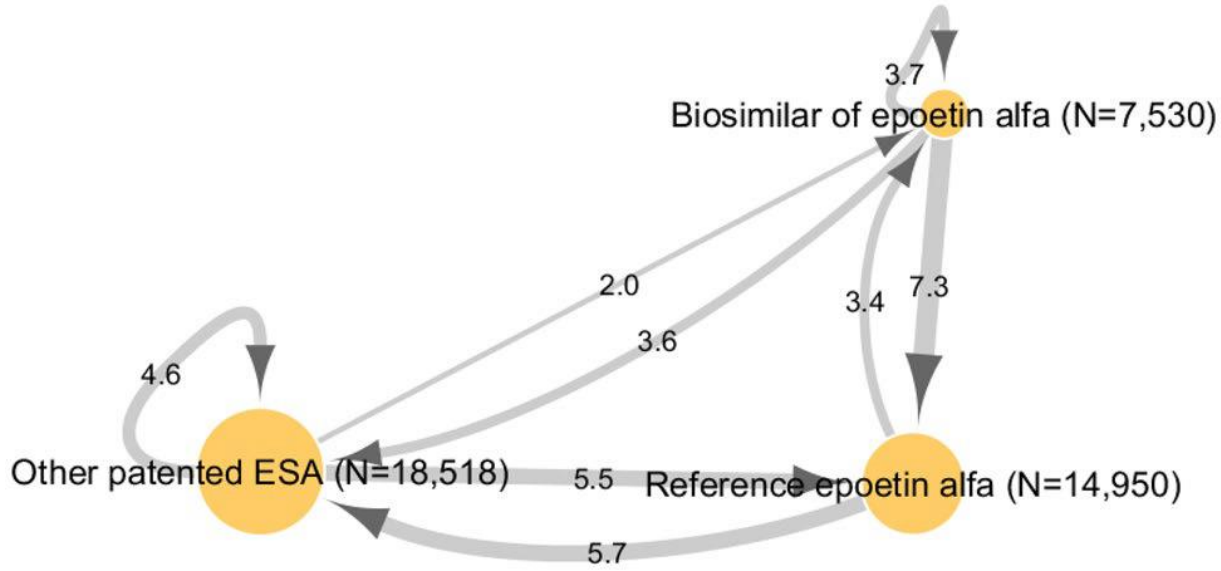


Fig. 3 Switching pattern of different erythropoiesis-stimulating agents (ESAs) during the first year of treatment in chronic kidney disease.



The size of the nodes indicates the number of ESA users and the size of the arrows indicates the proportion of users (minimum 2.1%) who switched from one product to another; only the first switch after the index date was considered. The percentage was calculated as the number of switchers out of the total number of incident ESA users. N number of users

Fig. 4 Switching pattern of different erythropoiesis-stimulating agents (ESAs) during the first year of treatment in cancer.



The size of the nodes indicates the number of users and the size of the arrows indicates the proportion of users (minimum 2.0%) who switched from one product to the another; only the first switch after the index date was considered. The percentage was calculated as the number of switchers out of the total number of incident ESA users. N number of users

Fig. 5 Switching pattern among incident erythropoiesis-stimulating agent users during the first year of treatment, stratified by type of switch.

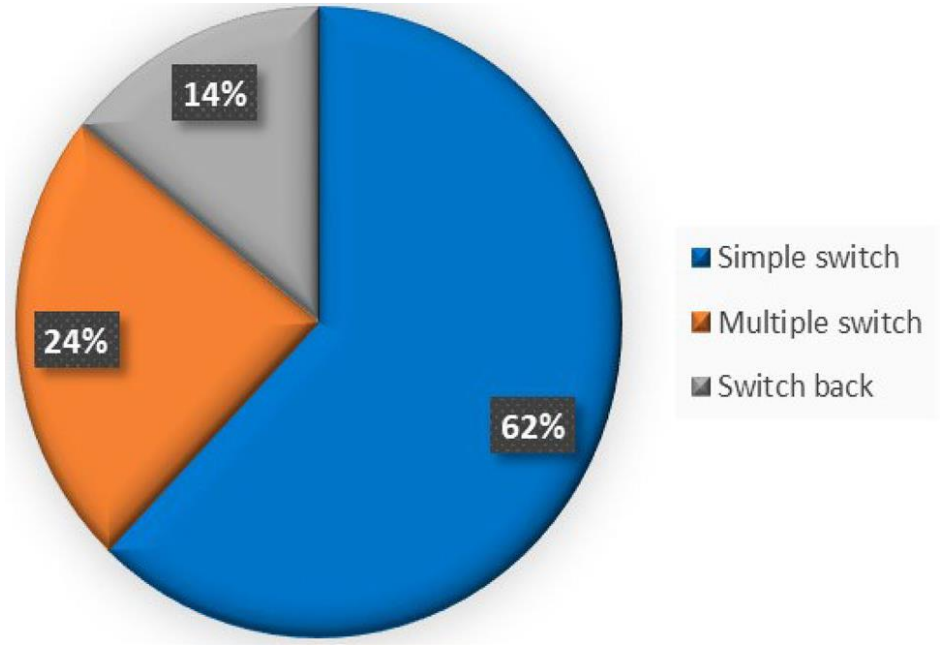


Table 2. Multivariate frailty Cox models to identify potential predictors of switching in chronic kidney disease.

	HR (95% CI) N= 61,242	**P-value**
Age	0.99 (0.99-1.00)	<0.001
Type of ESA		
Reference product	**Reference**	
Biosimilar	0.79 (0.70-0.90)	<0.001
Other ESAs covered by patent	0.56 (0.52-0.61)	<0.001
ESAs dispensing	1.00 (1.00-1.00)	<0.001
Previous blood transfusions	1.03 (1.01-1.06)	0.010
CKD stage		
1 (GFR ≥ 90)	**Reference**	
2 (90 > GFR ≥ 60)	0.83 (0.70 0.98)	0.030
3 (60 > GFR ≥ 30)	0.82 (0.71-0.95)	0.009
4 (30 > GFR ≥ 15)	0.95 (0.82-1.10)	0.532
5 (GFR < 15)	1.29 (1.11-1.49)	<0.001
Dialysis	1.55 (1.43-1.69)	<0.001
Concomitant drugs dispensed		
Vitamin A/D	1.02 (1.01-1.04)	0.003

CI confidence interval, CKD chronic kidney disease, ESA erythropoietin-stimulating agent, GFR glomerular filtration rate, HR hazard ratio

Table 3. Multivariate frailty Cox models to identify potential predictors of switching in cancer

	HR (95% CI) N= 40,998	**P-value**
Age	1.00 (1.00-1.01)	<0.001
Type of ESA		
Reference epoetin alpha	**Reference**	
Biosimilar of epoetin alpha	1.76 (1.60-1.92)	<0.001
Other patented ESA	1.56 (1.45-1.68)	<0.001
ESAs dispensed	1.01 (1.01-1.01)	<0.001
Previous blood transfusions	1.10 (1.08-1.13)	<0.001
Comorbidities		
Arterial and venous thrombosis	1.97 (1.31-2.98)	0.001
Hyperparathyroidism	2.07 (1.15-3.75)	0.016
Type of tumor		
Malignant Neoplasm Of Digestive Organs And Peritoneum	0.71 (0.61- 0.83)	<0.001
Concomitant drugs dispensed		
G-CSF	0.98 (0.96-0.99)	0.007
Iron preparations	1.02 (1.01-1.03)	<0.001
Antineoplastic agents	0.98 (0.97-0.99)	<0.001

CI confidence interval, ESA erythropoietin-stimulating agent, G-CSF granulocyte colony-stimulating factor, HR hazard ratio

Discussion

This population-based study provided real-world data on the switching pattern between ESAs and the potential predictors of switching in a large cohort of Italian patients. As reported in previous studies [12, 16], our results suggest that switching between different ESAs was frequent (15.5%) and the switch was more common toward an originator ESA than a biosimilar (82% vs. 18%) in both the CKD and cancer groups. This was in line with the findings of two other Italian drug utilization studies using claims databases [12, 15]. Debate is still ongoing, both from a scientific and regulatory perspective, about the interchangeability and automatic substitution of originators and biosimilars.

In Europe, decisions on substitution depend on the single national authority [14]; specifically in Italy, the Italian Drug Agency (AIFA) excluded the interchangeability status during the study years and did not allow automatic therapeutic substitution of reference products with biosimilars [20]. However, the most recent position paper on biosimilars took a position in favor of biosimilar and reference product interchangeability [10], without mentioning automatic substitution between originators and biosimilars.

Simple switch was common and, among switchers, around 15% switched back to the previously used epoetin, in line with a previous Italian study [15]. According to Lonnemann and Wrenger [21], the high frequency of switching among ESAs is likely to be attributed to ineffectiveness (missed achievement of a therapeutic goal, e.g., a predefined hemoglobin threshold), tolerability, or physician/patient preference due to differences in the frequency or route of administration between various ESAs, which may affect patient compliance. However, a recent Italian post-marketing database study has so far provided reassuring data on the effectiveness and safety of switching between originator and biosimilar ESAs [22].

Our study showed that variables such as type of ESA dispensed to naïve patients, severity of CKD, co-morbidities, or concomitant drugs were potential predictors of switching in both cohorts of patients. In CKD patients, we found that advanced CKD stages, compared with the early stages, as well as cumulative numbers of transfusions were associated with an increase of switching probability; this may be due to a hyporesponsiveness to the ESA drug dispensed at ID, with a consequent need for transfusions and drug switch. Nagata et al. [23] indicated that in cancer patients, anemia can be caused by various factors, including bleeding, malnutrition, bone marrow suppression due to chemotherapy or radiotherapy, and coexisting infectious disease, and these factors may contribute to ESA hyporesponsiveness [23], which may in turn increase the switching probability. Thus, it is not surprising that transfusions and iron preparations are considered possible predictors of switch in cancer patients.

In cancer patients, a history of arterial and venous thrombosis (potentially induced by epoetin itself) may be a potential predictor of switching, as high dosages of epoetins may increase cardiovascular risk; because of the high dosage of epoetins used for the treatment of chemotherapy-related anemia, thrombosis could be an adverse drug reaction, inducing the switching [24, 25]. Furthermore, a history of hyperparathyroidism was associated with a two-fold increased probability of switching because it may indirectly cause hyporesponsiveness to epoetins; as reported by Grützmacher et al. [26], hyperparathyroidism may decrease the synthesis of endogenous erythropoietin and decreases the half-life of erythrocytes, leading to the drug switch.

Strengths and Limitations

This population-based study has several strengths, the main one being the possibility to analyze the data on ESA dispensing from six large geographic areas, covering a total population of more than 13 million inhabitants over a period of 7 years. Moreover, since the first biosimilar ESA was marketed in Italy in 2007, around 15 years of real-world data have been cumulated on the switching pattern between ESAs. Finally, thanks to the availability of an electronic therapeutic plan, information on the indication for use and dosing regimen, beyond the exact brand name and number of dispensed packages, was available. However, the study also has some limitations. Firstly, claims data were available from all participating centers until 31 December 2014 but laboratory values were only available in the Treviso, Caserta, and Lazio centers. Secondly, the dispensing of some ESAs as well as concomitant drugs (i.e., iron preparations) might not have been fully captured by the LHUs' databases as these drugs may initially be dispensed directly by public hospitals, thus not being recorded in the study data sources. However, although this limitation may lead to a slight underestimation of the observed total epoetin consumption, it is unlikely that this would affect the study results. Thirdly, we were not able to ascertain any reasons for switching. Finally, despite good regional coverage of our data, our findings may not be fully generalized to the Italian general population in light of substantial regional differences. However, this database network has previously been used for the post-marketing assessment of biosimilar use, as described in more detail in previous publications [12, 27–29], and has generated realworld evidence that has been used in the updated guidelines on management of cancer-related anemia of the American Society of Clinical Oncology/American Society of Haematology [30]. Indeed, data on use of ESAs from these databases are consistent with that presented in the national report on medicines use in Italy regarding drug consumption [11].

Conclusions

This study provided real-world data on the switching pattern between ESAs and the potential predictors of switching in a large cohort of Italian patients. Numerous switches between different ESAs have been observed in CKD and cancer patients, but this occurs more frequently toward an originator than toward a biosimilar ESA, raising concerns about the interchangeability of different ESAs. These results may be very useful to support clinical decisions related to switching drug therapies and promote better health policies to improve the uptake of biosimilars in the general population.

References

1. Italian Association of Medical Oncology. Linee guida gestione della tossicità ematopoietica in oncologia. 2017. http://media.aiom.it/userfiles/files /doc/LG/2017_LGAIO M_Toss_emato poietica.pdf. Accessed 2 Oct 2019.
2. Aapro MS, Link H. September 2007 update on EORTC guidelines and anemia management with erythropoiesis-stimulating agents. Oncologist. 2008;13(Suppl 3):33–6.
3. Rizzo JD, Brouwers M, Hurley P, Seidenfeld J, Somerfield MR, Temin S. American society of clinical oncology/american society of hematology clinical practice guideline update on the use of epoetin and darbepoetin in adult patients with cancer. J Oncol Pract. 2010;6(6):317–20.

4. European Medicines Agency. European public assessment reports. https://www.ema.europa.eu/en/medicines/search_api_aggregation_ema_medicine_types/field_ema_med_biosimilar. Accessed 31 July 2019.
5. Quintiles. The impact of biosimilar competition in Europe. Quintiles IMS. 2017. http://www.medicinesforeurope.com/wp-content/uploads/2017/05/IMS-Biosimilar-2017_V9.pdf. Accessed 2 Oct 2019.
6. Dylst P, Vulto A, Simoens S. Barriers to the uptake of biosimilars and possible solutions: a Belgian case study. Pharmacoeconomics. 2014;32(7):681–91.
7. Rompas S, Goss T, Amanuel S, Coutinho V, Lai Z, Antonini P, et al. Demonstrating value for biosimilars: a conceptual framework. Am Health Drug Benefits. 2015;8(3):129–39.
8. Trifirò G, Marcianò I, Ingrasciotta Y. Interchangeability of biosimilar and biological reference product: updated regulatory positions and pre- and post-marketing evidence. Expert Opin Biol Ther. 2018;18(3):309–15.
9. European Medicines Agency (EMA). Biosimilars in the EU, Information guide for healthcare professionals. 2017. https ://www.ema.europ a.eu/en/docum ents/leafl et/biosi milar s-eu-infor matio n-guide-healt hcare -profe ssion als_en.pdf. Accessed 2 Oct 2019.
10. Agenzia Italiana del Farmaco (AIFA). Secondo position paper AIFA sui Farmaci Biosimilari. 2018.
11. Agenzia Italiana del Farmaco (AIFA). L'uso dei farmaci in Italia. Rapporto Nazionale anno 2017. 2018. http://www.aifa.gov.it/sites/defau lt/files /Rappo rto_OsMed 2017_AIFA.pdf. Accessed 2 Oct 2019.
12. Ingrasciotta Y, Giorgianni F, Bolcato J, Chinellato A, Pirolo R, Tari DU, et al. How much are biosimilars used in clinical practice? A retrospective Italian population-based study of erythropoiesis-stimulating agents in the years 2009–2013. BioDrugs. 2015;29(4):275–84.
13. Food and Drug Administration. Considerations in demonstrating interchangeability with a reference product guidance for industry. 2017. https ://www.fda.gov/downl oads/Drugs /Guida nceCo mplianceRe gulat oryIn forma tion/Guida nces/UCM53 7135.pdf. Accessed 2 Oct 2019.
14. European Medicines Agency (EMA). Committee for Medicinal Products for Human Use (CHMP): guideline on similar biological medicinal products. 2014. https ://www.ema.europ a.eu/en/documents/scien tific -guide line/guide line-simil ar-biolo gical -medic inalproducts-rev1_en.pdf. Accessed 2 Oct 2019.
15. Loiacono C, Sgroi C, Coppolino S, Cannata A, Ferrara R, Arcoraci V. How much are biosimilars used in Southern Italy? A retrospective analysis of epoetin utilization in the local health unit of Messina in the years 2010–2011. BioDrugs. 2012;26(2):113–20.
16. D'Amore C, Da Cas R, Rossi M, Traversa G. Switching between epoetins: a practice in support of biosimilar use. BioDrugs. 2016;30(1):27–32.
17. Locatelli F, Andrulli S, Memoli B, Maffei C, Del Vecchio L, Aterini S, et al. Nutritional-inflammation status and resistance to erythropoietin therapy in haemodialysis patients. Nephrol Dial Transplant. 2006;21(4):991–8.
18. KDOQI, National Kidney Foundation. KDOQI clinical practice guidelines and clinical practice recommendations for anemia in chronic kidney disease. Am J Kidney Dis. 2006;47(5 Suppl 3):S11–145.
19. Fine JP, Glidden DV, Lee KE. A simple estimator for a shared frailty regression model. J R Stat Soc Ser B Stat Methodol. 2003;65(1):317–29.

20. Agenzia Italiana del Farmaco (AIFA). Position paper sui farmaci biosimilari (28/05/2013). http://www.agenz iafar maco.gov.it/sites/defau lt/files /AIFA_POSITION_PAPERFARMA CI_BIOSIMILARI.pdf. Accessed 2 Oct 2019.
21. Lonnemann G, Wrenger E. Biosimilar epoetin zeta in nephrology—a single-dialysis center experience. Clin Nephrol. 2011;75(1):59–62.
22. Belleudi V, Trotta F, Addis A, et al. Italian Biosimilar Network (ItaBioNet). Effectiveness and safety of switching originator and biosimilar epoetins in patients with chronic kidney disease in a large-scale Italian cohort study. Drug Saf. 2019. 23. Nagata S, Ikegaya N, Ogino S, Uchida S, Itaya M, Momita A, et al. The resection of thyroid cancer was associated with the resolution of hyporesponsiveness to an erythropoiesis-stimulating agent in a hemodialysis patient with aceruloplasminemia. Intern Med. 2017;56(7):805–10.
24. Solomon SD, Uno H, Lewis EF, Eckardt K-U, Lin J, Burdmann EA, et al. Erythropoietic response and outcomes in kidney disease and type 2 diabetes. N Engl J Med. 2010;363(12):1146–55.
25. Gilbertson DT, Ebben JP, Foley RN, Weinhandl ED, Bradbury BD, Collins AJ. Hemoglobin level variability: associations with mortality. Clin J Am Soc Nephrol. 2008;3(1):133–8.
26. Grützmacher P, Ehmer B, Limbach J, Messinger D, Kulbe KD, Scigalla P. Treatment with recombinant human erythropoietin in patients with aluminum overload and hyperparathyroidism. Blood Purif. 1990;8(5):279–84.
27. Ingrasciotta Y, Giorgianni F, Marcianò I, Bolcato J, Pirolo R, Chinellato A, et al. Comparative effectiveness of biosimilar, reference product and other erythropoiesis-stimulating agents (ESAs) still covered by patent in chronic kidney disease and cancer patients: an Italian population-based study. PLoS One. 2016;11(5):1–16.
28. Marcianò I, Ingrasciotta Y, Giorgianni F, Bolcato J, Chinellato A, Pirolo R, et al. How did the introduction of biosimilar filgrastim influence the prescribing pattern of granulocyte colonystimulating factors? Results from a multicentre, population-based study, from five Italian centres in the years 2009–2014. BioDrugs. 2016;30(4):295–306.
29. Marcianò I, Ingrasciotta Y, Giorgianni F, et al. Pattern of use of biosimilar and originator somatropin in italy: a population-based multiple databases study during the years 2009–2014. Front Endocrinol (Lausanne). 2018;9:95.
30. Bohlius J, Bohlke K, Castelli R, Djulbegovic B, Lustberg MB, Martino M, et al. Management of cancer-associated anemia with erythropoiesis-stimulating agents: ASCO/ASH clinical practice guideline update. J Clin Oncol. 2019;37(15):1336–51. 31. Ministero della Salute, Agenzia Italiana del Farmaco (AIFA). Circolare AIFA del 3 agosto 2007. Linee guida per la classificazione e conduzione degli studi osservazionali sui farmaci. http://xoomer.virgi lio.it/pgiuff/osser vazio nali.pdf. Accessed 14 Dec 2015.

4.3. Effectiveness and safety of switching originator and biosimilar epoetins in patients with chronic kidney disease

Adapted from:

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Abstract

Introduction: Real-world data on the comparative effectiveness and safety of switching among different epoetins (including originators and biosimilars) are limited. In light of current debate about interchangeability, prescribers, some patient groups and decision makers are calling for additional post-marketing evidence on the clinical effects of switching between originator and biosimilar epoetins in chronic kidney disease (CKD) patients.

Objective: The objective of this study was to evaluate the effectiveness and safety of switching versus non-switching and of switching from originator/biosimilar epoetin alpha (ESA α) to any other epoetin in CKD patients.

Methods: An observational, record-linkage, multi-database, retrospective cohort study was carried out in four Italian geographical areas. All subjects with at least one ESA α dispensing between 1 January 2009 and 31 December 2015 were retrieved. Switching was defined as any transition between originator/biosimilar ESA α to any other epoetin in a series of two consecutive prescriptions up to 2 years. Switchers were matched 1:1 with non-switchers by baseline propensity score and by duration of ESA α treatment. Switchers and non-switchers were followed up from switching date to a maximum of 1 year. Lack of effectiveness and safety of switching versus non-switching were evaluated through Cox regression models (hazard ratio [HR], 95% confidence interval [CI]). A direct comparison between the two switcher categories (switchers from originator/biosimilar ESA α to any other epoetin) was also performed.

Results: Overall, 14,400 incident users of ESA α for anaemia due to CKD (61.4% originator, 38.6% biosimilar) were available for analysis. During the follow-up, we found no differences on effectiveness (HR 1.02, 95% CI 0.79–1.31 originators; HR 1.16, 95% CI 0.75–1.79 biosimilars) and safety outcomes (HR 1.08, 95% CI 0.77–1.50 originators; HR 1.20, 95% CI 0.66–2.21 biosimilars) between switchers and non-switchers of ESA α. Cumulative probabilities of recording an adverse event, either in terms of lack of effectiveness or safety issue, were the same for two switching categories.

Conclusions: In this large-scale Italian observational multi-database study, switching versus non-switching as well as switching from biosimilar/originator ESA α to any other epoetin in CKD patients is not associated with any effectiveness and safety outcomes.

Introduction

The erythropoiesis-stimulating agents (ESAs) play a major role in the management of anaemia in several therapeutic settings. In particular, benefits with these drugs for the treatment of anaemia that is induced by chemotherapy or associated to chronic kidney disease (CKD) are well-documented [1–6]. Since 2007 in Europe, the biosimilar version of epoetin alpha (ESA α) has been available, following approval by the European Medicines Agency (EMA) on the basis of absence of clinically meaningful differences in safety, efficacy and immunogenicity as compared to the reference product [7].

In general, the uptake of biosimilars is heterogeneous across countries and therapeutic areas, highlighting differences in the confidence of clinicians in prescribing these biologics [8]. In fact, the acceptance of biosimilars in the medical community continues to be limited in some countries and therapeutic areas even though they represent a great opportunity for the sustainability of the national health services (NHSs) [9–14]. Biosimilar consumption in Italy in 2017 represented 51% of the entire class of ESAs, which was strongly influenced by the implementation of different, regional healthcare policies [15]. Recent population-based studies documented that almost 20% of patients switched among different ESAs during the first year of treatment, even if this was more frequently toward originators rather than biosimilars [16–18].

A recent systematic review based on randomised clinical trial (RCT) data evaluating the evidence on switching among different ESAs highlighted an overall therapeutic equivalence in those switching to any ESA [19]. In addition, spontaneous reporting systems as well as post-marketing RCTs did not detect any drug safety signal concerning switching from one epoetin to another [20]. While post-marketing evidence has been satisfactorily cumulated about the comparable benefit/risk profile of CKD patients starting a firstever treatment with either biosimilar or originator ESAs in routine care [21–25], the effect of switching among different ESAs on 'hard' clinical outcomes (i.e. dyscrasias, major cardiovascular events [MACE], etc.) in a real-world setting remains not fully investigated [26].

For this reason, this large-scale observational study was aimed at evaluating the comparative effectiveness and safety of switching from ESA α (both originator or biosimilars) to other ESAs versus non-switchers in CKD patients. The secondary objective of this study was to assess a direct comparison among switchers, i.e. those switching from the ESA α originator versus those switching from biosimilars.

Methods

Study Design and Data Source

We conducted an observational, record-linkage, multi-database, retrospective cohort study using healthcare databases from four Italian areas, located in the central and southern part of the country, covering a total population of more than 12 million inhabitants.

Fully anonymised data were retrieved from administrative databases of the catchment area of each participating centre (Lazio and Tuscany Regions, and Caserta and Palermo Local Health Units). In particular, individual-level information was retrieved on dispensed drugs reimbursed by the NHS, hospital discharges, emergency department (ED) visits, exemptions from co-payment to healthcare services, and prescriptions of laboratory tests. The Anatomical Therapeutic Chemical (ATC) classification system was used to code drugs, while the International Classification of Disease, Clinical Modification, Ninth Revision (ICD9-CM) was

used to code diseases in relation to healthcare services payment exemption, the diagnoses at hospital discharges and the reasons for ED visits.

Study Population

All subjects with at least one ESA α (originator; Eprex®, Janssen-Cilag SpA, Milan, Italy) or biosimilar (Abseamed®, Medice Arzneimittel Pütter GmbH Co. KG, Iserlohn, Germany; Binocrit®, Sandoz GmbH, Kundl, Austria; and Retacrit®, Pfizer Europe MA EEIG, Bruxelles, Belgio) dispensing between 1 January 2009 and 31 December 2015 were considered. The date of the first dispensing was identified as the baseline date. In order to capture the clinical history through the health information system, only patients with at least 1 year of health assistance prior to the baseline date were selected. Furthermore, the study cohort was restricted to subjects without any ESA prescriptions in the 6 months before baseline (new users) and who were treated because they had a recorded diagnosis of CKD. Finally, patients who did not receive a second ESA dispensing within 120 days were discarded; this cut-off limit was chosen considering the mean duration of the therapy regimen recorded by the Therapeutic Plan Register [23].

Exposure

For each subject, all consecutive ESA prescriptions up to the 2 years following the baseline date were retrieved. Two prescriptions were defined as consecutive if the time between them was ≤ 120 days. ESAs were grouped into four mutually exclusive categories: (1) ESA α originator; (2) ESA α biosimilar; (3) short-acting epoetins (Neorecormon®, Roche Registration GmbH, Grenzach-Wyhlen, Germany; Eporatio®, Ratiopharm GmbH, Ulm, Germany); and (4) long-acting epoetins (Aranesp®, Amgen Europe B.V., Breda, Netherlands; Nespo®, Dompé Biotec S.p.A., Milan, Italy; Mircera®, Roche Registration GmbH, Welwyn Garden City, UK). Considering all consecutive ESA prescriptions, switching from ESA α (whether biosimilar or not) was defined as any transition to another ESA category, while the nonswitcher cohort consisted of subjects with at least two consecutive prescriptions and without any ESA transition.

Covariates

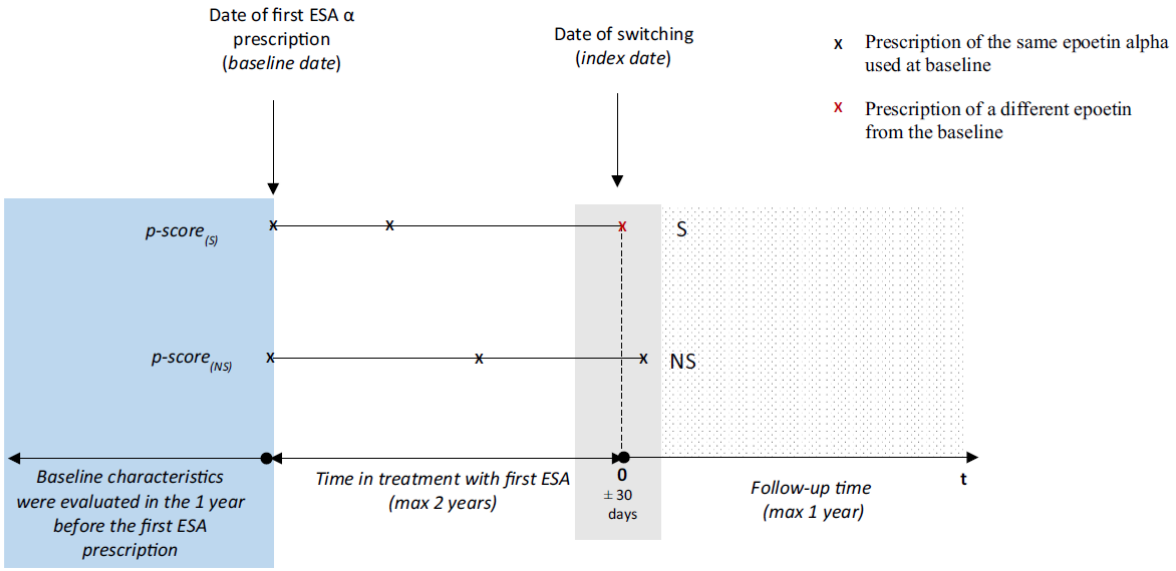
Demographic and clinical characteristics of the cohort at the baseline date were retrieved. More specifically, age, sex, geographical area, factors related to anaemia (blood transfusion, hospitalisation due to anaemia, iron supplementation), indication for ESA use (dialysed/non-dialysed CKD) and co-morbidities/concomitant medications (cancer, diabetes mellitus, hypertension, arrhythmia, heart failure, cerebrovascular events, thrombosis, respiratory disease, hyperparathyroidism, hyperkalaemia, hyperphosphataemia, folic acid, vitamins, non-steroidal anti-inflammatory drugs [NSAIDs]) were retrieved.

Matching

Within each ESA α users group (i.e. initiators of originator or biosimilar) a matched cohort was created to compare the risk of study outcomes in switchers versus non-switchers. For this purpose, we calculated a propensity score based on baseline characteristics. For the switcher group, the duration of ESA α treatment was measured considering the time difference between the baseline date and the date of switching (index date [ID]). Switchers were matched 1:1 with

nonswitchers by propensity score (caliper = 0.10), geographical area and duration of ESA α treatment (± 30 days) (**Fig. 1**).
Only subjects without lack of effectiveness and without safety events during the 90 days prior to switching were considered.

Fig. 1 Study design.



Switchers (S) were matched with non-switchers (NS) 1:1 by propensity score (caliper = 0.10) and time in treatment with first epoetin alpha (ESA α) (± 30 days). ESA erythropoiesis-stimulating agent, max maximum.

Follow-Up

All patients were followed from the ID until one of the following events, whichever came first: treatment discontinuation (i.e. 120 days lag time following the last dispensing), transferring out from the catchment area, study outcome, switch, 1 year or end of the study (31 December 2016).

Outcomes

The outcomes of interest concerned both the effectiveness and safety of ESAs. Blood transfusions or anaemia were considered as proxies for lack of effectiveness, while MACE, dyscrasias or hypersensitivity reactions were evaluated as proxies for safety.

Statistical Analysis

The comparison of patients' characteristics between switchers and non-switchers, before and after matching was performed within the two groups of ESA α users (i.e. originator or biosimilars). To assess the effectiveness and safety of switching, the adjusted hazard ratios (HRs) and related confidence intervals (CIs) were estimated by fitting Cox models within both ESA α originator and biosimilar initiators, using non-switchers as a reference group.

Sensitivity and subgroup analyses

Cox models were also fitted within by different switching subgroups and their matched non-switchers depending on the second ESA received within each initiator group:

• from originator of ESA α to (1) biosimilars; (2) shortacting patented epoetins; or (3) long-acting patented epoetins; and
• from biosimilars of ESA α to (4) originator; (5) shortacting patented epoetins; and (6) long-acting patented epoetins.

In order to analyse the robustness of our results, the following sensitivity and subgroup analyses were carried out:
• Analysis of the subgroup of subjects with a more conservative matching definition, i.e. reducing the duration of ESA α treatment from ± 30 days to ± 15 days, to increase the comparability between groups.
• Restriction of the risk window for the switching occurrence, i.e. from 2 years to 180 days following the initiation of the first ESA α treatment. This would mitigate the time-dependent bias due to baseline adjustment.
• Application of different definitions of follow-up, i.e. considering a fixed follow-up of 1 year and two different windows of follow-up (90 and 180 days).

Finally, a comparison between the two switcher cohorts (i.e. switchers from originator to any other ESAs or from biosimilars to any other ESAs) was performed in terms of lack of effectiveness and safety. In this analysis, only switchers were selected and the cumulative probabilities of observing an effectiveness or a safety event within each switching cohort for each category were estimated by Cox model, adjusting for baseline characteristics.

Results

During the study period, 52,178 ESA α users were identified; 86.3% (45,012) of these were new users with at least 1 year of health assistance history (**Fig. 2**). There were 18,612 patients using ESA α for anaemia due to CKD, despite 22.6% of them showing a sporadic use (i.e. only one ESA dispensing in the following 4 months). Considering the overall study population (n = 14,400), 8843 (61.4%) subjects started the therapy with an ESA α originator while 5557 (38.6%) received a biosimilar. In the two groups of ESA α initiators, the percentages of switching within 2 years from the first epoetin prescription (originator or biosimilars) were 21.1% and 11.5%, respectively. Switchers who showed no effectiveness and safety events during the 90 days prior to the switching date were excluded (10.2%) as were switchers for whom there were no matching non-switchers (6.6%). In the ESA α originator group, the most frequent switch occurred to long-acting epoetins (58.5%), while only 14.2% of the patients experienced a switch to biosimilars; instead, among biosimilar initiators the most frequent switch occurred towards ESA α originators (43.1%). Characteristics of originator/biosimilar switchers and non-switchers, before and after the matching, are shown in **Table 1**. Overall, younger patients with a greater severity of CKD and with more co-morbidities or a greater number of hospitalizations prior to the ESA α therapy start were more frequent among switchers. After the matching, the baseline characteristics of patients were well-balanced. Furthermore, for both initiator groups, more than 50% of the switching occurred during the first 6 months of ESA therapy (**Fig. 3**). Overall, lack of effectiveness and safety outcomes occurred in 7.7% and 4.5% of the originator ESA α initiators, respectively; while in the biosimilar group these percentages were 7.8% and 4.0%.
The adjusted HRs for the main analysis, the subgroup as well as the sensitivity analyses for all considered outcomes are presented separately for the two ESA α initiators groups in **Fig. 4a–d**.

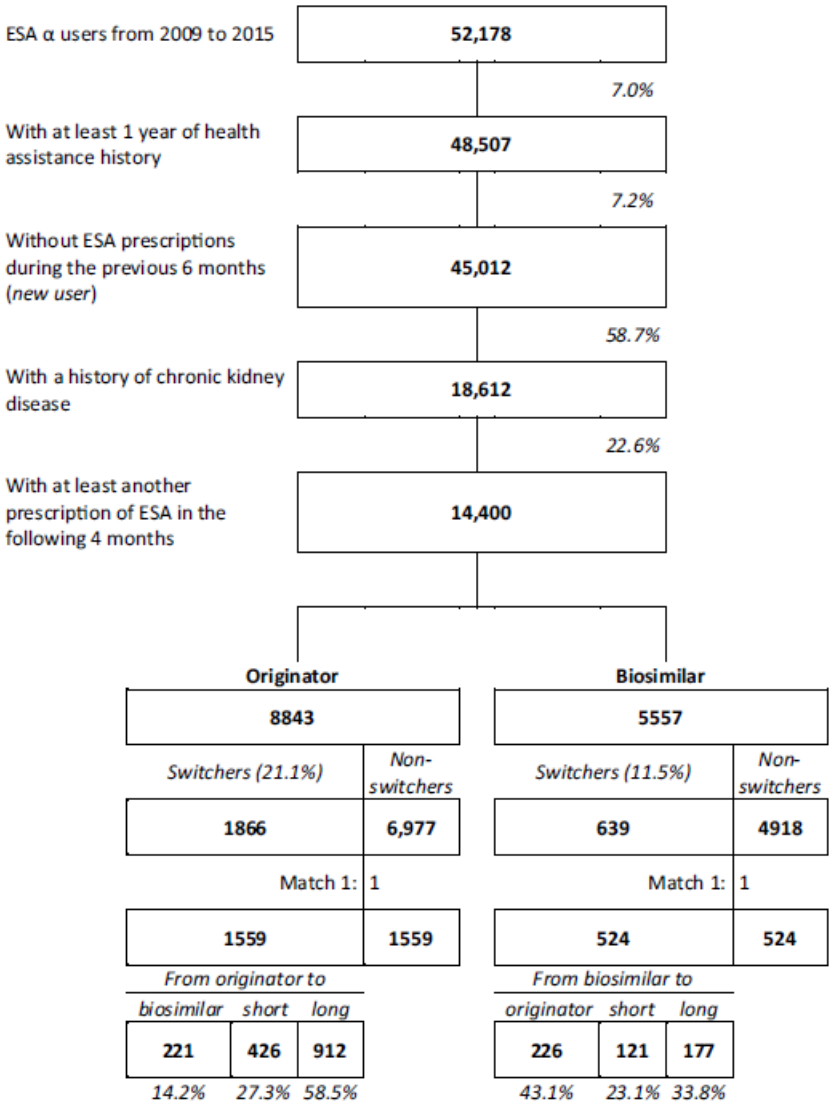
In the originator initiator group (**Fig. 4a**), no difference in the risk of lack of effectiveness between switchers and non-switchers was found (HR 1.02, 95% CI 0.79–1.31). In the biosimilar initiator group (**Fig. 4b**), a slight, non-statistically significant risk increase in terms of lack of effectiveness was observed for switchers versus nonswitchers (HR 1.16, 95% CI 0.75–1.79). When considering the safety outcome, a non-statistically significant risk for switchers was observed in both originator (HR 1.08, 95% CI 0.77–1.50) or biosimilar (HR 1.20, 95% CI 0.66–2.21) ESA α initiators (**Fig. 4c, d**).

Results showed in the main analysis on lack of effectiveness risk between switchers and non-switchers for originator and biosimilar initiator groups were consistent across different switching subgroups. In particular, in the subgroup of switchers from ESA α originator to biosimilar, the risk was 0.86 (95% CI 0.44–1.66). Results also remained unchanged in the sensitivity analyses, i.e. when using a more conservative matching definition (subgroup analysis 2: HR 1.02, 95% CI 0.76–1.37 for originator initiator group; HR 1.02, 95% CI 0.60–1.73 for biosimilar initiator group), restricting the period for the switching occurrence to 180 days (subgroup analysis 2: HR 1.05, 95% CI 0.76–1.45 for originator initiator group; HR 1.08, 95% CI 0.65–1.78 for biosimilar initiator group) or considering different definitions of follow-up.

The main analysis on safety risk was substantially confirmed from subgroup and sensitivity analyses. A slight increase in the subgroup of switchers from originator to biosimilar (HR 1.18, 95% CI 0.49–2.83) and from biosimilar to originator (HR 1.52, 95% CI 0.54–3.90) was found without reaching statistical significance.

As shown in **Fig. 5a, b**, cumulative probabilities of occurrence of any lack of effectiveness or safety outcomes were found to be highly similar for both switching groups; the estimated HRs (switching from ESA α biosimilars vs. switching from ESA α originator) were equal to 1.03 (95% CI 0.69–1.53) and 0.92 (95% CI 0.54–1.59), respectively.

Fig. 2 Study population.



ESA erythropoiesis-stimulating agent, ESA α epoetin alpha.

Table 1. Switcher and non-switcher baseline characteristics before and after matching by epoetin alpha initiator group.

Characteristic	Originator						Biosimilar					
	Pre-match			Post-match			Pre-match			Post-match		
	Switchers ($n = 1866$)	Non-switchers ($n = 6977$)	p value	Switchers ($n = 1559$)	Non-switchers ($n = 1559$)	p value	Switchers ($n = 639$)	Non-switchers ($n = 4918$)	p value	Switchers ($n = 524$)	Non-switchers ($n = 524$)	p value
Sex												
Male	51.8	51.8	0.9594	51.6	52.0	0.8019	48.0	50.0	0.3572	48.9	50.6	0.5782
Female	48.2	48.2		48.4	48.0		52.0	50.0		51.1	51.1	
Age group (years)												
< 45	4.7	3.2	< 0.0001	4.7	4.9	0.9356	1.4	1.9	< 0.0001	1.7	1.3	0.4568
45–64	16.1	12.9		16.4	16.7		16.4	10.5		16.2	13.0	
65–84	57.7	51.5		57.5	57.8		54.8	53.1		54.8	57.8	
85+	21.5	32.4		21.4	20.6		27.4	34.5		27.3	27.9	
Factors related to anaemia												
Transfusion	14.7	14.3	0.6585	13.1	13.6	0.7126	14.7	12.4	0.1056	11.8	12.0	0.9241
Iron supplementation	16.0	20.8	< 0.0001	15.2	14.7	0.6878	18.2	20.4	0.1839	17.9	17.6	0.8715
Anaemia	19.2	19.5	0.7870	17.3	17.0	0.8123	17.4	14.7	0.0803	16.2	15.1	0.6100
Severity of CKD disease												
Dialysed	22.9	14.8	< 0.0001	23.6	23.8	0.8995	17.2	10.1	< 0.0001	16.0	16.0	1.0000
Hospital admissions												
0	32.2	33.7	0.4134	33.5	36.9	0.1256	38.0	42.8	0.0085	40.1	44.5	0.3550
1	30.1	29.0		29.7	27.8		26.8	27.8		27.1	25.0	
> 1	37.7	37.4		36.8	35.2		35.2	29.4		32.8	30.5	
Co-morbidities/drug use												
Tumour	15.8	13.8	0.0287	14.6	12.5	0.0844	11.1	10.3	0.5215	9.9	8.6	0.4556
Diabetes mellitus	40.6	39.9	0.6260	40.3	38.6	0.3407	42.4	42.1	0.8776	42.4	41.2	0.7071
Hypertension	48.1	41.2	< 0.0001	48.2	46.6	0.3699	44.8	44.0	0.7101	43.5	44.3	0.8034
Arrhythmia	24.2	28.3	0.0004	23.9	23.6	0.8663	25.2	24.4	0.6518	26.0	26.3	0.8882
Heart failure	17.6	19.4	0.0806	17.1	15.7	0.2876	17.4	18.2	0.6180	17.6	17.0	0.8063
Cerebrovascular disease	8.8	10.5	0.0331	8.7	6.8	0.0518	8.9	8.4	0.6552	7.8	6.9	0.5539
Respiratory disease	7.5	9.6	0.0049	7.2	7.6	0.6822	6.9	8.6	0.1372	6.9	7.1	0.9034
Hyperkalaemia	6.8	4.6	0.0001	6.8	6.5	0.7191	6.4	3.9	0.0026	6.3	7.4	0.4637
Vitamin B_{12}	1.7	2.3	0.1366	1.7	2.4	0.1296	2.7	2.7	0.9961	2.3	2.1	0.8330
Folic acid	12.4	14.6	0.0155	11.4	12.4	0.3756	13.5	13.7	0.8647	13.0	13.0	1.0000
Vitamins A and D	19.2	15.8	0.0050	19.6	19.8	0.8753	19.9	17.5	0.1338	19.7	18.7	0.6948
NSAID	19.1	20.2	0.3024	18.9	20.1	0.3901	19.2	17.2	0.2090	19.5	18.5	0.6937

CKD chronic kidney disease, NSAID non-steroidal anti-inflammatory drug

Fig. 3 Switching time in originator (a) and biosimilar (b) initiator groups.

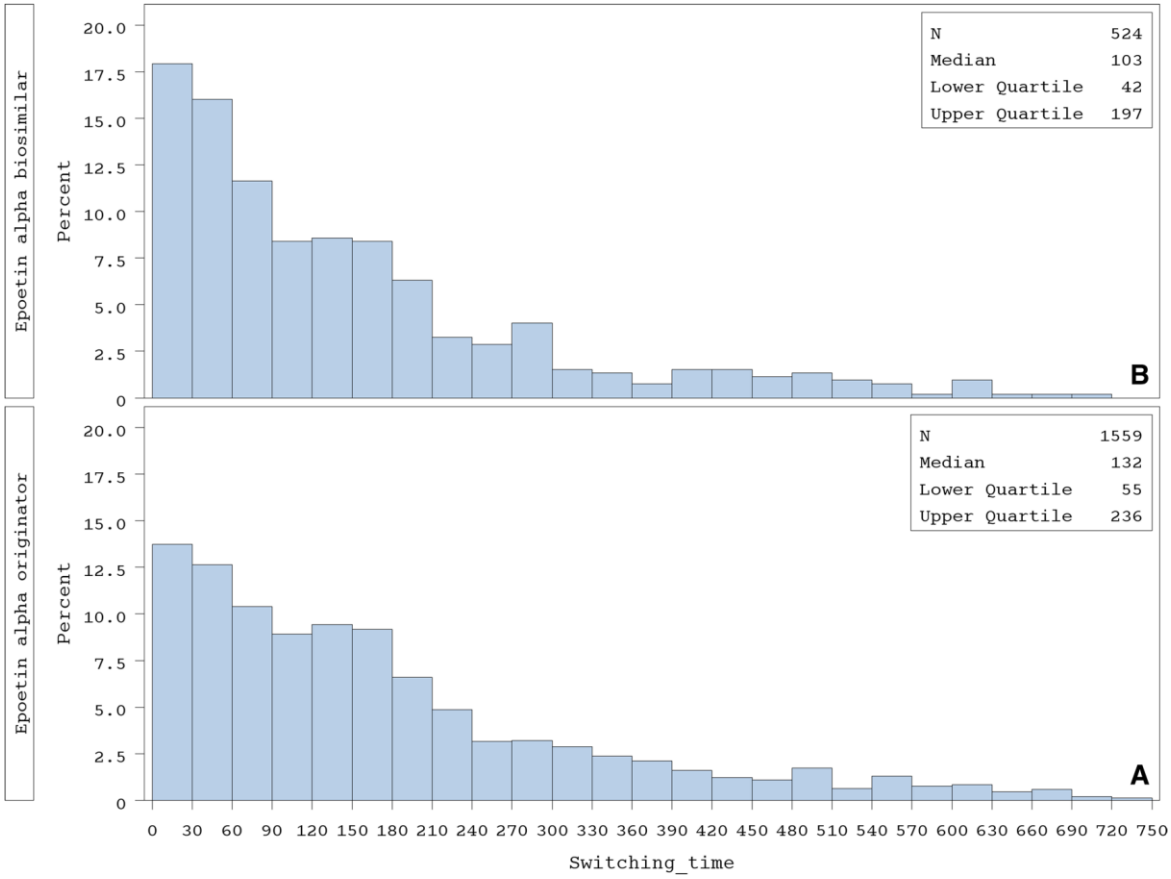
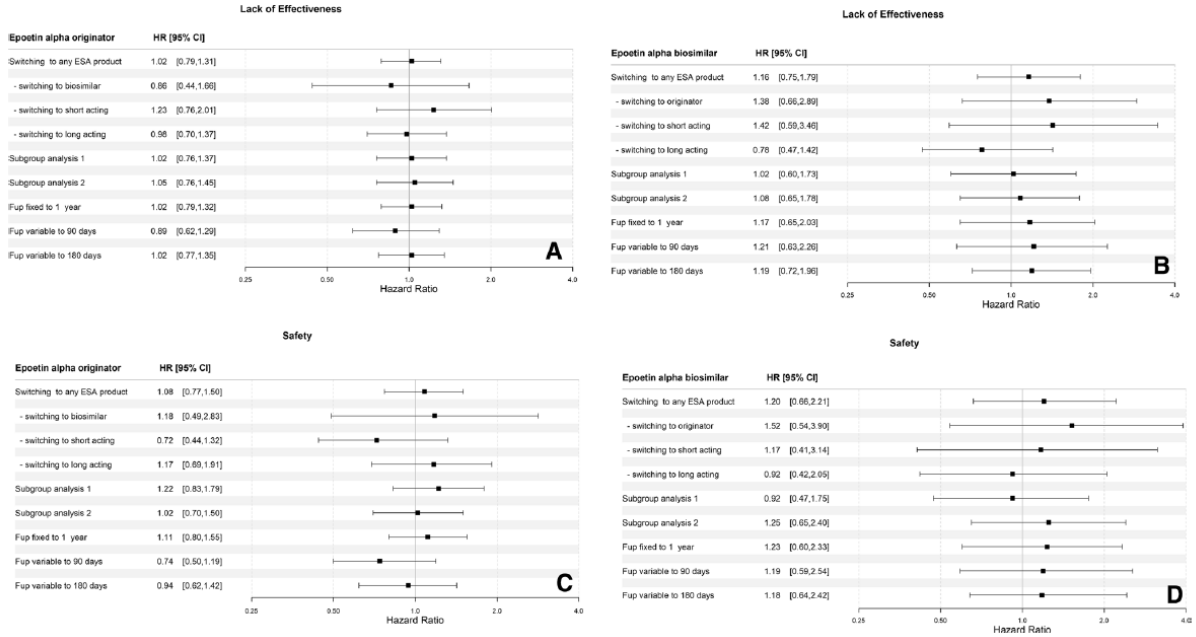
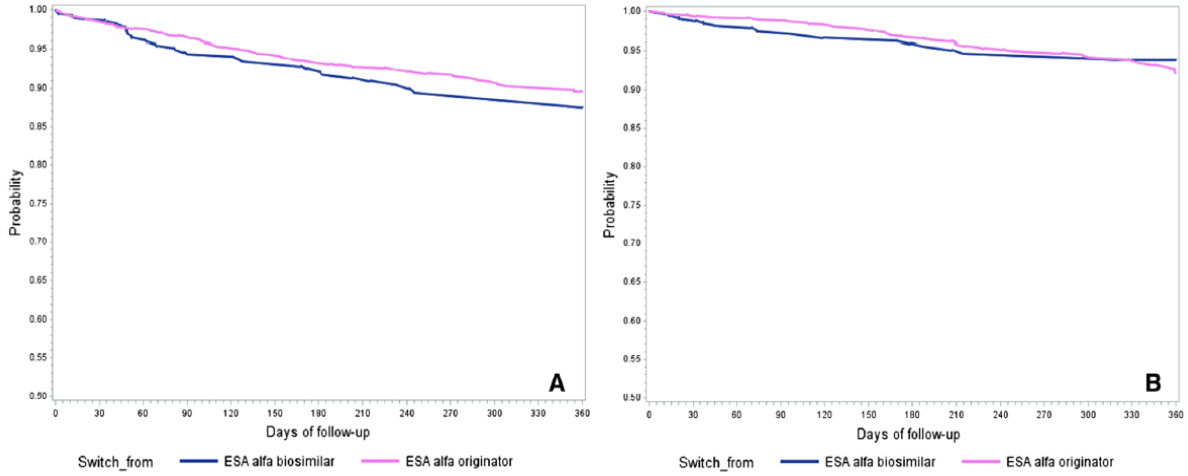


Fig. 4 Adjusted hazard ratios (HRs) and sensitivity analyses for all considered outcomes in epoetin alpha initiator groups.



A HR lack of effectiveness outcomes for switchers versus non-switchers in the originator initiators group; **B** HR lack of effectiveness outcomes for switchers versus non-switchers in the biosimilar initiators group; **C** HR safety outcomes for switchers versus non-switchers in the originator initiators group; and **D** HR safety outcomes for switchers versus non-switchers in the biosimilar initiators group. Subgroup analysis 1: subject with a more conservative definition matching, i.e. time in treatment with first epoetin alpha ± 15 days. Subgroup analysis 2: subjects switching within 180 days from beginning of first epoetin alpha treatment. CI confidence interval, ESA erythropoiesis-stimulating agent, Fup follow-up.

Fig. 5 Cumulative probabilities of recording a lack of effectiveness (a) or safety event (b) between epoetin switchers.



ESA α epoetin alpha

Discussion

This study provided real-world data on switching from ESA α originator or biosimilar to any other ESA in a large cohort of Italian CKD patients. The results suggest that originator/biosimilar ESA α initiators who switched to any other ESA during the first 2 years of treatment did not experience an increased risk of lack of effectiveness or safety outcomes in the year following switching when compared with non-switchers. These findings were consistent among subgroups and were confirmed by sensitivity analyses. Furthermore, switchers from ESA α biosimilar treatment did not experience an increased risk of lack of effectiveness or safety outcomes in the year following switching when compared with switchers from ESA α originator.

Comparison with Other Available Evidence in the Field

To our knowledge, this is the first study aimed at evaluating the impact of switching in a large cohort of ESA α users with CKD from the real-world setting using hard clinical outcomes.

To date, the available evidence has been derived from a few studies investigating the efficacy of ESA switching in terms of maintenance of haemoglobin levels in the nephrology setting [27–31]; moreover, all of these studies enrolled a small sample population (from 125 up to almost 800 subjects) and mainly referred to haemodialysis settings. In this context, it is of utmost importance to underline that none of the studies conducted performed a direct comparison among different switching groups. In particular, three of these studies showed conflicting results in terms of the doses of ESA α that were required to control anaemia in CKD patients switching from originator to biosimilar [29–31].

Several reviews also contributed to ascertaining the available evidence on the consequences of switching from originators to related biosimilars, although they were not focused exclusively on ESAs [20, 22, 32]. In particular, these three studies did not find any differences in terms of immunogenicity, safety or efficacy between those continuing therapy with originators or those switching to biosimilars, thus indicating that concerns related to switching have been so far unsupported.

Implication for Policy

Relevance of all issues related to the switch phenomenon led the national and international regulatory authorities to define guidance summarising the requirements necessary to establish the safety and efficacy of all biologic medicines that could be switched [13, 14, 33]. In the EU context, the EMA declared that in case of naïve patients there is no need for additional evaluation by the member states for starting with a biosimilar, including cases where extrapolation of the indication was applied. Even though the EMA declared that it "does not regulate interchangeability, switching and substitution of a reference medicine by its biosimilar" [34], several authors and European national drugs agencies stated that switching between biological drugs is safe [35]. In particular, in Italy, the national regulatory body for medicines took the position in favour of biosimilar and reference product interchangeability as part of the remit by the prescribers [14].

The switching phenomenon is not only related to the potential cost saving offered by biosimilars, but is something to be considered as a medical issue, especially as it may also occur among different originators. In fact, all new drugs coming onto the market with an existing therapeutic indication are potential switches for current patients treated chronically. In particular, in our study, as well as in previously published analyses [16–18], the majority of switching took place among originators. Thus, as suggested by several authors [36, 37], switching studies will help to uncover any residual uncertainty between the actions of two drugs, and, in the case of interchangeability, that uncertainty needs to be as minimal as possible because of safety concerns related to immunogenicity.

Strengths and Weaknesses of the Study

This is an observational study based on health information systems, without direct access to clinical records. The main limitations of our study are the lack of important information on disease severity such haemoglobin and iron levels. However, some information on patient characteristics were identified through multiple database linkages, ensuring proper control of confounding for measurable characteristics. Another possible concern was the choice of study design. We decided to use a 2-year period to define switcher and non-switcher groups and then we matched them by propensity score and duration of previous drug use before the switch. Thus, the reference group included patients that did not switch for at least 2 years. Since switching could have been caused by clinical issues, we might have selected less severe patients in the non-switcher group. This potential selection bias could result in a slight increase of risk.

We hypothesise that replicating the study considering non-switcher/switcher times instead of the non-switchers/switcher groups would mean the estimated risk for switchers would be lower than for non-switchers. However, we chose to adopt a more comprehensible approach with a more conservative reference group and performed an analytical approach to balance the study groups taking into account baseline factors. Furthermore, several pre-specified subgroup analyses were also performed in order to evaluate consistency of findings which were in line with those obtained from the main analysis. Moreover, the sample size for the biosimilar initiator group was lower than for the originator group and this led to wider CIs and thus a less precise estimation of the HRs. In this context, a product-specific analysis could bring more information, but it would require a larger cohort of patients exposed to all different kinds of ESAs. In fact, our analysis does not allow consideration of differences between specific products within the same group (i.e.

Retacrit® vs. Abseamed®/Binocrit®). Another limitation of our study was that we analysed only a single switch from originator to biosimilar. Suggestions have been made that there may be an increased safety risk if patients are switched back and forth multiple times between a reference biologic and one or more biosimilars.

Conclusions

This large-scale observational study suggests that switching from ESA α to other ESAs in CKD patients is effective and safe when compared with non-switching, both within biosimilar and within originator initiators, and that switching from originator is effective and safe when compared with switching from a biosimilar in a real-world setting. These results may be very useful to support clinical decisions related to switching drug therapies and promote better health policies to improve the uptake of biosimilars in the population.

References

1. Associazione Italiana di Oncologia Medica. Linee Guida Gestione della tossicità ematopoietica in oncologia Milan; 2017. http://media.aiom.it/userf iles/files/doc/LG/2017_LGAIO M_Toss_ematopoiet ica.pdf. Accessed 25 Jan 2018.
2. Kidney Disease: Improving Global Outcomes (KDIGO) Anemia WorkGroup. KDIGO clinical practice guideline for anemia in chronic kidney disease. Kidney Int Suppl. 2012;2(4). https://kdigo .org/wp-conte nt/uploa ds/2016/10/KDIGO -2012-Anemia-Guide line-Engli sh.pdf. Accessed 25 Jan 2018.
3. Sistema Nazionale Linee Guida -Istituto Superiore di Sanità, Società Italiana di Nefrologia, Ministero della Salute. Linea Guida "Identificazione, prevenzione e gestione della Malattia Renale Cronica nell'adulto". 2015. https ://www.fadoi .org/wp-conte nt/uploa ds/2017/05/linee guida -Malattia-renale-cronica-adult o.pdf. Accessed 25 Jan 2018.
4. Aapro MS, Link H. September 2007 update on EORTC guidelines and anemia management with erythropoiesis-stimulating agents. Oncologist. 2008;13(Suppl 3):33–6.
5. Rizzo JD, Brouwers M, Hurley P, Seidenfeld J, Arcasoy MO, Spivak JL, et al. American Society of Clinical Oncology, American Society of Hematology. American Society of Clinical Oncology/American Society of Hematology clinical practice guideline update on the use of epoetin and darbepoetin in adult patients with cancer. J Clin Oncol. 2010;28(33):4996–5010.
6. National Comprehensive Cancer Network (NCCN). NCCN® guidelines. Cancer- and chemotherapy-induced anemia (version 2.2018). 2017. http://oncol ife.com.ua/doc/nccn/Cance r-and_Chemo thera py-Induc ed_Anemi a.pdf. Accessed 25 Jan 2018.
7. Biosimilar development and approval in the EU. European public assessment reports. London: The European Medicines Agency. https://www.ema.europa.eu/en/medicines/search_api_aggregation_ema_medicine_types/field_e ma_med_biosimilar. Accessed 25 May 2019.
8. IMS Institute for Healthcare Informatics. The impact of biosimilar competition in Europe. QuintilesIMS; 2017. https ://www.medicinesforeurope.com/wp-conte nt/uploa ds/2017/05/IMS-Biosi milar-2017_V9.pdf. Accessed 15 Apr 2017.
9. Dylst P, Vulto A, Simoens S. Barriers to the uptake of biosimilars and possible solutions: a Belgian case study. Pharmacoeconomics. 2014;32(7):681–91.

10. Rompas S, Goss T, Amanuel S, Coutinho V, Lai Z, Antonini P, et al. Demonstrating value for biosimilars: a conceptual framework. Am Health Drug Benefits. 2015;8(3):129–39.
11. Lyman GH, Zon R, Harvey RD, Schilsky RL. Rationale, opportunities, and reality of biosimilar medications. N Engl J Med. 2018;378(21):2036–44.
12. Trifirò G, Marcianò I, Ingrasciotta Y. Interchangeability of biosimilar and biological reference product: updated regulatory positions and pre- and post-marketing evidence. Expert Opin Biol Ther. 2018;18(3):309–15.
13. European Medicines Agency. Biosimilars in the EU: information guide for healthcare professionals. 2017. http://www.ema.europa.eu/docs/en_GB/document_library/Leaflet/2017/05/WC50022664 8.pdf. Accessed 15 Apr 2017.
14. Agenzia Italiana del Farmaco (AIFA). Secondo Position Paper AIFA sui Farmaci Biosimilari. http://www.agenz iafar maco.gov.it/sites /defau lt/files /2_Posit ion-Paper -AIFA-Farma ci-Biosi milari.pdf. Accessed 15 Apr 2017.
15. Osservatorio Nazionale sull'impiego dei Medicinali. L'uso dei farmaci in Italia. Rapporto Nazionale 2017. Roma: Agenzia Italiana del Farmaco; 2018. http://www.aifa.gov.it/sites /defau lt/files/Rappo rto_OsMed 2017_AIFA.pdf. Accessed 18 Jun 2018.
16. Ingrasciotta Y, Giorgianni F, Marcianò I, Bolcato J, Pirolo R, Chinellato A, et al. Comparative effectiveness of biosimilar, reference product and other erythropoiesis-stimulating agents (ESAs) still covered by patent in chronic kidney disease and cancer patients: an Italian population-based study. PLoS One. 2016;11(5):e0155805.
17. Loiacono C, Sgroi C, Coppolino S, Cannata A, Ferrara R, Arcoraci V, et al. How much are biosimilars used in southern Italy? A retrospective analysis of epoetin utilization in the local health unit of Messina in the years 2010–2011. BioDrugs. 2012;26(2):113–20.
18. D'Amore C, Da Cas R, Rossi M, Traversa G. Switching between epoetins: a practice in support of biosimilar use. BioDrugs. 2016;30(1):27–32.
19. Cohen HP, Blauvelt A, Rifkin RM, Danese S, Gokhale SB, Woollett G. Switching reference medicines to biosimilars: a systematic literature review of clinical outcomes. Drugs. 2018;78(4):463–78.
20. Ebbers HC, Muenzberg M, Schellekens H. The safety of switching between therapeutic proteins. Expert Opin Biol Ther. 2012;12(11):1473–85.
21. Palmer SC, Saglimbene V, Mavridis D, Salanti G, Craig JC, Tonelli M, et al. Erythropoiesis-stimulating agents for anaemia in adults with chronic kidney disease: a network meta-analysis. Cochrane Database Syst Rev. 2014;12:CD010590.
22. Amato L, Addis A, Saulle R, Trotta F, Mitrova Z, Davoli M. Comparative efficacy and safety in ESA biosimilars vs. originators in adults with chronic kidney disease: a systematic review and meta-analysis. J Nephrol. 2018;31(3):321–32.
23. Trotta F, Belleudi V, Fusco D, Amato L, Mecozzi A, Mayer F, et al. Comparative effectiveness and safety of erythropoiesis-stimulating agents (biosimilars vs originators) in clinical practice: a population-based cohort study in Italy. BMJ Open. 2017;7(3):e011637.
24. Stoppa G, D'Amore C, Conforti A, Traversa G, Venegoni M, Taglialatela M, et al. Comparative safety of originator and biosimilar epoetin alfa drugs: an observational prospective multicenter study. BioDrugs. 2018;32(4):367–75.

25. Motola D, Vaccheri A, Roncadori A, Donati M, Bonaldo G, Covezzoli A, et al. Comparative risk/benefit profile of biosimilar and originator erythropoiesis-stimulating agents (ESAs): data from an Italian observational study in nephrology. Eur J Clin Pharmacol. 2018;74(6):805–10.
26. Ingrasciotta Y, Giorgianni F, Bolcato J, Chinellato A, Pirolo R, Tari DU, et al. How much are biosimilars used in clinical practice? A retrospective Italian population-based study of erythropoiesis-stimulating agents in the years 2009–2013. BioDrugs. 2015;29(4):275–84.
27. Hörl WH, Locatelli F, Haag-Weber M, Ode M, Roth K, Epo-PASS Study Group. Prospective multicenter study of HX575 (biosimilar epoetin-α) in patients with chronic kidney disease applying a target hemoglobin of 10–12 g/dl. Clin Nephrol. 2012;78(1):24–32.
28. Donck J, Gonzalez-Tabares L, Chanliau J, Martin H, Stamatelou K, Manamley N, et al. Preservation of anemia control and weekly ESA dosage after conversion from PEG-Epoetin beta to darbepoetin alfa in adult hemodialysis patients: the TRANSFORM study. Adv Ther. 2014;31(11):1155–68.
29. Arrieta J, Moina I, Molina J, Gallardo I, Muñiz ML, Robledo C, et al. Switch from epoetin to darbepoetin alfa in hemodialysis: dose equivalence and hemoglobin stability. Int J Nephrol Renovasc Dis. 2014;7:353–9.
30. Minutolo R, Borzumati M, Sposini S, Abaterusso C, Carraro G, Santoboni A, et al. Dosing penalty of erythropoiesis-stimulating agents after switching from originator to biosimilar preparations in stable hemodialysis patients. Am J Kidney Dis. 2016;68(1):170–2.
31. Minutolo R, Bolasco P, Chiodini P, Sposini S, Borzumati M, Abaterusso C, et al. Effectiveness of switch to erythropoiesisstimulating agent (ESA) biosimilars versus maintenance of ESA originators in the real-life setting: matched-control study in hemodialysis patients. Clin Drug Investig. 2017;37(10):965–73.
32. Inotai A, Prins CPJ, Csanádi M, Vitezic D, Codreanu C, Kaló Z. Is there a reason for concern or is it just hype? A systematic literature review of the clinical consequences of switching from originator biologics to biosimilars. Expert Opin Biol Ther. 2017;17(8):915–26.
33. Food and Drug Administration. Scientific considerations in demonstrating biosimilarity to a reference product: guidance for industry. Silver Spring: Food and Drug Administration; 2015. https://www.fda.gov/downl oads/drugs /guida nces/ucm29 1128.pdf. Accessed 15 Apr 2017.
34. Biosimilar medicines. Positioning statements on physician-led switching for biosimilar medicines. https: //www.medic inesfo reurope.com/wp-conte nt/uploa ds/2017/03/M-Biosi milar s-Overv iewof-posit ions-on-physi cian-led-switc hing.pdf. Accessed 25 May 2019.
35. Kurki P, van Aerts L, Wolff-Holz E, Giezen T, Skibeli V, Weise M. Interchangeability: a European perspective. BioDrugs. 2017;31(2):83–91.
36. Barlas S. FDA Guidance on biosimilar interchangeability elicits diverse views: current and potential marketers complain about too-high hurdles. P&T. 2017;42(8):509–12.
37. Aronson JK, Goldacre B, Ferner RE. Prescribing biosimilars. BMJ. 2018;362:k3141.

4.4. Direct healthcare costs of chronic kidney disease management: cost-savings achieved with higher biosimilar uptake and more appropriate use of erythropoiesis-stimulating agents

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Abstract

Purpose: Erythropoiesis-stimulating agents (ESAs), are used for treating chronic kidney disease (CKD)-related anemia, contributing to CKD costs. The study was aimed at investigating direct healthcare costs of CKD patients treated with ESAs and the potential savings achievable by increasing the use of biosimilars and preventing inappropriate ESA use.
Methods: A multi-center, cohort study was conducted using claims databases of five large Italian geographic areas. Yearly mean direct healthcare costs per patient were estimated, stratifying by CKD stage. The total yearly cost and potential savings related to ESA use were estimated: a) considering 25/50/75% of originator ESA substitution with biosimilars; b) eliminating inappropriate ESA dispensing.
Results: During the study period, the ESA-related yearly mean cost represented 17% of total yearly costs in stage I-III, decreasing to 13% in stage IV-V and 6% in dialysis. Among originator users, assuming a 25% of biosimilar uptake, the annual cost-savings of ESA treatment would represent 10.5% of total ESA costs in CKD stage I-V and 7.7% in dialysis. Among incident ESA users for which hemoglobin levels were available, 9% started inappropriately ESA treatment, increasing to 62.0% during the first year of maintenance therapy. Hypothesizing prevention of the first inappropriate ESA dispensing, the total yearly cost-savings would amount to €35,772, increasing to €167,641 eliminating the inappropriate dispensing during maintenance therapy.
Conclusions: Higher use of lowest cost ESA, prevention of inappropriate ESA use as well as other strategies aimed at slowing down the progressive renal impairment are essential for minimizing clinical and economic burden of CKD.

Introduction

Chronic kidney disease (CKD) is an important public health issue affecting 10-16% of the world's adult population with an increasing incidence.[1] In Italy, the results of CAHERES (Cardiovascular risk in Renal Patients of the Italian Health Examination Survey) study showed a CKD crude prevalence of 7.5% in men and 6.5% in women, with overall higher prevalence of CKD stage I (2.6%), II (1.5%), and IIIa (2.1%) than IIIb (0.5%), IV (0.2%) and V and dialysis (0.1%).[2] The transition from one CKD stage to the next is associated with an increased clinical and economic burden.[3,4] In Italy, the annual direct treatment cost of a patient on dialysis was estimated to be around €38,821,[4] specifically €29,800 for peritoneal dialysis and €43,800 for hemodialysis.[5] The economic impact of dialysis on the Italian National Health Service (NHS) was estimated to be €2.1 billion per year.[5] Anemia is one of the most clinically important complications of chronic kidney disease and has a negative effect on the patient's quality of life both directly, when symptomatic, and indirectly, increasing cardiovascular risk, the risk of other adverse drug reactions and of mortality. In particular, the prevalence of anemia increases in frequency and severity in the more advanced stages of CKD, from 8.4% at stage 1 to 53.4% at stage 5[6] and is present in almost all dialyzed patients.[7,8] As recommended by the Italian Medicines Agency (Agenzia Italiana del Farmaco, AIFA), erythropoiesis-stimulating agents (ESAs) should be used for the treatment of CKD-related anemia, to be started when hemoglobin (Hb) levels are lower than 11 g/dL. Regarding maintenance therapy, ESAs are indicated when Hb levels are between 11 and 12 g/dL, but avoiding an increase in Hb greater than 2 g/dL over a four weeks period,[9] as this may increase the risk of cardiovascular events. Blood transfusions are only recommended when Hb levels are lower than 8 g/dL.

ESAs account for a substantial economic burden in CKD management,[10] posing a challenge to healthcare services in terms of sustainability and affordability.[11] Data from an Italian claims database network showed a slight increase of the use of ESAs for the treatment of both CKD or chemotherapy-induced anemia between 2009-2013, with the prevalence of ESA use ranging from 2.9 per 1,000 inhabitants in 2009 to 3.4 per 1,000 inhabitants in 2011, with a slight decrease in the following 2 years (3.0 per 1,000 in 2013).[12]

In 2007, the European Medicines Agency (EMA) approved the marketing of biosimilar epoetin alpha, whose use can reduce ESA pharmaceutical expenditure by 20-30%.[13] In Italy, a significant cross-regional heterogeneity in biosimilar uptake was observed between 2009 and 2013, due to different regional healthcare policies concerning biosimilar use.[12] Moreover, almost 20% of patients started ESA treatment inappropriately,[14] and this may lead to a worsening of clinical outcomes as well as incurring additional, preventable costs.

To date, the patent of methoxy polyethylene glycol-epoetin beta has not expired in Europe. The patent of darbepoetin alfa will expire in the US in May 2024, but has expired in Europe in 2016. Nevertheless, biosimilar competitors have not yet been marketed in Europe, while darbepoetin alpha biosimilars are available in Japan.[15,16] The choice to treat a CKD patient with an originator rather than a lower cost biosimilar ESA may be influenced by demand-side incentives (e.g. 'rewarding' hospitals for the use of cheapest ESA among eligible patients) are significant factors influencing biosimilar use and resulting savings. The Italian Medicines Agency does not allow automatic substitution of originator with biosimilars at the pharmacy level, although the use of the cheapest biological drug in naïve patients is strongly recommended and, in its last position paper, AIFA considers biological originator and biosimilar to be interchangeable,

based on their comparable benefit-risk profile.[17,18] The 2017 National Report on Medicines use in Italy showed an increased use of all biosimilars compared to the previous year, especially for ESAs (+ 65.1%), with a decrease of 27.7% of the total ESA expenditure.[19] Currently, no information is available on the possible cost savings associated with a wider use of epoetin alpha biosimilars among ESA users in a real-world setting. In addition, the impact of inappropriate ESA use on pharmaceutical cost in Italy has not been described. Therefore, the aim of this population-based, multi-regional, Italian study was to investigate the overall direct healthcare costs of CKD management, with emphasis on the cost of ESA treatment and the potential savings that could be achieved by either increasing the extent of ESA biosimilar uptake or preventing inappropriate ESA use, using real-world data from five large Italian geographic areas.

Methods

Data Source

The present study is an observational, multi-center, retrospective cohort study using fully anonymized data extracted from the claims databases of Treviso, Caserta and Palermo Local Health Units (LHUs), and the Tuscany and Umbria regions. Altogether the database network used in this study covers a total population of 7,939,874 inhabitants (i.e. 13.2% of the whole Italian population). Italy has a universal healthcare system, where all NHS beneficiaries (i.e. all residents in any given catchment area) are registered in a demographic database. All hospitalizations are fully reimbursed by the Italian NHS and are therefore accurately recorded as claims. Concerning outpatient diagnostic tests and specialist visits, they are almost completely reimbursed by NHS as well, unless patients decide to access to private healthcare services (on average, around 15% of all specialist visits/diagnostic tests). Concerning drugs, almost 80% of all drugs are fully reimbursed by NHS (including ESAs as well as high cost drugs) with remaining being in charge of citizens (e.g. over the counter drugs and other prescription drugs such as paracetamol and benzodiazepines). Moreover, Italian patients with severe chronic diseases, like chronic kidney disease, according to the D.L. 124/98 of the Italian Health Ministry, may receive after request a health-care service co-payment exemptions code, which allow them to receive even larger coverage of healthcare services by the NHS. So all their claims are traced in this study. Concerning the emergency department claims database, although all persons admitted to the emergency department will have a claim, the associated diagnoses and costs are missing in more than 30% of records and this claims database is therefore rarely used in pharmacoepidemiology studies.

Considering this specific study, using unique anonymized patient identifier, pharmacy claims can be linked to all other population-based claims databases, such as hospital discharge records databases, health-care service co-payment exemptions databases, outpatient diagnostic tests and specialist's visits database, and other claims in all five centers. Moreover, in Caserta and Treviso LHUs, ESA pharmacy claims can additionally be linked to an electronic therapeutic plan that is filled by specialists and which includes the indication of use, ESA drug name and dosing regimen, and number of dispensed packages. After linkage, ESA users treated specifically for CKD-related anemia were identified using electronic therapeutic plans or, in absence of this information, through other sources within the claims databases by applying a

validated algorithm as described elsewhere.[12] Drug information is coded using the Anatomical Therapeutic Chemical (ATC) classification system and the Italian national drug code (AIC code), which allows distinction among epoetin alfa biosimilars and reference product and other originator ESAs. Information on diagnoses and procedures is coded using the International Classification of Disease, ninth revision, with clinical modification (ICD 9-CM). Due to the NHS setting from which the data are derived and because healthcare data collection is mandatory as per Italian law, the healthcare data used in this study are considered to have a high level of completeness. Italian claims databases have been frequently used to conduct drug utilization, safety and effectiveness studies[20] and, specifically, the databases included in this study have already been used for pharmacoepidemiology research on the use and comparative effectiveness of originator and biosimilar drugs in the context of the same project as the present study.[12,13,21-25]

Study Population

All persons living in the catchment areas of Treviso, Caserta, and Palermo LHUs and Tuscany region from 2009 to 2014 were considered eligible for inclusion in the study. For the Umbria region, the available observation period was from 2011 to 2014, as showed elsewhere.[21,22] From the source population, patients were included in the study if they met all the following criteria **(Fig. 1**): a) had at least two ESA pharmacy claims during the study period (first pharmacy claim: Index date, ID) separated by < 365 days and no ESA pharmacy claims within one year prior to ID (i.e. incident ESA users); b) had at least 365 days pre- and post-index continuous enrollment in their database; c) had at least one medical claim with a diagnosis of chronic kidney disease any time prior to the ID, including the ID. Finally, among incident ESA users with CKD, all patients with known CKD stage were identified. CKD stage, available only for a subgroup of patients, was evaluated any time prior to the ID based on ICD-9 CM diagnoses from hospitalizations and diagnostic tests (**Online Resource 1**). In the presence of conflicting classifications of CKD stage, a conservative approach was taken whereby the most severe stage trumped the less severe one. In general, applying all inclusion criteria, the final study cohort was made up of new ESA users with CKD and with at least one year pre- and post-ID continuous enrollment in their database. Concerning the pre-ID year: a) index date of incident ESA users from Caserta and Tuscany databases started from 2009 because claims data were available from 2002 and 2007, respectively; b) index date of incident ESA users from Palermo and Treviso databases started from 2010 (claims data were available from 2009); c) index date of incident ESA users from Umbria database started from 2012 (claims data were available from 2011).

Study Drugs

During the study period, the use of the following ESAs was identified: epoetin alfa (ATC: B03XA01; Eprex®, Abseamed®, Binocrit®); epoetin beta (B03XA01; Neorecormon®); darbepoetin alfa (B03XA02; Aranesp®); epoetin zeta (B03XA01; Retacrit®); and methoxy polyethylene glycol-epoetin beta (B03XA03; Mircera®). The epoetin alfa reference product was Eprex®, while biosimilars of epoetin alfa included Binocrit®, Abseamed® and Retacrit®. Other originator ESAs included Neorecormon®, Aranesp® and Mircera®. For each ESA, the national drug code and proprietary name, pharmacy claim date and number of dispensed drug packages were retrieved from electronic therapeutic plan (if available) or pharmacy claims. Based on the

ESA dispensed at ID, incident ESA users were mutually classified as users of: a) epoetin alfa reference product; b) epoetin alfa biosimilar; or c) other originator ESAs.

Data analysis

Incident ESA users with CKD included in the study cohort were described at baseline in terms of demographic and clinical characteristics, number of hospitalizations, concomitant drugs as well as CKD stage (i.e. stage I-III, stage IV-V and dialysis). All analyses were stratified by type of ESA dispensed at ID. Annual direct healthcare costs covered by the NHS for incident ESA users treated for CKD-related anemia were estimated. Indirect costs such as transport costs, pension costs, productivity losses and any other direct or indirect costs not covered by NHS (including private healthcare expenditure) were not considered. Direct healthcare costs per patient during the first year of treatment were calculated from the perspective of the Italian NHS. Direct healthcare costs during the first year of treatment were divided into four main cost categories: pharmacy claims costs, hospitalization costs, diagnostic test/specialist visit costs, and dialysis costs. Pharmacy claims costs were divided into the costs of ESA drugs and concomitant non-ESA drugs. Costs concerning pharmacy claims, hospitalizations and diagnostic tests/specialist visits were recorded directly in the claims databases as the actual cost paid out by the respective Regional Health System for that specific healthcare service. Costs were expressed in Euros. In details, for each patient, the cost of individual pharmacy claim was recorded in the claims database based on the cost of the drug (with discount) in a specific region. So, the total cost of drugs was calculated by multiplying the total number of dispensed packages for the actual cost of the drug. The hospitalization costs were also available and calculated by multiplying each admission for the unit cost for each regional diagnosis-related group (DRG) tariff; diagnostic procedure costs were calculated by multiplying each procedure for its regional tariff. Cost of healthcare resources was reported as yearly mean unadjusted direct healthcare costs per patient during the first year of treatment and stratified by severity of CKD (i.e. stage I-III, stage IV-V, and dialysis). Moreover, hypothesizing a budget impact market scenario where 25%, 50% and 75% of ESA originator users (i.e. reference product/other originator ESAs) would be treated with epoetin alpha biosimilars, the yearly overall ESA cost savings and mean ESA cost savings per patient for each CKD stage were estimated. An exploratory analysis was conducted among incident ESA users for which Hb levels were available. Inappropriate ESA use was identified as inappropriate initiation (i.e. incident ESA users with Hb levels ≥11 g/dL within one month prior to ID) and inappropriate maintenance therapy (incident ESA users with at least 2 Hb levels >12 g/dL during the year after ESA initiation). An exploratory analysis calculating the total annual ESA cost-savings achievable by preventing inappropriate ESA use was performed.

Descriptive statistics were presented for all the study variables as absolute values, percentages, and means with 95% confidence intervals (95% CI) or medians with interquartile range (IQR) as appropriate. For multiple comparisons (reference product vs. biosimilar; other originator ESAs vs. biosimilar), Bonferroni's correction was applied, for which the significance alpha level 0.050 was divided by the number of the possible pairwise comparisons that can be performed with three groups; the new "adjusted" significance level for this analysis was therefore equal to 0.050 / 3 = 0.017. Analyses were conducted using SAS® for Windows, version 9.2 (SAS Institute, Cary, NC, USA) and SPSS®/ PC, version 15 (SPSS Inc., Chicago, IL, USA).

Results

During the study period, on a total population of 7,939,874 subjects registered in the five study centers (13.2% of the total Italian population), 7,810 (0.1%) incident ESA users with CKD were treated for at least one year (reference product: 1,139, 14.6%; biosimilars: 1,204, 15.4%; other originator ESAs: 5,467, 70.0%). For 2,921 (37.4%) of these incident ESA users, information on CKD stage was available. As shown in **Table 1**, there were no statistically significant age and sex differences across incident users of different ESA types. As regards CKD staging at baseline, 40% of patients were at stage I-III, 27% were at stage IV-V and 33% were on dialysis. Around 60% of the study population was hospitalized at least once within one year prior to the ID. On average, incident CKD ESA users received 9 other drugs within three months prior to the ID, with one third receiving more than 10 drugs.

The total direct mean healthcare costs of CKD management per patient during the first year of ESA treatment was lower in non-dialyzed patients than dialyzed patients, ranging from € 8,917 in CKD stages I-III to € 31,985 in dialysis patients (**Fig. 2**). The ESA-related yearly mean cost made up 17.4% [€1,551; 95% Confidence Interval (CI): €1,471-1,631] of total yearly costs in CKD stage I-III, decreasing to 13.2% [€1,493; 95% CI: €1,413-1,573] in stage IV-V and to 6.4% [€2,045; 95% CI: €1,946-2,144] in dialysis (**Fig. 2**). In CKD stage I-V, more than 50% of total costs were attributable to hospitalizations (€5,265), while in dialysis the highest cost (39.6%) was attributable to dialysis procedure (€12,672).

Overall, incident biosimilar ESA users (yearly mean ESA cost: €1,051) made up 15% of total ESA users during the study period. Assuming that 25% of ESA originator users were treated with a biosimilar instead, the annual cost-savings of ESA treatment in the study population would amount to €161,417 (10.0% of total ESA costs) in CKD stage I-III, €112,512 (10.9%) in CKD stage IV-V and €136,972 (7.7%) in dialysis, ranging from €163.5 to €175.3 the mean ESA cost savings per patient. Assuming 50% or 75% substitution of originator with biosimilar ESA, these cost-savings would increase up to 15-30% of total ESA costs (**Table 2**).

An exploratory analysis, conducted among 254 incident ESA users for which Hb levels were available at baseline, showed that 23 (95%CI: 20-27) patients (9% of patients with available Hb levels within one month prior to the ID) started ESA treatment inappropriately. During the first year of ESA maintenance treatment, 111 (95% CI: 103-117) CKD patients (62.0% of patients with at least 2 Hb levels >12 g/dl during the first year after ID) were inappropriately treated with ESAs. The cost of inappropriately initiating ESA was €35,772, while the cost of inappropriate ESA maintenance therapy was € 167,641 in the first year of treatment.

Table 1. Characteristics of the study cohort, stratified by type of ESA.

	Epoetin alpha reference product N= 1,139 (%)	Epoetin alpha biosimilars N= 1,204 (%)	Other originator ESAs N= 5,467 (%)	P-value: epoetin alpha biosimilar vs reference product*	P-value: epoetin alpha biosimilar vs Other originator ESAs*
Sex					
Female	585 (51.4)	613 (50.9)	2,752 (50.3)	0.829	0.718
Male	554 (49.6)	591 (49.1)	2,715 (49.7)		
Mean age ± SD (Years)	75.1±13.6	77.8±10.9	75.2±14.0	0.119	0.089
Age categories (Years)					
< 45	42 (3.7)	17 (1.4)	229 (4.2)	<0.001	<0.001
45-64	173 (15.2)	129 (10.7)	736 (13.5)	0.001	0.010
65-79	395 (34.7)	433 (36.0)	1,956 (35.8)	0.516	0.903
≥ 80	529 (46.4)	625 (51.9)	2,546 (46.5)	0.008	<0.001
Mean follow-up ± SD (Years) †	3.1±1.3	1.9±0.7	2.9±1.3	0.023	0.017
Catchment area					
Caserta	78 (6.8)	235 (19.5)	618 (11.3)	<0.001	<0.001
Palermo	334 (29.3)	131 (10.9)	728 (13.3)	<0.001	0.022
Treviso	52 (4.6)	117 (9.7)	154 (2.8)	<0.001	<0.001
Tuscany	651 (57.2)	710 (59.0)	3,420 (62.6)	<0.373	0.020
Umbria	24 (2.1)	11 (0.9)	547 (10.0)	0.017	<0.001
CKD stage					
I-III	146 (12.8)	206 (17.1)	827 (15.1)	0.004	0.085
IV-V	77 (6.8)	134 (11.1)	565 (10.3)	<0.001	0.415
Dialysis patients	184 (16.1)	128 (10.7)	654 (12.0)	<0.001	0.193
Unknown	732 (64.3)	736 (61.1)	3,421 (62.6)	0.117	0.349
Number of previous hospitalizations ‡					
0	500 (43.9)	491 (40.8)	2,427 (44.4)	0.127	0.022
1	279 (24.5)	358 (29.7)	1,519 (27.8)	0.004	0.173
2	172 (15.1)	182 (15.1)	780 (14.3)	0.992	0.448
3	100 (8.8)	87 (7.2)	391 (7.1)	0.165	0.928
>3	88 (7.7)	86 (7.2)	350 (6.4)	0.590	0.346
Mean ±SD number of distinct ATCs§	8.9±4.7	9.1±4.9	9.2±4.4	0.497	0.632
Number of concomitant ATCs§					
0	40 (3.5)	82 (6.8)	82 (1.5)	<0.001	<0.001

1	19 (1.7)	12 (1.0)	77 (1.4)	0.155	0.259
2	25 (2.2)	24 (2.0)	142 (2.6)	0.733	0.223
3	57 (5.0)	40 (3.3)	195 (3.6)	0.041	0.677
4	60 (5.3)	57 (4.7)	278 (5.1)	0.553	0.614
5-10	561 (49.2)	543 (45.1)	2,730 (49.9)	0.044	0.002
>10	377 (33.1)	446 (37.1)	1,963 (35.9)	0.046	0.457

Legend: CKD: Chronic kidney Disease; ESA: Erythropoiesis-Stimulating Agent; SD: standard deviation; ATC: Anatomical Therapeutic Chemical Coding System.

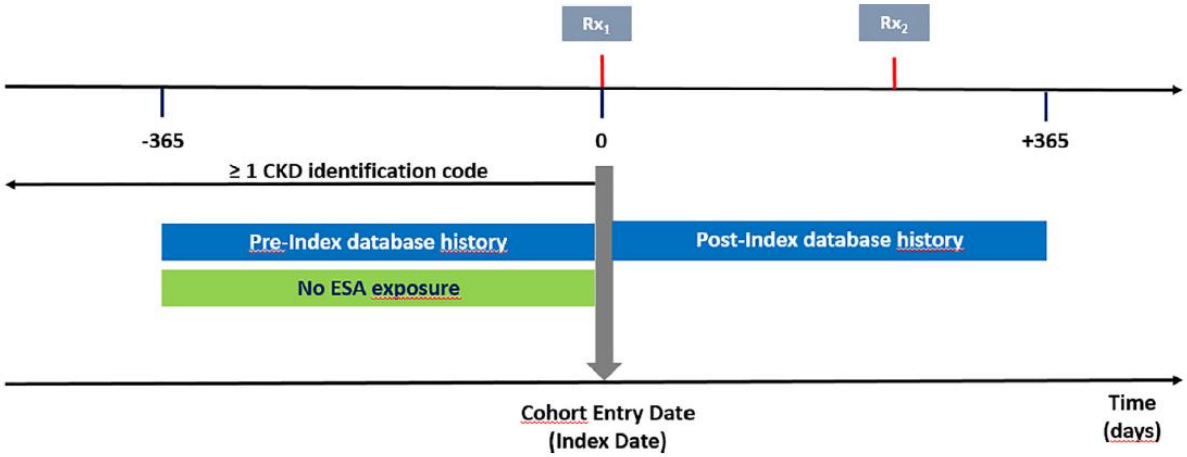
* p-value from two-sample t-test or Chi-Square test (or Fisher's exact test when appropriate) for continuous and categorical variables, respectively;

† The follow-up period was defined as the period from the index date until the occurrence of one of the following events for each patient (whichever occurred first): patient's death, patient's transfer out of the database or end of the study period (December 2014);

‡ Evaluated within one year prior to ID;

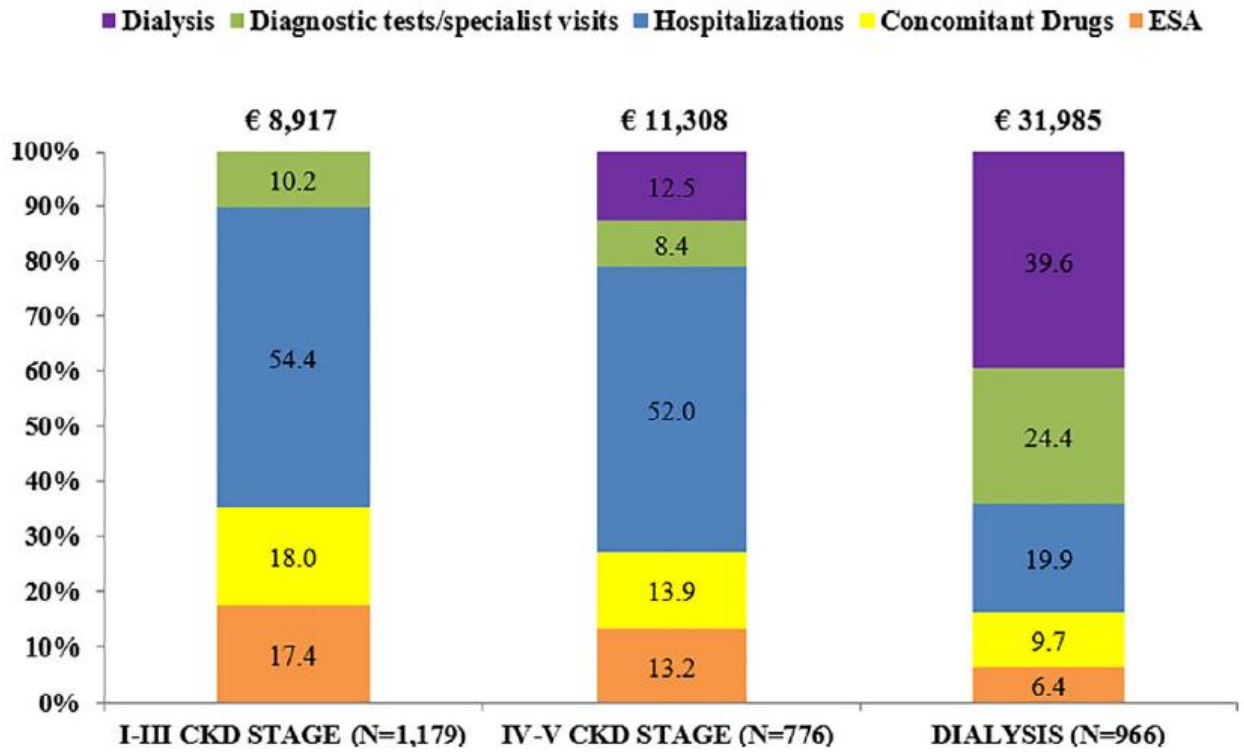
§ Evaluated within three months prior to ID.

Fig. 1 Depiction of the study cohort identification criteria.



ESA: Erythropoiesis-stimulating agent; Rx: Erythropoiesis-stimulating agent dispensing; CKD: chronic kidney disease

Fig. 2 Mean cost (€) per patient during the first year of ESA treatment, stratified by CKD stage.



CKD, chronic kidney disease; ESA, erythropoiesisstimulating agent. A proportion of patients (N = 118, 15.2%) identified as stage IV-V at the index date had a dialysis request within 1 y after ID.

Table 2. Yearly, overall and per patient, ESA cost-savings in the study population with hypothetical increased extent of biosimilar uptake for incident ESA users with known CKD stage.

			CKD stage I-III N=973	CKD stages IV-V N=642	Dialysis N=838	Total N=2,444
Total ESA costs			**€1,622,125**	**€1,036,193**	**€1,786,452**	**€4,444,769**
Hypothesized biosimilar replacement of originator market share	**25%**	**ESA cost savings € (%)†**	€ 161,417 (10.0)	€112,512 (10.9)	€136,972 (7.7)	€410,900 (9.2)
	50%		€ 322,833 (19.9)	€225,023 (21.7)	€273,944 (15.3)	€821,800 (18.5)
	75%		€ 484,250 (29.9)	€343,397 (33.1)	€410,916 (23.0)	€1,238,562 (27.9)
	25%	**Mean ESA cost savings per patient €†**	€165.9	€175.3	€163.5	€504.6
	50%		€331.8	€350.5	€326.9	€1,009.2
	75%		€497.7	€525.8	€490.4	€1,513.8

Legend: CKD: Chronic kidney disease, ESA: Erythropoiesis-Stimulating Agent.

† Cost savings: total cost-savings on pharmaceutical expenditure if 25, 50, or 75% of patients treated with reference product or other originator ESAs were treated with biosimilar ESA drugs.

Discussion

This large-scale population-based database study set in 5 Italian regions explored the direct healthcare costs associated with CKD management, yielding several findings. The main finding of this study was that ESA users starting treatment with a biosimilar made up only 15% of all ESA users during the study period, with the remainder using reference products or other originator ESAs. The updated ASCO/American Society of Hematology (ASH) clinical practice guideline for anemia management in cancer patients[26] cited several multi-database studies demonstrating the comparability of epoetin-α, originator and biosimilar, as well as other epoetins still covered by patents (e.g. darbepoetin, epoetin-β) in terms of effectiveness and safety.[23,27-29] Despite this guideline refers to cancer patients, this consideration may be extended to CKD patients. Our results suggest that if 25% of originator ESA users (i.e. alpha reference product and other ESA which are still patented) were treated with a biosimilar, the annual cost-savings would range from 8% to 11% of the total ESA costs, depending on the CKD stage. Assuming a 50% or 75% of biosimilar uptake, these cost-savings would increase up to 20-30% of the total ESA costs. The highest number of ESA biosimilar pharmacy claims and the highest ESA-related costs were recorded in Caserta and Treviso catchment areas. This finding can be explained by healthcare policies promoting biosimilar use that were implemented at different times in the various catchment areas. For example, in 2009, the Campania region, where Caserta is located, was the first Italian region to issue healthcare policy interventions promoting biosimilar use in ESA-naive patients,[30] followed by Veneto, where Treviso is located.[31] Other regions such as Tuscany, followed in 2010[32] and Sicily in 2014.[33] Furthermore, in both Palermo (Sicily Region) and Caserta, the cost related to the prescription was directly charged to prescribers, in case the cheapest ESA was not prescribed in naıve patients, and if the rationale for prescribing an ESA other than the cheapest one was not provided. In Tuscany and Treviso, minimum thresholds of biosimilar use were defined yearly and prescribers and general directors in Treviso received incentives to reach the above-mentioned targets. These different approaches in healthcare policies, in addition to potential regional differences in the marketing of ESA by pharmaceutical companies, different tender processes for purchase of reference products and biosimilars and biological drugs still covered by patent, as well as clinicians' skepticism about the comparability of reference products and biosimilars may have contributed to the heterogeneity of ESA use in the Italian Regions. Previous studies using data from these catchment areas evaluating the pattern of use of ESAs,[12] granulocyte-colony stimulating factors (G-CSF)[21] and recombinant Growth Hormones (rGH)[22] showed a high degree of heterogeneity of biosimilars ESA use across each catchment area, mainly as a result of differences biosimilar-related healthcare policy interventions. Moreover, most of our study cohort were treated with long-acting ESAs. This is probably due to the patient preference because of the differences in the frequency of administration between short- and long-acting ESAs. As known, because of their relatively short half-life, short-acting ESAs are administered two or three times weekly; owing to a longer half-life, long-acting ESAs can be administered less frequently (single injection once weekly or once every two weeks). This does not mean necessarily that darbepoetin alfa has a cost advantage compared to short acting ESAs. A recent review on the comparative efficacy, safety, economic, and health-related quality-of-life outcomes of short- and long-acting ESAs in the treatment of chemotherapy-induced anemia and chronic kidney disease anemia showed that systematic literature reviews comparing short-acting and long-

acting ESAs found conflicting results or little differences in their cost-effectiveness.[34] Indeed, some systematic literature reviews suggested a cost advantage for epoetin alfa relative to darbepoetin alfa,[35,36] others reported that there was no evidence of any relevant cost differences[37] or alluded that drug-cost savings could be achieved with darbepoetin alfa.[38,39]

Another major finding of this study was that increasing biosimilar use is not the only way to reduce costs among ESA users. Indeed, we found that the possible cost-savings that can be achieved by avoiding the inappropriate use of ESA in CKD maintenance treatment, i.e. the use of ESA among patients with Hb levels exceeding 12 g/dL at least twice, amounted to well over € 165,000 per year in the catchment areas considered. Lower preventable costs were observed concerning the inappropriate initiation of ESA treatment, i.e. the use of ESA among patients with Hb levels equal to or greater than 11 g/dL, amounting to €35,772 per year. While these results were generated from an exploratory analysis conducted in a small sample of CKD patients for which Hb levels were available, they are a sobering reminder of the economic consequences of inappropriate ESA use, over and above the potential clinical consequences. As reported in the Summary of Product Characteristics of ESAs from the European Medicines Agency, caution should be exercised with escalation of ESA doses in patients with CKD, and in presence of Hb levels > 12g/dl, since high cumulative ESA doses may be associated with an increased risk of mortality, serious cardiovascular and cerebrovascular events.[40] Indeed, it is known that optimizing iron status is a prerequisite for the effective treatment of anemia due to CKD. Low transferrin saturation levels and/or low ferritin levels are common factors leading to ESA hyporesponsiveness.[41] This can in turn lead to inappropriate dose escalation of ESA therapy, which is associated with higher risk cardiovascular adverse events and all-cause mortality.[42-44] Such circumstances may lead to other potential costs due, for example, to hospital admissions or prolonged hospital stay. This highlights that the cost savings resulting from the use of biosimilars may be offset by inappropriate use of any ESAs, irrespective of the type. Therefore, to reduce pharmaceutical expenditure, the increased use of biosimilars must occur in a more appropriate manner.

Other findings from this study are broadly comparable to previous studies. The overall mean yearly costs of CKD management in non-dialyzed patients were much lower than those of dialyzed patients, as expected. Studies investigating the cost of pre-dialysis CKD management are heterogeneous in terms of disease stage analyzed, methods, perspective of analysis, target population, so comparisons between the present study and other studies must be made with caution.[45] For instance, an Italian cross-sectional cost of illness study,[3] estimated the mean annual cost per patient with CKD by stage (IV and V pre-dialyses stages), stratifying by direct medical and non-medical costs and indirect costs, using the information collected from hospital patient records of 14 nephrology centers in Tuscany. Comparing the total direct mean costs per patient of CKD stages IV and V (pre-dialyses) using Tuscan data to the present study, a variation of -60% in less (€4,508.2 per patient) was observed. Results of the Tuscan study showed that drugs constitute the main cost component of the total direct medical costs, followed by hospitalizations and diagnostic/specialist visits. This contrasts with the present study, which demonstrated that hospitalizations have the highest impact on direct medical costs. Nevertheless, our results are in line with other published studies. Similarities were observed with a recent retrospective observational study,[4] which evaluated direct healthcare costs and resource use in CKD patients new to dialysis in the 2 years before beginning dialysis and in the

first year of dialysis using the Lombardy Regional Healthcare Service database during 2011. The results of this study using Lombardy data showed a dialysis mean cost per patient equal to €12,982 in the 6-12 months from the start of dialysis and it is therefore in line with our results, which show a dialysis mean cost per patient during the first year of treatment of €12,794 (40% of the total costs). If on the other hand we consider the total costs of patients in dialysis, our results are also in line with those of a cost-effectiveness study, which reported a total yearly mean cost of dialyzed patients of €38,821, compared to €31,985 of our study population.[4] In general, the economic burden increases with disease severity.[3,5]

Another expected finding is that the ESA-related yearly mean cost increased with advancing CKD in absolute terms, from €1,551 in CKD stage I-III to €2,045 in dialysis patients. Indeed, this increase in cost is driven by the high cost of dialysis, which accounts for over a third of direct healthcare costs in this population. This increase occurred despite a decrease in the proportion of the total mean costs attributed to ESA drugs: from 17.4% in CKD stage I-III to 6.4% in dialysis patients. As demonstrated by Ingrasciotta et al., among CKD patients, 49.8% and 45.2% received at least one prescription for a contraindicated nephrotoxic drug, mainly NSAIDs, within one year prior or after first CKD diagnosis, respectively.[46] In general, drug policies aimed at promoting use of low cost ESAs must be implemented along with strategies to slow down progression to dialysis in order to impact significantly on the healthcare expenditure reduction. From a payer perspective, beyond promoting the use of the lowest cost ESA use, it's important to implement strategies aimed for instance at reducing significantly the prescription of nephrotoxic drugs, which may increase the risk of preventable renal function deterioration. Ultimately, this may lead to delaying dialysis entry, thus minimizing clinical and economic burden of CKD.

The present study has several strengths and limitations. The main strength of this population-based study is the use of real-world data reflecting ESA use among CKD patients in routine clinical practice as well as the large study population, covering a total population of around 8 million persons (13.2% of the total Italian population) over a total period of 5 years. The cost analyses in this study were based on pharmacy claims for dispensed ESA drugs, and as such, can be considered to more accurately reflect drug costs than drug prescriptions, which patients may not always fill. A further strength is the detailed description of real healthcare costs, comprising several facets of CKD patient healthcare, including hospitalizations, concomitant drug use and diagnostic tests. However, our study also has some limitations. Some pharmacy claims, including ESA as well as non-ESA concomitant drugs, might not have been captured by the LHU databases (i.e. the first therapeutic cycle, intravenous iron infusion), as drugs are dispensed directly in the hospital. In addition, because this study was carried out using data from the regional NHS databases, private healthcare expenditure (e.g. diagnostic tests and specialist visit in private outpatient clinics) was not included. Cost analyses reflect the use of ESA for at least one year. This criterion of drug utilization was chosen in order to facilitate comparison of results across all categories of CKD stages. However, in clinical practice, the duration of treatment may be longer or shorter than one year. As a result, findings are not generalizable to other durations of treatment. Concerning inappropriate prescribing of ESAs, the availability of laboratory tests results, in particular hemoglobin levels within one month prior and within one year after the ESA start treatment date, is very limited to a small sample of our study cohort. It's important to highlight that this was an exploratory analysis and results

cannot be generalized to other populations. However, our results showed that, even if the numbers are low, the possible cost-savings achievable removing all first inappropriate ESA dispensing, could be equal to €35,772 for patients starting inappropriately (i.e. Hb level ≥11 g/dL) the ESA therapy, and it increases to €167,641 removing all inappropriate ESA dispensing during the first year of maintenance therapy. Another potential limitation may be that a proportion of inappropriate ESA users was due to dose escalation of ESA because of low transferrin saturation levels. Moreover, ICD-9-CM codes and costs related to emergency department visits were not taken into account because they were missing in more than 30% of records. Our findings may not be fully generalizable to the whole Italian general population, although the major geographic areas associated with specific trends in drug utilization and patient characteristics, i.e. southern, central, and northern Italy, were all represented. The database network has been previously used for the post-marketing assessment of biosimilar use, as described in more detail in previous publications,[12,21-23] and has generated real-world evidence which has been used in guidelines on management of cancer-related anemia of the American Society of Clinical Oncology/American Society of Hematology.[26] Indeed, comparison with the National Report on Medicines use in Italy supports the reliability of these databases in providing information about ESA use in the Italian outpatient setting in the respective catchment areas. Finally, the data used in the study was more than five years old. Costs associated with ESA utilization patterns in CKD have not yet been described in detail in Italy during the study years, so the findings of this paper can be considered novel. However, they may not reflect more recent trends in drug utilization.

Conclusions

The high costs of CKD management among dialysis patients was observed in this study as it was elsewhere, but an unexpected level of inappropriate ESA use contributed at least more than 165,000 Euros in preventable costs per year. The use of biosimilar products was observed in 15% of new ESA users with CKD treated for at least one year while the remainder used reference products or other originator ESAs. With a higher use of biosimilar ESAs the annual cost-savings would range from 8% to 30% of the total ESA costs. Appropriate use of ESAs as well as of other therapeutic interventions aimed at slowing down the progressive renal impairment is essential for minimizing clinical and economic burden of CKD in general population.

References

1. Dhaun N, Mackenzie J, Goddard J, Whitworth C. Prospective management of end-stage renal failure within a conservative care programme. *BMJ Qual Improv Reports* 2013;2(1). pii: u201182.w727.

2. De Nicola L, Donfrancesco C, Minutolo R, Lo Noce C, Palmieri L, De Curtis A, et al. Prevalence and cardiovascular risk profile of chronic kidney disease in Italy: results of the 2008-12 National Health Examination Survey. *Nephrol Dial Transplan*t 2015;30(5):806-14.

3. Bellelli S, Turchetti G. The social cost of chronic kidney disease in Italy. *Value Heal* 2014;17(3): A292.

4. Roggeri A, Roggeri DP, Zocchetti C, Bersani M, Conte F, ReNe (Renal Lombardy Network), et al. Healthcare costs of the progression of chronic kidney disease and different dialysis techniques estimated through administrative database analysis. *J Nephrol* 2017;30(2):263-269.
5. Cicchetti A, Ruggeri M, Codella P, Ridolfi A. I costi socio-sanitari dell'insufficienza renale cronica. *Farm e percorsi Ter* 2011; 12(1): 21-28.
6. Melissa E. Stauffer, et al. Prevalence of anemia in chronic kidney disease in the United States. *PLoS One* 2014;9(1):e84943.
7. National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). Anemia in chronic kidney disease. 2014. Available from: https://www.niddk.nih.gov/health-information/kidney-disease/anemia Accessed April 20, 2020.
8. Regione Emilia Romagna. Linea guida per la valutazione e il trattamento dell'anemia cronica nell'insufficienza renale cronica. 2005. Available from: http://www.asmn.re.it/allegati/qualitaclinica/Anemia/LG_AnemiaIRC_DICEMB_051.pdf Accessed April 20, 2020.
9. Determinazione AIFA. Aggiornamento del Piano terapeutico AIFA per prescrizione SSN di Eritropoietine (ex Nota 12). 2009. Available from: http://www.agenziafarmaco.gov.it/content/piano-terapeutico-la-prescrizione-di-eritropoietine-ex-nota-12 Accessed April 20, 2020.
10. Menditto E, Orlando V, Coretti S, Putignano D, Fiorentino D, Ruggeri M. Doctors commitment and long-term effectiveness for cost containment policies: Lesson learned from biosimilar drugs. *Clin Outcomes Res* 2015;7:575–81.
11. Koh E, Do V, Barton M. Frontiers of cancer care in Asia-Pacific region: cancer care in Australia. *Biomed Imaging Interv J* 2008;4(3):e30.
12. Ingrasciotta Y, Giorgianni F, Bolcato J, Chinellato A, Pirolo R, Tari DU, et al. how much are biosimilars used in clinical practice? A retrospective Italian population-based study of erythropoiesis-stimulating agents in the years 2009-2013. *BioDrugs* 2015;29(4):275–84.
13. Ingrasciotta Y, Belleudi V, Trotta F, Addis A, Fontana A, Chinellato, et al. In search of predictors of switching between erythropoiesis-stimulating agents in clinical practice: a multi-regional cohort study. *BioDrugs* 2020;34(1):55-64.
14. Genazzani AA, Biggio G, Caputi AP, Del Tacca M, Drago F, Fantozzi R, Canonico PL. Biosimilar drugs: concerns and opportunities. *BioDrugs* 2007;21(6):351–6.
15. Germedpharma. Scadenze brevettuali. Available from: http://www.germedpharma.it/scadenze_brevettuali.php Accessed April 20, 2020.
16. Gabi Online. Biosimilars of darbepoetin alfa. 2019. Available from: http://gabionline.net/Biosimilars/General/Biosimilars-of-darbepoetin-alfa Accessed April 20, 2020.
17. Agenzia Italiana del Farmaco (AIFA). Secondo Position Paper AIFA sui Farmaci Biosimilari. 2018.
18. European Medicines Agency (EMA). Biosimilars in the EU, Information guide for healthcare professionals. 2017. Available from: https://www.ema.europa.eu/en/documents/leaflet/biosimilars-eu-information-guide-healthcare-professionals_en.pdf Accessed April 20, 2020.
19. Osservatorio nazionale sull'impiego dei medicinali (AIFA). L'uso dei farmaci in Italia. 2017;91:399–404.

20. Trifirò G, Gini R, Barone-Adesi F, Beghi E, Cantarutti A, Capuano A. The role of European healthcare databases for post-marketing drug effectiveness, safety and value evaluation: where does Italy stand? *Drug Saf*. 2019;42(3):347-363.
21. Marcianò I, Ingrasciotta Y, Giorgianni F, Bolcato J, Chinellato A, Pirolo R, et al. How did the introduction of biosimilar filgrastim influence the prescribing pattern of granulocyte colony-stimulating factors? Results from a multicentre, population-based study, from five Italian centres in the years 2009–2014. *BioDrugs* 2016;30(4):295–306.
22. Marcianò I, Ingrasciotta Y, Giorgianni F, Ientile V, Chinellato A, Tari DU, et al. Pattern of use of biosimilar and originator somatropin in Italy: a population-based multiple databases study during the years 2009-2014. *Front Endocrinol (Lausanne)* 2018;9:95.
23. Ingrasciotta Y, Giorgianni F, Marcianò I, Bolcato J, Pirolo R, Chinellato A, et al. Comparative effectiveness of biosimilar, reference product and other erythropoiesis-stimulating agents (ESAs) still covered by patent in chronic kidney disease and cancer patients: an Italian population-based study. *PLoS One* 2016;11(5):1–16.
24. Ingrasciotta Y, Lacava V, Marcianò I, Giorgianni F, Tripepi G, D'Arrigo G, Chinellato A, Tari Daniele U, Santoro D and Trifirò G. In search of potential predictors of erythropoiesis-stimulating agents (ESAs) hyporesponsiveness: a population-based study. *BMC Nephrol* 2019;20(1):359.
25. Belleudi V, Trotta F, Addis A, Ingrasciotta Y, Ientile V, Tari M, Gini R, Pastorello M, Scondotto S, Cananzi P, Traversa G, Davoli M, Trifirò G. Effectiveness and safety of switching originator and biosimilar epoetins in patients with chronic kidney disease in a large-scale Italian cohort study. *Drug Saf* 2019; 42(12):1437-1447.
26. Bohlius J, Bohlke K, Castelli R, Djulbegovic B, Lustberg MB, Martino M, et al. Management of cancer-associated anemia with erythropoiesis-stimulating agents: ASCO/ASH clinical practice guideline update. *J Clin Oncol* 2019; 15(7):399-402.
27. Giordano G, Mondello P, Tambaro R, Perrotta N, D'Amico F, D'Aveta A, et al. Biosimilar epoetin α is as effective as originator epoetin-α plus liposomal iron (Sideral®), vitamin B12 and folates in patients with refractory anemia: A retrospective real-life approach. *Mol Clin Oncol* 2015;3(4):781–4.
28. Garzotto AR, Heine O, Turner M, Rebollo Laserna F, Lorenz A. Erythropoiesis-stimulating agents for the treatment of chemotherapy-induced anemia: comparisons from real-world clinical experience. *J Blood Med*. 2014;5:43–8.
29. Trotta F, Belleudi V, Fusco D, Amato L, Mecozzi A, Mayer F, et al. Comparative effectiveness and safety of erythropoiesis-stimulating agents (biosimilars vs originators) in clinical practice: a population-based cohort study in Italy. *BMJ Open* 2017; 7(3):e011637.
30. Decreto Commissariale (DC) n. 15: Piano di contenimento della spesa farmaceutica ospedaliera. 2009. Available from: http://www.aiopcampania.it/public/normativa/decreto_15_deliberazioni_del_commissario_ad_acta.pdf Accessed December 14, 2015.
31. Linee guida per l'impiego e l'acquisto dei farmaci biosimilari: parere espresso dalla Commissione Terapeutica del Prontuario Terapeutico Ospedaliero Regione Veneto (PTORV). 2010. Available from: http://bur.regione.veneto.it/BurvServices/pubblica/HomeConsultazione.aspx AccessedApril 20, 2016.

32. Decreto n. 592: Farmaci biosimili: direttive alle aziende sanitarie ed agli Enti per i Servizi Tecnico-Amministrativi di Area Vasta (ESTAV) della Regione Toscana. 2010. Available from: http://web.rete.toscana.it/burt/?LO=01000000d9c8b7a6030000000f000000514300000a8a5340000000000100481000000000000000000000000000000000000000000000000000000000000000000000000000000&MItypeObj=application/pdf Accessed December 14, 2015.
33. D. A. n. 540/14: Misure volte a promuovere l'utilizzo di farmaci originatori o biosimilari a minor costo di terapia. Chiarimenti del 17/06/2014. Available from: http://pti.regione.sicilia.it/portal/page/portal/PIR_PORTALE/PIR_LaStrutturaRegionale/PIR_AssessoratoSalute Accessed April 20, 2016.
34. Arantes LA, Crawford J, Gasconc P, Latymerd M, Launay-Vachere V, Rolland C, Scotte F, Wish J. A quick scoping review of efficacy, safety, economic, and health-related quality-of-life outcomes of short- and long-acting erythropoiesis-stimulating agents in the treatment of chemotherapy-induced anemia and chronic kidney disease anemia. *Crit Rev Oncol Hematol* 2018;129:79-90.
35. Duh MS, Weiner JR, White LA, Lefebvre P, Greenberg PE. Management of anaemia: a critical and systematic review of the cost effectiveness of erythropoiesis stimulating agents. *Pharmacoeconomics* 2008; 26 (2), 99–120.
36. Wilson J, Yao GL, Raftery J, Bohlius J, Brunskill S, Sandercock J, et al. A systematic review and economic evaluation of epoetin alpha, epoetin beta and darbepoetin alpha in anaemia associated with cancer, especially that attributable to cancer treatment. *Health Technol Assess* 2007;11(13):1-202, iii-iv.
37. Tonelli M, Klarenbach S, Wiebe N, Shrive F, Hemmelgarn B, Manns B. Overview of erythropoiesis-stimulating agents for anemia of chronic kidney disease: systematic review and economic evaluation. Technology Report No. 106. Canadian Agency for Drugs and Technologies in Health (CADTH). 2008; Ottawa. Available from: http://www.crd.york.ac.uk/CRDWeb/ShowRecord.asp?ID=32008000111 Accessed December 20, 2017.
38. Bonafont X, Bock A, Carter D, Brunkhorst R, Carrera F, Iskedjian M, et al. A meta-analysis of the relative doses of erythropoiesis-stimulating agents in patients undergoing dialysis. *NDT Plus* 2009; 2 (5), 347–353.
39. Cremieux PY, Van Audenrode M, Lefebvre P. The relative dosing of epoetin alfa and darbepoetin alfa in chronic kidney disease. *Curr. Med. Res. Opin* 2006; 22 (12), 2329–2336.
40. European Medicines Agency. Summary of product characteristics of Epoetin alfa HEXAL, INN-epoetin alfa. Available from: https://www.ema.europa.eu/en/documents/product-information/epoetin-alfa-hexal-epar-product-information_en.pdf Accessed April 20, 2020.
41. Kalantar-Zadeh K, Lee GH, Miller JE, Streja E, Jing J, Robertson JA, et al. Predictors of hyporesponsiveness to erythropoiesis-stimulating agents in hemodialysis patients. *Am J Kidney Dis* 2009;53(5):823–34.
42. Szczech LA, Barnhart HX, Inrig JK, Reddan DN, Sapp S, Califf RM, et al. Secondary analysis of the CHOIR trial epoetin-alpha dose and achieved hemoglobin outcomes. *Kidney Int* 2008;74(6):791–8.
43. Suttorp MM, Hoekstra T, Rotmans JI, Ott I, Mittelman M, Krediet RT, et al. Erythropoiesis-stimulating agent resistance and mortality in hemodialysis and peritoneal dialysis patients. *BMC Nephrol* 2013;14:200.

44. Gilbertson DT, Ebben JP, Foley RN, Weinhandl ED, Bradbury BD, Collins AJ. Hemoglobin level variability: associations with mortality. *Clin J Am Soc Nephrol* 2008;3(1):133–8.
45. Polder JJ, Meerding WJ, Bonneux L, Van Der Maas PJ. A cross-national perspective on cost of illness: A comparison of studies from The Netherlands, Australia, Canada, Germany, United Kingdom, and Sweden. *Eur J Heal Econ* 2005;6(3):223–32
46. Ingrasciotta Y, Sultana J, Giorgianni F, Caputi AP, Arcoraci V, Tari DU, et al. The burden of nephrotoxic drug prescriptions in patients with chronic kidney disease: a retrospective population-based study in Southern Italy. *PLoS One* 2014;9(2):e89072.

Online Resource 1. The ICD-9-CM disease codes and national exemption codes used to identify patients with chronic kidney disease.

Code	Description	Claims database
250.4	Diabete with renal manifestations	Electronic therapeutic plans/Hospital discharge form (ICD-9 CM codes)
285.21	Anemia in chronic kidney disease	
V56*	Encounter for dialysis and dialysis catheter care	
E870.2	Kidney dialysis or other perfusion	
585*	Chronic kidney disease (CKD)	
792.5	Cloudy (hemodialysis) (peritoneal) dialysis effluent	
996.1	Mechanical complication of other vascular device, implant and graft	
996.56	Due to peritoneal dialysis catheter	
996.68	Due to peritoneal dialysis catheter	
996.73	Due to renal dialysis device, implant, and graft	
E871.2	Kidney dialysis or other perfusion	
E872.2	Kidney dialysis and other perfusion	
E879.1	Kidney dialysis	
E874.2	Kidney dialysis and other perfusion	
403*	Hypertensive chronic kidney disease	
404*	Hypertensive heart and chronic kidney disease	
583*	Nephritis and nephropathy, not specified as acute or chronic	
586*	Renal failure, unspecified	
585.1	Chronic kidney disease, Stage I	
585.2	Chronic kidney disease, Stage II (mild)	
585.3	Chronic kidney disease, Stage III (moderate)	
585.4	Chronic kidney disease, Stage IV (severe)	
585.5	Chronic kidney disease, Stage V	
585.6	End stage renal disease	
792.5	Cloudy (hemodialysis) (peritoneal) dialysis effluent)	
996.1	Mechanical complication of other vascular device, implant, and graft	
996.56	Due to peritoneal dialysis catheter	
996.68	Due to peritoneal dialysis catheter	
996.73	Due to renal dialysis device, implant, and graft	
V45.1*	Renal dialysis status	
V56*	Encounter for dialysis and dialysis catheter care	
E870.2	Kidney dialysis or other perfusion	

E871.2	Kidney dialysis or other perfusion	
E872.2	Kidney dialysis and other perfusion	
E879.1	Kidney dialysis	
E874.2	Kidney dialysis and other perfusion	
39.27	Arteriovenostomy for renal dialysis	
38.95	Venous catheterization for renal dialysis	
39.42	Revision of arteriovenous shunt for renal dialysis	
39.43	Removal of arteriovenous shunt for renal dialysis	
39.95	Hemodialysis	
54.98	Peritoneal dialysis	
023	Chronic Kidney Disease	Co-payment exemption (national exemption codes)

Legend: CKD: Chronic Kidney Disease; ICD-9-CM: International Classification of Diseases, ninth Revision, and Clinical Modification. * refers to additional sub-code.

CHAPTER 5.
GENERAL DISCUSSION

General discussion

Drug prescriptions, especially biologic drugs, to elderly is challenging due to limited scientific evidence on the effectiveness as well as safety of these drugs in this specific population. The increasing use of biologics in clinical practice gave rise to safety concerns, such as the risk of hypersensitivity reactions, immunogenicity, infections and cancer. The pressing need for thorough post-marketing monitoring of these drugs became clear [1]. The availability and secondary use of claims databases with electronic health records of millions of persons offer the opportunity to get better insights into real-world drug use and the risks and benefits of those medications in community dwelling elderly persons. In this chapter, the main findings of this research thesis and the main methodological issues of pharmacoepidemiological studies are discussed to facilitate a proper interpretation of the results described in the thesis.

Main findings

Real-world use of analgesics and biologics among elderly

Abuse of opioids in Italy is not as common as in the United States (U.S.). The study presented in **Chapter 2.1** showed that most elderly analgesic users were prescribed non-opioid analgesics than opioid analgesics and, among opioids, weak opioids were more commonly used than strong opioids. This is in line with the recommended stepped use of analgesic drugs, where non-opioids are first-line agents, followed by weak and strong opioids.

This finding was in line with results from the study presented in **Chapter 2.2**, where a higher use of traditional non-steroidal anti-inflammatory drugs (NSAIDs) and COX-2 inhibitors at baseline among Italian patients with reumathoid arthritis (RA), compared to U.S. patients, was showed. On the contrary, we found that half of RA patients from U.S. had received at least one dispensing for opioids before the RA diagnosis date. Zamora-Legoff JA et al., in a population-based study including RA patients from the Rochester Epidemiology Project (REP), a special record-linkage system that records all inpatient and outpatient encounters among the residents of Olmsted County, Minnesota, showed that over one-third of RA patients used opioids, and in more than a tenth the use was chronic [2]. Recent years have seen an 'opioid crisis' take place in the U.S., with widespread misuse and over-use of opioids, leading to a large number of overdose-related deaths [3]. In Italy there has been a four-fold increase in the number opioid prescriptions from 2007 to 2017, as reported by the Italian Society of Pharmacology; however, this increase is modest compared to other European countries [4].

Evaluating the appropriateness of opioid prescribing is a challenge, as this depends on an accurate classification of the severity of pain. For instance, the observational study included in **Chapter 2.1** found that weak and strong opioids were commonly used for bone and joint disorders, although less commonly than non-opioid analgesics. However, in this case, they should only be used for moderate to severe pain associated to bone and joint disorders [5]. On the other hand, opioids were commonly used in cancer patients as an indication, in line with the indication of these drugs in palliative care [6]. In the context of frailty, we also found that strong opioids were used more commonly in frailer persons compared to persons with a better cognition and functional status; this is surprising because elderly persons who are frail are likely to have poorer

mobility [7]. This is likely to predispose such elderly persons to adverse drug reactions (ADRs), such as falling with risk of facture, increasing the risk of hospitalization and disability [8].

Similarly, the appropriateness of other analgesic drugs in the context of pain severity was not possible. It is worth noting that the appropriate use of medications in frail persons may go beyond the available guidance on the appropriate use of medications. For example, while acute and chronic kidney disease may be caused, exacerbated or worsened by non-opioid analgesics, it may be misleading to monitor renal function in elderly persons through creatinine levels alone in patients with sarcopenia, i.e. reduced muscle mass and strength.

Concerning the use of biologics for the treatment of immune-mediated inflammatory diseases (IMIDs), according to the guidelines, biologics represent the 2nd line of therapy usually reserved for patients who have failed or have contraindications to conventional drugs [9-11]. The VALORE project network presented in **Chapter 3.3** showed an increasing use of biologics, approved for the treatment of IMIDs, in 13 Italian regions over a period of 10 years, with a slightly heterogeneity across regions. The heterogeneity may be explained by the regional drug policies, the availability of highly qualified specialist centers, and the characteristics of underlying population which could all account for differences in biologic access across Italian regions. In general, we identified more than 140,000 biologic users with a cumulative 507,745 PYs of exposure. As compared with 2010, the total number of biologic users was fourfold larger in 2019, with a yearly prevalence of users increasing overall on average from 0.7 per 1,000 in 2010 to 2.1 per 1,000 in 2019. This was in line with the increased use of several biologics over the years reported by the national reports on medicine use in Italy [12-15] and with the results from other population-based studies [16, 17].
One of the factors related to the increased yearly prevalence of use of biologics across all the regions during the study period could be represented by the marketing of several biological drugs (e.g., secukinumab, vedolizumab), including biosimilars, in more recent years as well as the extensions of the approved indications for use for many frequently prescribed biologics (e.g., adalimumab), thus expanding the number of patients eligible for the biological treatments. Our study showed that tumor necrosis factor-alpha (TNFα) inhibitors were the most frequently dispensed biologics (82%), followed by interleukin inhibitors (26%), and selective immunosuppressants (12%). Overall, more than 40,000 users (almost 30% of total users) of biosimilars of TNFα inhibitors (i.e., etanercept, adalimumab, and infliximab) were identified in the last 5 years of observation. The proportion of biosimilar users increased in all the Italian regions over time. In general, the use of biosimilars has increased significantly over recent years, albeit with heterogeneity across Italian regions, as documented in the national reports on medicine use in Italy [12-15] and previous Italian real-world studies [18, 19]. This finding is probably due to the implementation of different regional health policies for promoting biosimilar use [20]. As regards to specific age groups, more than 10,000 (7%) biologic users were aged < 18 years and more than 46,000 (32%) were aged >65 years. Among elderly patients, 8,886 (6.2% of total biologic users) were aged >80 years.
In **Chapter 2.2** we focused on the pattern of use of real-world use of drugs for the treatment of reumathois arthritis, both adult and elderly people, in Caserta Local Health Unit (LHU) versus the United States. Although RA therapy has made major advances over the past few decades, especially with the introduction of biologics as a treatment option for RA patients, most of the

patients included in the study were found to be initially treated with anti-inflammatory drugs or conventional disease-modifying antirheumatic drugs (csDMARDs) rather than biologics. This may be due to the patients in the study having had less severe RA or a state of low disease activity that warranted no treatment with biologics. It could also be that patients may still have been kept on csDMARDs despite not achieving remission or low disease activity as recommended in the RA guidelines [9, 10]. Given that claims databases do not collect clinical data on effectiveness or disease activity, we were not able to evaluate these hypotheses.

Another reason justifying the low use of of biologics may be the access, as public payers take longer than private payers to recognize criteria for use and issue approval of advanced therapeutic agents. Indeed, the access to biologics still represents an insight. In Italy, although biologics are fully reimbursed by the National Health Service (NHS), the access barrier is due to the guidelines, which recommend these high-cost treatments if the treatment target is not achieved with the csDMARD strategy. On the contrary, in the U.S., the access barrier to these high-cost treatments could be explained by the high median out-of-pocket cost (e.g. $ 40) related to biologics.

The low use of biologics for the treatment of RA was confirmed by an Italian retrospective observational study using claims databases from five Italian regions [21]; the study showed that, as a first treatment, 5% of RA patient received biologics versus 52% were not treated with DMARDs and received no treatment at all or only NSAIDs/glucocorticoids versus 43% of RA patients receiving csDMARDs. Another U.S. study showed that only 3% of RA patients initiated the biologic treatment within 1 year after the diagnosis [22], confirming the low use of this drug class in our two cohorts, especially in elderly patients from U.S. Indeed, results from our study showed that treatment escalation was less frequent in old RA patients than in young adult patients. Compared to 6% of young adult RA patients, only 1% of elderly RA patients from U.S. was treated with biologics, with or without csDMARDs, while only 1% of RA patients from Italy received biologic dispensing, without any statistically significant differences observed in the two age groups. It's known that old RA patients may be less aggressively treated than they should be [23-26]. The Ruban study reported that despite higher disease activity at diagnosis, elderly-onset RA (EORA) patients were less likely to receive combination DMARD therapies or biologics compared with young-onset RA (YORA) patients, even though these drugs (biologics in particular) have been shown to have similar efficacy in old and young patients [26]. Time to first biologic may be strongly associated with age. The ≥75s were more likely to be on less intensive therapies compared to the <65s (csDMARD monotherapy or steroid alone, versus csDMARD combination therapy or bDMARD).

The low use of biologics in elderly was confirmed in **Chapter 2.3** focusing on real-world use of biologics in elderly patients with inflammatory bowel diseases from Lazio region during the years 2010-2020. The cohort study showed that the prevalence of elderly users of biologics was low during the study years with a slight growing trend during the study period (from 0.4 per 1,000 inhab. in 2010 to 1.3 per 1,000 inhab. in 2020). Specifically, stratifying the prevalence of use by single molecule and calendar year, adalimumab was the most used biologic in the study period showing an increasing trend of use from 0.3 per 1,000 inhab. in 2010 to 0.7 per 1,000 inhabitants in 2020. Focusing on the two study diseases (i.e. Crohn's disease (CD) and ulcerative colistis), almost half of CD elderly patients was more likely to be started the treatment with

adalimumab (47%), while UC patients were mostly treated with infliximab (46.0%). Despite few patients with IBD in Lazio Region were treated with biologics, their adherence (MPR≥80%: 89%) and persistence (98%) during the first year of treatment was very high (MPR≥80%: 89%).

Post-marketing monitoring of the benefit-risk profile of biologics

Biologics are large molecules, more complex than traditional small chemically synthesized molecules. Their complexity, as well as the way in which they are produced, may result in a degree of variability in molecules of the same active substance, particularly across different batches of the medicine [27]. In general, safety issues, such as the risk of infection, malignancy, or administration reactions, may arise during therapy with biologics. Unlike chemically synthetized small molecules, systemic adverse effects of biologics are often due to the pharmacodynamic effects of the drug (so-called '*on-target risks*'). The safety profile of biologics includes adverse reactions related to their pharmacologic actions and immunologic reactions, such as immunogenicity and administration-site reactions [28-30]. Most biologics, such as monoclonal antibodies, have a prolonged half-life and increased durations of action in comparison with chemically synthesized small molecules; moreover, they are usually injectable drugs, frequently associated with mild, cutaneous, or hypersensitivity reactions.

As clearly described in **Chapter 3.1**, one of the main concern of biologics is the immunogenicity which may induce immune responses, including mild hypersensitivity, infusion reactions, or cross-reactions to endogenous molecules, and can trigger the production of anti-drug antibodies (ADAs), which are antigen-specific but are not crossreacting even with molecules displaying comparable pharmacological activity [31, 32]. The best-known example of biologic-related immunogenicity was the development of pure red cell aplasia (PRCA), occurring in patients with CKD who were switched from intravenous to subcutaneous formulation of recombinant epoetin alpha. PRCA was caused by a combination of factors related to the production, handling, and route of administration of the formulation of an epoetin alpha reference product, in which the stabilizer albumin was substituted by polysorbate 80 and glycine [33].A special focus on the safety of biologics in elderly patients with inflammatory bowel disease (IBD) was described in **Chapter 3.2**. We provided an overview of the safety and potential drug-drug interactions of immunosuppressive drugs for the treatment of IBD in elderly patients. It's known that patients enrolled in randomized clinical trials (RCTs) are often "selected patients", without comorbidities and concomitant drugs; moreover, elderly patients, as well as pregnant women and children, and those with common medical conditions are frequently excluded from RCTs. Such exclusions may impair the generalizability of RCT results in real-world settings and the assessment of the post-marketing monitoring safety and drug-drug interactions onset.
Evidences from the literature showed that the use of immunosuppressive therapy is a challenge in the management of elderly patients with IBD in clinical practice. In particular, the use of thiopurine may increase the risk of malignancies such as lymphomas [34], non-melanoma skin cancers (NMSC) [35] and urinary tract cancers [36] raising concerns about their use in this population. On the other hand, TNFα inhibitors are associated with higher rate of opportunistic infection, such as pneumonia, sepsis, candidiasis, herpes zoster, and Clostridioides difficile colitis, compared with younger IBD patients [37]. This is confirmed by a multi-center nested case-control study performed by the Italian Group for Inflammatory Bowel Disease, that showed

higher rate of severe infections and mortality in elderly patients treated with TNFα inhibitors as compared with younger patients with the same treatment and with patients of the same age that did not receive these therapeutics [38]. Concerning drug-drug interactions, evidences from literature don't show specific differences between young and old IBD patients. Therefore, if possible, biologics with lower infection or malignancy risk, such as vedolizumab, may be preferred in elderly patients with IBD [39]. Concomitant therapies and comorbidities should be thoroughly investigated before starting any immunosuppressive or biological treatment in order to minimize the risk of drug-drug interactions.

Since RCTs are not able to detect rare adverse outcomes or those with a long latency, the safety profiles of biologics should always be intensively monitored in the real-world setting. In **Chapter 3.3** we demonstrated that a multi-database healthcare network may be very useful to estimate the number of drugs that could be monitored for surveillance of a range of safety outcomes with different background incidence rates [40]. Specifically, the VALORE project, funded by the Italian Medicines Agency, showed that the distributed multi-database network had enough statistical power to adequately detect even weak associations between individual biological drugs approved for IMIDs and specific safety outcomes of interest. For instance, for SARSCoV-2 infection, 12,439 person-years (PYs) of exposure to any biologic would be required to detect a weak (IRR 1.5) association, which would allow investigation of nine of the 15 individual biologics aprroved for the treatment of IMIDs.

Moreover, one of the main concerns of biologics, including biosimilars, is the hyporesponsiveness. A previous population-based study, conducted using two Italian claims databases, showed that 20% of users of either biosimilar or originator erythropoiesis-stimulating agents (ESAs) for the treatment of chronic kidney disease (CKD)- and cancer-related anemia were "non-responsive" (Ingrasciotta Y, 2016), that is patients who need high doses of ESAs to increase and/or maintain their hemoglobin (Hb) levels within the acceptable range. However, higher doses of ESA may increase the risk of developing cardiovascular diseases, stroke in older patients with Hb levels above the target range and, ultimately, death [41]. In **Chapter 3.4** we investigated the potential factors associated to ESA hyporesponsiveness in anaemic patients with CKD. We found that that C-reactive protein was a predictor of ESA hyporesponsiveness in CKD patients. As confirmed by different published studies [42-44], inflammatory cytokines may affect the development of anemia through the suppression of bone marrow erythropoiesis, suppression of erythropoietin production, or interfering with the iron status [45]. On the other hand, we found that concomitant use of high dosage of angiotensin-converting enzyme inhibitors/angiotensin II-receptor blockers and of iron preparations could be protective factors against ESA hyporesponsiveness; concerning iron intake, there is no general consensus regarding the role of iron status as a predictor of ESA responsiveness, although previous studies on hemodialysis patients showed that an altered iron, is a common factor inducing ESA hyporesponsiveness [46]. Finally, our study confirmed that the type of dispensed ESA (biosimilar or originator) was not a predictor of ESA hyporesponsiveness in CKD patients.

Interchangeability and switching practices of biologics

To date, interchangeability of biosimilars and reference products still represents an important issue from a scientific and regulatory perspective. This is based on concerns of immunogenicity

related to the switching between biological products, which may cause lack of effect and toxicity (**Chapter 4.1**).

Biosimilars have established similarity to the biologic reference product in terms of safety and efficacy according to the guidelines and procedures provided for by the European Medicines Agency (EMA) and the Food and Drug Administration (FDA). However, since they are not exact copies of biological reference products, questions arise regarding the use of a biosimilar in place of a reference product. The medical practice of changing one medicine for another that is expected to achieve the same clinical effect in a given clinical setting and in any patient, on the initiative, or with the agreement, of the prescriber has been described as interchangeability by the EMA [47]. This change can be done by the prescriber when he decides to exchange one medicine for another one with the same therapeutic intent (switching) or at the pharmacy level where a medicine is dispensed in place of another equivalent and interchangeable one without consulting the prescribing doctor (automatic substitution) (**Chapter 4.1**). Switching can be medical which is initiated by a prescriber due to adverse events or convenience dosing or it can be non-medical whereby issues such as price and availability are the main concern [48].

Whilst there are no statutory requirements by EMA to demonstrate interchangeability, the EMA has agreed that the decision with respect to interchangeability, substitution and switching should be decided by each national competent authority [49]. The regulatory framework on interchangeability in Europe is therefore heterogenous. Many countries in Europe have guidelines and legislation influencing the decision on substitution and switching. Such guidelines are prepared jointly by Health Technology Assessment (HTA) bodies, national regulatory bodies and regional authorities that discuss switching and substitution, the conditions under which they are to be done as well as the target population (treatment naive or previously treated patients) and indications specified in marketing authorisation [50]. The FDA defines a biological product to be interchangeable with the reference product if it is a biosimilar and it can be expected to produce the same clinical result as the reference product in any given patient. It further states that for a biological product that is administered more than once to an individual, the risk in terms of safety or diminished efficacy or alternating or switching between the use of the biological product and the reference product is no greater than the risk of using the reference product without the switch [51]. As a result, the BPCI Act allows for interchangeable biosimilars to be substituted for their reference product at the pharmacy level. Laws passed by individual state legislature provide the legal mechanism and requirements for the substitution of a reference biological with the biosimilars. The newly published guidance by FDA on demonstration of interchangeability require switching/ cross over studies with at least three switches carried out in blinded and randomised fashion for an appropriate period of time in line with the patients most likely to switch [52].

In the U.S., 43 states have state legislation governing substitution practices. The majority allows for non-medical substitution of an interchangeable product as long as the prescribing doctor has not prohibited it in writing. In Europe, although marketing authorisation of biosimilars is centrally done by the EMA, the policies on interchangeability and substitution are related to utilisation practices which are outside the scope and mandate of the EMA [53]. Unlike in the U.S. where there is a perception that interchangeability can be synonymous with automatic substitution, in Europe, interchangeability between the reference and biosimilars is generally accepted, but this does not infer substitution as it is not recommended in most countries.

Switching in the U.S. is a practice that is left to the prescriber, whereas in Europe switching is determined at national level. For instance, Germany, Italy, Norway, the United Kingdom, and the Netherlands had legislation or policy from the medicines regulatory agency regarding the substitution and switching of biosimilars [53]. In particular, the Italian Medicines Agency took a position in favor of biosimilar and reference product interchangeability, without mentioning automatic substitution between originators and biosimilars, in the most recent position paper on biosimilars [54]. Substitution is permitted in Germany and France and requires for the patient to be notified and is only possible if the prescribing doctor does not prohibit dispensing of biosimilars of the biological on the prescription. Furthermore, in Germany it is limited to specific groups of biologicals and particularly biosimilars manufactured by the same manufacturer. However, in France the substitution is allowed, but it is not yet being implemented [55].

There are two main concerns with regards to interchangeability of biosimilars and their reference products. The first one is that most of these biological drugs are meant to treat chronic illnesses which mean that switching could be expected from the reference product to biosimilars and viceversa and even between biosimilars of the same reference products.
In **Chapter 4.2**, our retrospective, multi-Regional cohort study showed that switching between originators and biosimilars and viceversa is frequent (15.5%) in CKD and cancer patients; this is confirmed by other drug utilisation Italian studies (e.g. 15–20% for epoetins [18, 56, 57], and 20% for filgrastim [19] during the first year of therapy and 46% for etanercept, adalimumab, and infliximab during the follow-up (**Chapter 3.3**). The switch was more common toward an originator ESA than a biosimilar (82% vs. 18%) and simple switch was more common (62.2% of the switchers) than multiple (23.5%) or backward switch (14.3%) (**Chapter 4.2**). However, the probability of switches occurring was dependant on the duration of treatment [56]. Several factors could lead to switching from a biological drug to another one, such as ineffectiveness (missed achievement of a therapeutic goal, e.g., a predefined hemoglobin threshold), tolerability, or physician/patient preference due to differences in the frequency or route of administration between various ESAs, which may affect patient compliance [58]. Our study found that variables as severity of CKD, history of comorbidities or concomitant drugs, previous bood transfusions as well as type of ESA dispensed to naïve patients were potential predictors of switching in both CKD and cancer patients.
The second concern is that the switch from the reference product to the corresponding biosimilar may have an impact on efficacy and safety. In theory, changes in safety and efficacy might be associated with a switch from the reference product to the biosimilar if the two products have a diffrent inter-individual variation in pharmacokinetics [59]. However, data from the NOR-SWITCH study [60], and from a review [61] including both data from clinical trials conducted worldwide and from the EudraVigilance database, including suspected serious adverse drug reactions reported to the regulatory authorities in the EU, in Norway, and Iceland, showed no differences in terms of efficacy and safety between switchers and non-switchers, especially for I generation biosimilars and for infliximab, as a biosimilar monoclonal antibody.

In **Chapter 4.3** our large-scale Italian observational multi-database study demonstrated that switching versus non-switching during the first 2 years of treatment in CKD patients was not associated with any effectiveness and safety outcomes. In particular, switching from originator ESA α to biosimilars is effective and safe when compared with switching from a biosimilar. The

safety of switching between originators and biosimilars was confirmed by other real-worls studies [56, 62-64]. Given the limitations of pre-marketing randomized clinical studies, safety of switching between originators and biosimilars requires additional investigation in real-life settings and can be further addressed by generating clinical evidence of biosimilarity from pre-marketing studies and intensified post-marketing surveillance. Distributed database networks, potentially linkable to clinical charts and registries, may assess frequency and benefit-risk profile of different switching patterns in clinical practice, thus integrating and strengthening pre-marketing evidence (**Chapter 3.3 and Chapter 4.1**). Therefore, since the comparative effectiveness and safety of biosimilar and originator have been demonstrated, the problem is not the use or not of the biosimilar, but the prevention of inappropriate use of biologics.

In **Chapter 4.4**, we demonstrated that higher use of lowest cost ESA, as biosimilars, but mostly the prevention of inappropriate ESA use in CKD could represent the best strategy to reduce the risk of renal function deterioration. Consequently, this could lead to delaying dialysis entry, thus also reducing direct healthcare costs in CKD.

The management of chronic kidney disease is very difficult and, especially in dialysis, it is very expensive. The passage from one stage to the next one of CKD causes extra clinical but also economic complications, especially in dialysed patients. In our large-scale population-based database study, conducted in the context of a project funded by Italian Health Ministry (RF-2010-2320172), through the building of an Italian claims database network and covering a population of almost 8 million people (13.3% of the whole Italian population), we showed that the ESA-related yearly mean cost was 17% of total yearly costs in CKD stage I-III, decreasing to 13% in stage IV-V and to 6% in dialysis. In CKD stage I-V, more than 50% of total costs were attributable to hospitalizations, as confirmed by another Italian retrospective observational study [65], while in dialysis the highest cost (39.6%) was attributable to dialysis procedure. Second, we found that only 15% of all ESA users included in the study cohort received a biosimilar as a first ESA, with the remainder using reference products or other originator ESAs; this was in contrast with the position paper of the Italian Medicines Agency, which recommends prescribing biosimilars to treat naive patients [e.g. patients never previously treated with erythropoiesis-stimulating agents (ESAs) or with previous exposure that is sufficiently distant in time] [66] and with the updated ASCO/American Society of Hematology (ASH) clinical practice guideline [67] that cited several multidatabase studies demonstrating the comparability of epoetin-α, originator and biosimilar, as well as other ESAs still covered by patents (eg, darbepoetin, epoetin-β) in terms of effectiveness and safety [68-71]. Despite this guideline refers to patients with cancer, this consideration may be extended to patients with CKD. Third, we demonstrated that if 25% of originator ESA users were treated with a biosimilar, the annual cost-savings of the total ESA treatment cost would range from 8% to 11%, depending on the CKD stage. Assuming a 50% or 75% of biosimilar uptake, these cost-savings would increase up to 20-30% of the total ESA costs. Fourth, we found that 9% of our study cohort started inappropriately ESA treatment, increasing to 62.0% during the first year of maintenance therapy. Hypothesizing prevention of the first inappropriate ESA dispensing (that is, the use of ESA among patients with Hb levels equal to or greater than 11 g/dL), the total yearly cost-savings would amount to over €35,000, increasing to over €167,000 eliminating the inappropriate dispensing during maintenance therapy.

Methodological considerations

According to the FDA, "real-world data" are routinely collected medical data relating to patient health status and/or the delivery of healthcare. Such data are available through electronic health records (EHRs), medical claims, drug and disease registries, patient lifestyle-related activities and health-monitoring devices [72]. Real-world data may overcome some limitations of data from RCTs: less detailed information on drug efficacy but longer observational periods and larger, more heterogeneous study populations reflecting clinical practice because individuals who would not usually be recruited in RCTs, such as elderly, are included [73]. Real-world data can be collected in various types of electronic sources, such as claims databases, electronic health records, and drug or disease registries.

In all the observational studies presented in this thesis, data have been drawn from:

- The Caserta Local Health Unit (LHU) - Italy and Optum's de-identified Clinformatics® Data Mart (CDM) - United States claims databases, covering 1.1 million and 53.3 million individuals, respectively, over a period of 10 years (**Chapter 2.2**). Caserta LHU database [74-77]; and Optum CDM [78, 79] have been shown to provide accurate and reliable information for pharmacoepidemiological research;
- The Arianna database, which is a longitudinal general practice (GP) database from Southern Italy, which was set up in 2000. It currently contains information on a population of almost 300,000 individuals (225 GPs) living in the catchments area of Caserta (**Chapters 2.1, 2.2**), linkable with patient-level claims data from Caserta claims databases. This database has been used for some previous epidemiological studies [80, 81];
- Multi-regional claims databases, including data from 13 Italian regions (**Chapter 3.3**) covering almost 50 million inhabitants (83.3% of the Italian population) for a period of 10 years and from 6 Italian regions (**Chapters 2.3, 3.4, 4.2-4.4**), covering a total population of more than 13 million inhabitants over a period of 7 years. The latter database network has previously been used for the post-marketing assessment of biosimilar use, as described in more detail in previous publications [18, 19, 68, 82].

Italy has a universal healthcare system, where all NHS beneficiaries (i.e., all residents in any given catchment area) are registered in a demographic database. In the early 2000s, the Italian government established that the collection of claims data should be mandatory to account for regional healthcare service provision and the resulting expenditures. All Italian healthcare claims include data on healthcare utilisation in separate data tables or databases, such as NHS-covered drug dispensing in community and hospital pharmacies, hospital discharge records, emergency department visits, outpatient specialist care, diagnostic tests and outpatient procedures, co-payment exemptions, and birth certificates [73]. All hospitalizations are fully reimbursed by the Italian NHS and are therefore accurately recorded as claims. Concerning outpatient diagnostic tests and specialist visits, they are almost completely reimbursed by NHS as well, unless patients decide to access private healthcare services (on average, around 15% of all specialist visits/diagnostic tests). Concerning drugs, almost 80% of all drugs are fully reimbursed by NHS (including biologics as well as other high-cost drugs) with the remaining being in charge of citizens (e.g., over the counter drugs and other prescription drugs, such as NSAIDs or acetaminophen). All of these claims are traced in almost all the observational studies of this thesis. Moreover, in Italy, biologics are fully reimbursed by the NHS and for each biologic drug prescription, specialists have to fill a therapeutic plan, which indicates the exact drug name,

number of dispensed packages, dosing regimen, and indication for use. These data can be linked through unique and anonymous patient identifiers to other claims databases, which contain several types of information, including causes of hospitaliza-tion and reasons for healthcare service co-payment exemptions.
Real-world data from different databases, including those in different countries or regions, can be pooled to increase statistical power of a study. An additional benefit of such pooling is the increased generalisation of the evidence generated to broad and heterogeneous populations, increasing the value of such evidence [83]. By combining databases, the effects of a wide variety of healthcare services, including medications and other medical interventions, can be studied and compared on ever increasing scales [40, 84, 85].
Four studies (**Chapters 3.4, 4.2-4.4**), presented in this thesis, are an exemple of the potential of multi-regional database network. These studies were conducted in the context of an Italian project, funded by the Italian Health Ministry, through a network of six regional claims databases from Palermo, Caserta, Treviso LHUs and the Tuscany, Umbria and Lazio regions, covering a total population of around 13 million inhabitants (25% of the Italian population). Our studies highlighted that therapeutic substitution between biosimilars and originators of the same therapeutic class is frequent in clinical practice, despite ongoing debates about their comparative safety and effectiveness. Moreover, other three observational studies conducted in the same context of this project showed an increasing trend in the use of biosimilar epoetins, filgrastim and somatropin [18, 19, 82] and other two multi-regional studies, including the same data sources, have so far provided reassuring data on the effectiveness and safety of biosimilars of epoetins [68, 71]. This database network has also generated real-world evidence that has been used in the updated American Society of Clinical Oncology (ASCO)/American Society of Hematology (ASH) clinical practice guideline for anemia management in cancer patients [67].

In **Chapter 3.3** we described the potential of The VALORE project. This is an ongoing multi-regional pharmacovigilance project funded by the Italian Medicines Agency, through the multi-database network capturing data from 13 Italian regions, including almost all the most densely populated areas (e.g., Lombardy, Campania, Lazio, Sicily, and Veneto regions). The nework, through the use of the open-source R-based tool (TheShinISS), developed for distributed analyses within a CDM framework, not only enabled to involve a large and growing number of regions but also, once customized, provided the opportunity to rapidly update the data and analytical dataset, in line with data privacy regulations. This network has a great potential to generate real-world evidence on the pattern of use and the comparative benefit–risk assessments of individual biologics, including biosimilars, in patients with IMIDs as well as on the interchangeability of originators and biosimilars. Since the study focused on 13 Italian regions from Northern, Central, and Southern Italy, and the trends of biologic users over the years from these databases were consistent with those documented in the national reports on drug consumption in Italy, findings from this study could be considered representative of the whole Italian population. Moreover, the VALORE project database network had enough statistical power to adequately detect even weak associations between individual biologics approved for autoimmune diseases in dermatology, rheumatology, and gastroenterology and specific safety outcomes of interest. Reliance on a single database could reduce statistical power [86], whereas combining multiple databases offers the ability to evaluate exposures to a larger variety of biologics within a wider range of patients and with heterogeneous patterns of use. Furthermore, given the different safety

profiles of individual biologics, the gained statistical power of this network may enable comparative safety studies to be conducted for almost all individual IMID-approved biologics. Moreover, through the linkage of regional claims data and COVID-19 regional registries, available in some Italian regions, the VALORE project distributed database network may properly investigate this important safety outcome in large cohorts of biologic users. This approach has already been adopted to investigate the relationship between COVID-19 prognosis and hydroxychloroquine/chloroquine or angiotensin receptor blockers/angiotensin-converting enzyme inhibitors and other csDMARDs in rheumatic patients and to measure the survival rate of hospitalized patients with COVID-19 [87-89].

On the other hand, some limitations of these data sources should be acknowledged as well. First, information is collected in the outpatient setting only and as a consequence the study findings (especially those from drug utilization studies) may not directly pertain to patients that are treated in different settings, like hospital or nursing homes. Second, the use of medications, which are not prescribed by GPs, is not consistently and completely registered. As a consequence, missing information on over the counter medications and on biologics administered to inpatients during a hospitalization that might not have been captured by the databases, should be always taken into account, when interpreting results of the research presented in this thesis. Third, information on the indication for use may not be always available since electronic therapeutic plans, including also information on the indication for use of biologic, are not available for all Italian LHUs/regions claims databases; however, it is unlikely that this limitation affected the study results because validated studies of coding algorithms for identifying the indications for use were consulted. Fourth, safety outcomes (especially those with a long latency period, e.g., neoplasms) observed during follow-up could not be associated with the drug dispensed at the index date but could be associated with a drug other than the index drug/small molecule after a switch; therefore, a proper methodological approach would be required. Fifth, another limitation is represented by the lack of data in the administrative claims databases on clinical outcome measures, such as the effectiveness of treatment, disease severity, and other potential confounders that could have influenced results. For this reason, one of the ambitious goals of the VALORE project is to enrich claims data with clinically relevant information such as disease activity scores, exact indication of use, and reasons for treatment discontinuation through linkage with population-based disease registries from the same catchment area, which are available in some Italian regions [90-92].

Future directions

Recent years have seen the introduction of highly innovative and complex drugs, leading to improved management of cancer and immune-mediated inflammatory diseases. Most of them are biotechnological drugs, including blood components, allergenics, gene therapies, interleukins, recombinant therapeutic proteins and mRNA vaccines. However, due to the high costs, biologics may have a negative impact on the sustainability of NHS. After the expiration of the patent of a biologic, a biosimilar (that is a biological medicinal product similar to the reference medicinal product in terms of quality characteristics, biological, activity, safety and efficacy based on a comprehensive comparability exercise) could be approved, thus representing a therapeutic alternative for saving healthcare resources to be reallocated to innovative drugs.

Since the uptake of biologics and biosimilars is continuously growing, post-marketing monitoring of their benefit-risk profile is necessary. The controlled nature of RCTs includes a limited number of patients, who may not always be representative of the population of all potential users of a drug, and a relatively short observation period, making it difficult to detect safety signals with a long latency. Hence, it is imperative to continue monitoring the safety of a drug once it is on the market. The increasing availability of electronic healthcare records offers important chances to investigate a wide spectrum of adverse drug reactions related to real-world use as these types of databases record information for large populations and for long follow-up periods.

This thesis shows both the potential of secondary use of claims database to assess the real-world use and benefit-risk profile of biologics and frequently prescribed drugs in the elderly. A great need exists to better describe and explore the use and the effects of these drugs in elderly, due to their wide use in real practice setting and little clinical trial evidence availability. Future research on real-world use of drugs, including biologics, in elderly should therefore take three different directions:

1. Encouraging research on geriatric populations, for whom electronic medical information is currently limited;
2. Exploring and testing new methodologies for assessing the pattern of use and the benefit-risk profile of these drugs through the use of distributed multi-database networks;
3. Identifying the best strategies for the aggregation of data coming from multiple electronic healthcare databases.

In Europe there is a general lack of evidence about drug use and effects in specific geriatric populations, such as the oldest old (patients aged ≥85 years old). This may partly be explained by the fact that currently very little electronic health record data are available from these settings.

Different international projects and networks (e.g. SENTINEL, EU-ADR, DARWIN) have been usufel to test the potential of signal detection using longitudinal electronic health record databases. Moreover, distributed multi-database networks, such as VALORE project, collecting all routinely provided healthcare services provided to biologic users, can be linked with active surveillance data and data from consolidated clinical registries, thus offering the opportunity to assess both short- and long-term effectiveness and safety of biologics, including biosimilars, and reassuring about the safety of the switch in real-world settings, with a special focus also in special populations (e.g elderly people or children or pregnant women), often not included in RCTs.

Although aggregation of data from multiple databases is ambitious, currently it is challenging, especially in Europe, due to the differences in terminology and language systems being adopted as well as the differences in quality and type of gathered information. This strategy however may provide the statistical power to study rare adverse events and rare drug exposures. In particular, the VALORE project database network demonstrated enough statistical power to adequately detect even weak associations between individual biological drugs approved for IMIDs and specific safety outcomes of interest, such as SARS-CoV-2 infection. Reliance on a single database could reduce statistical power, whereas combining multiple databases offers the ability to assess exposures to a larger variety of biologics within a wider range of patients and with

heterogeneous patterns of use. The best methodologies for analyzing aggregated data that are drawn from different data sources should be sought in the future.

References

1. Su CG, et al. Influence of immunogenicity on the long-term efficacy of infliximab in Crohn's disease. Gastroenterology. 2003 Nov; 125 (5):1544–6.
2. Zamora-Legoff JA, Achenbach SJ, Crowson CS, Krause ML, Davis JM 3rd., Matteson EL. Opioid use in patients with rheumatoid arthritis 2005-2014: a population-based comparative study. Clin Rheumatol. 2016, 35(5):1137-44.
3. Skolnick P. The Opioid Epidemic: Crisis and Solutions. Annu Rev Pharmacol Toxicol. 2018, 58:143-159.
4. Italian Society of Pharmacology. Trattamento del dolore cronico in Italia: appropriatezza terapeutica con oppiacei e timore di addiction: situazione italiana vs USA. 2018 April 3. Available from: https://sif-website.s3.amazonaws.com/uploads/position_paper/attachment/139/sif_position_paper_dolore_oppiacei_apr18.pdf
5. Marras F, Leali PT. The role of drugs in bone pain. Clin Cases Miner Bone Metab. 2016 May-Aug; 13 (2):93–96.
6. Bruera E, Paice JA. Cancer pain management: safe and effective use of opioids. Am Soc Clin Oncol Educ Book. 2015:e593–9.
7. Sultana J, Fontana A, Giorgianni F, Basile G, Patorno E, Pilotto A et al. Can information on functional and cognitive status improve short-term mortality risk prediction among community-dwelling older people? A cohort study using a UK primary care database. Clin Epidemiol. 2017 Dec 19; 10:31–39.
8. Daoust R, Paquet J, Moore L,E´ mond M, Gosselin S, Lavigne G et al. Recent opioid use and fall-related injury among older patients with trauma. CMAJ. 2018 Apr 23; 190(16):E500–E506.
9. Smolen JS, Landewé RBM, Bijlsma JWJ, Burmester GR, Dougados M, Kerschbaumer A, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. Ann Rheum Dis. 2020, 79(6):685-699
10. Smolen JS, Landewé RBM, Bijlsma JWJ, Burmester GR, Chatzidionysiou K, Dougados M, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. Ann Rheum Dis. 2017, 76(6):960-977.
11. Parisi S, Bortoluzzi A, Sebastiani GD. Conti F, Caporali R, Ughi N, et al. The Italian Society for Rheumatology clinical practice guidelines for rheumatoid arthritis. Reumatismo. 2019, 71(S1):22-49.
12. Agenzia Italiana del Farmaco (AIFA). L'uso dei farmaci in Italia - rapporto OsMed 2016. Available from: https:// www. aifa. gov. it/ docum ents/20142/ 241052/ Rappo rto_ OsMed_2016_ AIFA- acc. pdf/ b44a6 258-6a84- 4293- 0cdb- 1d6f7 c4be6

13. Agenzia Italiana del Farmaco (AIFA). L'uso dei farmaci in Italia - rapporto OsMed 2017. Available from: http:// www. agenz iafar maco. gov. it/sites/ defau lt/ files/ Rappo rto_ OsMed_ 2017_ AIFA. pdf.
14. Agenzia Italiana del Farmaco (AIFA). L'uso dei farmaci in Italia - rapporto OsMed 2018. Available from: Ahttps:// www. aifa. gov. it/ docum ents/20142/0/ Rappo rto_ OsMed_ 2018. pdf/ c9eb7 9f9- b791- 2759- 4a9ee56e1348a9 76. Accessed 15 May 2021.
15. Agenzia Italiana del Farmaco (AIFA). L'uso dei farmaci in Italia - rapporto OsMed 2019. Available from: https:// www. aifa. gov. it/ docum ents/20142/ 12059 84/ rappo rto- osmed- 2019. pdf/ f41e5 3a4- 710a- 7f75-4257- 40464 7d0fe 1e. Accessed 15 May 2021.
16. Fassmer AM, Garbe E, Schmedt N. Frequency and trends of disease-modifying antirheumatic drug (DMARD) use in Germany. Pharmacol Res Perspect. 2016;4(5): e00254.
17. Mendelsohn AB, Nam YH, Marshall J, McDermott CL, Kochar B, Kappelman MD, Brown JS, Lockhart CM. Utilization patterns and characteristics of users of biologic anti-inflammatory agents in a large, US commercially insured population. Pharmacol Res Perspect. 2021;9(1): e00708.
18. Ingrasciotta Y, Giorgianni F, Bolcato J, Chinellato A, Pirolo R, Tari DU, Troncone C, Fontana A, Ientile V, Gini R, Santoro D, Santarpia M, Genazzani A, Uomo I, Pastorello M, Addario WS, Scondotto S, Cananzi P, Caputi AP, Trifirò G. How Much Are Biosimilars Used in Clinical Practice? A Retrospective Italian Population-Based Study of Erythropoiesis-Stimulating Agents in the Years 2009-2013. BioDrugs. 2015 Aug;29(4):275-84.
19. Marcianò I, Ingrasciotta Y, Giorgianni F, Bolcato J, Chinellato A, Pirolo R, Di Giorgio A, Manna S, Ientile V, Gini R, Santarpia M, Genazzani AA, Uomo I, Pastorello M, Pollina Addario SW, Scondotto S, Cananzi P, Da Cas R, Traversa G, Rossi M, Sottosanti L, Caputi AP, Trifirò G. How did the Introduction of Biosimilar Filgrastim Influence the Prescribing Pattern of Granulocyte Colony-Stimulating Factors? Results from a Multicentre, Population-Based Study, from Five Italian Centres in the Years 2009-2014. BioDrugs. 2016 Aug;30(4):295-306.
20. Agenzia Italiana del Farmaco (AIFA). Medicinali biosimiari – analisi di sicurezza. Available from: https:// www. aifa. gov. it/ docum ents/ 20142/0/190712_ MedBi o19. pdf/ 05b20 f88- 0202- c0cb- 3079- c6c29 66e7006.
21. Perrone V, Losi S, Rogai V. Antonelli S, Fakhouri W, Giovannitti M, et al. Treatment Patterns and Pharmacoutilization in Patients Affected by Rheumatoid Arthritis in Italian Settings. Int J Environ Res Public Health. 2021, 18(11):5679.
22. Bonafede M, Johnson BH, Shah N, Harrison DJ, Tang D, Stolshek BS. Disease-Modifying Antirheumatic Drug Initiation Among Patients Newly Diagnosed With Rheumatoid Arthritis. Am. J. Manag. Care. 2018, 24(8 Spec No.):SP279-SP285.
23. Tutuncu Z, Kavanaugh A. Rheumatic disease in the elderly: rheumatoid arthritis. Rheum Dis Clin North Am. 2007;33(1):57-710 70.
24. Kato E, Sawada T, Tahara K, et al. The age at onset of rheumatoid arthritis is increasing in Japan: a nationwide database study. Int J Rheum Dis. 2017;20(7):839-845.
25. Kobak S, Bes C. An autumn tale: geriatric rheumatoid arthritis. Ther Adv Musculoskelet Dis. 2018;10(1):3-11.

26. Ruban TN, Jacob B, Pope JE, Keystone EC, Bombardier C, Kuriya B. The influence of age at disease onset on disease activity and disability: results from the Ontario Best Practices Research Initiative. Clin Rheumatol. 2016;35(3):759-763.
27. European Medicines Agency. Questions and answers on biosimilar medicines (similar biological medicinal products) 2012. EMA/837805/2011. Available from: https://www.medicinesforeurope.com/wp-content/uploads/2016/03/WC500020062.pdf Accessed 10 February 2022.
28. Giezen T, Schneider CK. Safety assessment of biosimilars in Europe: a regulatory perspective. GaBI J. 2014;3(4):180–3.
29. Giezen TJ, Mantel-Teeuwisse AK, Straus SMJM, Schellekens H, Leufkens HG, Egberts AC. Safety-related regulatory actions for biologicals approved in the United States and the European Union. JAMA. 2008;300(16):1887–96.
30. Giezen TJ, Mantel-Teeuwisse AK, Meyboom RH, Straus SM, Leufkens HG, Egberts TC. Mapping the safety profile of biologicals: a disproportionality analysis using the WHO adverse drug reaction database. VigiBase. Drug Saf. 2010;33(10):865–78.
31. Vincent FB, Morand EF, Murphy K, et al. Antidrug antibodies (ADAb) to tumour necrosis factor (TNF)-specific neutralising agents in chronic inflammatory diseases: a real issue, a clinical perspective. Ann Rheum Dis. 2013;72(2):165–178.
32. Bendtzen K, Ainsworth M, Steenholdt C, et al. Individual medicine in inflammatory bowel disease: monitoring bioavailability, pharmacokinetics and immunogenicity of anti-tumour necrosis factor-alpha antibodies. Scand J Gastroenterol. 2009;44(7):774–781.
33. Boven K, Stryker S, Knight J, et al. The increased incidence of pure red cell aplasia with an Eprex formulation in uncoated rubber stopper syringes. Kidney Int. 2005 Jun;67(6):2346–2353.
34. Beaugerie L, Brousse N, Bouvier AM, et al. Lymphoproliferative disorders in patients receiving thiopurines for inflammatory bowel disease: a prospective observational cohort study. Lancet. 2009;374(9701):1617-1625.
35. Peyrin-Biroulet L, Khosrotehrani K, Carrat F, et al. Increased risk for nonmelanoma skin cancers in patients who receive thiopurines for inflammatory bowel disease. Gastroenterology. 2011;141(5):1621-28.e285.
36. Bourrier A, Carrat F, Colombel JF, et al. Excess risk of urinary tract cancers in patients receiving thiopurines for inflammatory bowel disease: a prospective observational cohort study. Aliment Pharmacol Ther. 2016;43(2):252-261.
37. Khan N, Vallarino C, Lissoos T, Darr U, Luo M. Risk of Infection and Types of Infection Among Elderly Patients With Inflammatory Bowel Disease: A Retrospective Database Analysis. Inflamm Bowel Dis 2020;26:462–8.
38. Cottone M, Kohn A, Daperno M, et al. Advanced age is an independent risk factor for severe infections and mortality in patients given anti-tumor necrosis factor therapy for inflammatory bowel disease. Clin Gastroenterol Hepatol. 2011;9(1):30-35.
39. Macaluso FS, Fries W, Renna S, Viola A, Muscianisi M, Cappello M, et al.; Sicilian Network for Inflammatory Bowel Disease (SN-IBD). Effectiveness and safety of vedolizumab in biologically naïve patients: A real-world multi-centre study. United European Gastroenterol J 2020;8:1045–55.

40. Coloma PM, Trifirò G, Schuemie MJ, Gini R, Herings R, Hippisley-Cox J, Mazzaglia G, Picelli G, Corrao G, Pedersen L, van der Lei J, Sturkenboom M, EU-ADR Consortium. Electronic healthcare databases for active drug safety surveillance: is there enough leverage? Pharmacoepidemiol Drug Saf. 2012;21(6):611–21.
41. Solomon SD, Uno H, Lewis EF, Eckardt KU, Lin J, Burdmann EA, de Zwwuw D, Ivanovich P, Levey AS, Parfrey P, Remuzzi G, Singh AK, Toto R, Huang F, Rossert J, McMurray JJ, Pfeffer MA. Erythropoietic response and outcomes in kidney disease and type 2 diabetes. N Engl J Med. 2010;363:1146–55.
42. Kalantar-Zadeh K, McAllister CJ, Lehn RS, Lee GH, Nissenson AR, Kopple JD. Effect of malnutrition-inflammation complex syndrome on EPO hyporesponsiveness in maintenance hemodialysis patients. Am J Kidney Dis. 2003;42:761–73.
43. Kimachi M, Fukuma S, Yamazaki S, Yamamoto Y, Akizawa T, Akiba T, Saito A, Fukuhara S. Minor elevation in C-reactive protein levels predicts incidence of erythropoiesis-stimulating agent hyporesponsiveness among hemodialysis. Patients Nephron. 2015;131(2):123–30.
44. López-Gómez J, Portolés J, Aljama P. Factors that condition the response to erythropoietin in patients on hemodialysis and their relation to mortality. Kidney Int. 2008;74(Suppl 111):S75–81.
45. De Francisco ALM, Stenvinkel P, Vaulont S. Inflammation and its impact on anaemia in chronic kidney disease: from haemoglobin variability to hyporesponsiveness. NDT Plus. 2009;2 [Suppl 1:i18–26. https://doi.org/10.1093/ndtplus/sfn176.
46. Kalantar-Zadeh K, Lee GH, Miller JE, Streja E, Jing J, Robertson JA, Kovesdy CP. Predictors of hyporesponsiveness to erythropoiesis stimulating agents in hemodialysis patients. Am J Kidney Dis. 2009;53:823–34.
47. European Medicines Agency. EMA: Biosimilars in the EU - Information guide for healthcare professionals. 2019 [internet]. Available from: https://www.ema.europa.eu/en/documents/leaflet/biosimilars-eu-information-guide-healthcare-professionals_en.pdf4. Accessed 12 May 2020.
48. McKinnon RA, Cook M, Liauw W, Marabani M, Marschner IC, Packer NH, et al. Biosimilarity and Interchangeability: Principles and Evidence: A Systematic Review. BioDrugs [Internet]. 2018;32(1):27–52. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5814534/ Accessed 28 July 2020.
49. European Medicines Agency. Guideline-similar-biological-medicinal-products-rev1_en.pdf. 2014 [Internet]. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-similar-biological-medicinal-products-rev1_en.pdf7 Accessed 2020 Apr 9.
50. Rémuzat C, Kapuśniak A, Caban A, Ionescu D, Radière G, Mendoza C, et al. Supply-side and demand-side policies for biosimilars: an overview in 10 European member states. Journal of Market Access & Health Policy. 2017 Jan 1;5(1):1307315.
51. Food and Drug Administration. Considerations in Demonstrating Interchangeability with a Reference Product Guidance for Industry. FDA; Rockville, MD, USA: 2019. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/considerations-demonstrating-interchangeability-reference-product-guidance-industry Accessed 2020 May 21.

52. White J, Goldman J. Biosimilar and Follow-on Insulin: The Ins, Outs, and Interchangeability. J Pharm Technol [Internet]. 2019 Feb;35(1):25–35. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6313268/ Accessed 5 Apr 2020.
53. Portela M da CC, Sinogas C, Albuquerque de Almeida F, Baptista-Leite R, Castro-Caldas A. Biologicals and biosimilars: safety issues in Europe. Expert Opinion on Biological Therapy [Internet]. 2017 Jul 3;17(7):871–7.
54. Agenzia Italiana del Farmaco (AIFA). Secondo Position Paper AIFA sui Farmaci Biosimilari. 2018. Available from: https://www.aifa.gov.it/sites/default/files/pp_biosimilari_27.03.2018.pdf Accessed 10 February 2022.
55. GABI Journal. France to allow biosimilars substitution [Internet]. 2014. Available from: www.gabionline.net/Policies-Legislation/France-to-allow-biosimilars-substitution Accessed 28 September 2017.
56. D'Amore C, Da Cas R, Rossi M, Traversa G. Switching Between Epoetins: A Practice in Support of Biosimilar Use. BioDrugs. 2016 Feb;30(1):27-32.
57. Loiacono C, Sgroi C, Coppolino S, Cannata A, Ferrara R, Arcoraci V. How much are biosimilars used in Southern Italy? A retrospective analysis of epoetin utilization in the local health unit of Messina in the years 2010–2011. BioDrugs. 2012;26(2):113–20.
58. Lonnemann G, Wrenger E. Biosimilar epoetin zeta in nephrology—a single-dialysis center experience. Clin Nephrol. 2011;75(1):59–62.
59. Pasina L, Casadei G, Nobili A. Biological agents and biosimilars: Essential information for the internist. European Journal of Internal Medicine. 2016 Sep 1;33:28–35.
60. Jørgensen KK, et al. Switching from originator infliximab to biosimilar CT-P13 compared with maintained treatment with originator infliximab (NOR-SWITCH): a 52-week, randomised, double-blind, non-inferiority trial. Lancet. 2017 Jun 10;389(10086):2304-2316.
61. Ebbers HC, Muenzberg M, Schellekens H. The safety of switching between therapeutic proteins. Expert Opin Biol Ther. 2012;12 (11):1473–1485.
62. Glintborg B, Sørensen IJ, Loft AG, et al. A nationwide non-medical switch from originator infliximab to biosimilar CT-P13 in 802 patients with inflammatory arthritis: 1-year clinical outcomes from the DANBIO registry. Ann Rheum Dis. 2017;76(8):1426–1431.
63. Nikiphorou E, Kautiainen H, Hannonen P, et al. Clinical effectiveness of CT-P13 (Infliximab biosimilar) used as a switch from Remicade (infliximab) in patients with established rheumatic disease. Report of clinical experience based on prospective observational data. Expert Opin Biol Ther. 2015;15 (12):1677–1683.
64. Dolinar R, Kohn CG, Lavernia F, Nguyen E. The non-medical switching of prescription medications. Postgraduate Medicine. 2019 Jul 4;131(5):335–41. Available from: https://doi.org/10.1080/00325481.2019.1618195. Accessed 31 May 2020.
65. Roggeri A, Roggeri DP, Zocchetti C, et al. Healthcare costs of the progression of chronic kidney disease and different dialysis techniques estimated through administrative database analysis. J Nephrol. 2017; 30(2):263-269.
66. Agenzia Italiana del Farmaco (AIFA). Position paper sui farmaci biosimilari (28/05/2013). Available from: http://www.agenziafarmaco.gov.it/sites/default/files/AIFA_POSITION_PAPER_FARMACI_BIOSIMILARI.pdf.

67. Bohlius J, Bohlke K, Castelli R, et al. Management of cancer associated anemia with erythropoiesis-stimulating agents: ASCO/ASH clinical practice guideline update. J Clin Oncol. 2019;15 (7):399-402.
68. Ingrasciotta Y, Giorgianni F, Marcianò I, Bolcato J, Pirolo R, Chinellato A, Ientile V, Santoro D, Genazzani AA, Alibrandi A, Fontana A, Caputi AP, Trifirò G. Comparative Effectiveness of Biosimilar, Reference Product and Other Erythropoiesis-Stimulating Agents (ESAs) Still Covered by Patent in Chronic Kidney Disease and Cancer Patients: An Italian Population-Based Study. PLoS One. 2016 May 17;11(5):e0155805.
69. Giordano G, Mondello P, Tambaro R, et al. Biosimilar epoetin α is as effective as originator epoetin-α plus liposomal iron (Sideral®), vitamin B12 and folates in patients with refractory anemia: a retrospective real-life approach. Mol Clin Oncol. 2015;3(4):781-784.
70. Garzotto AR, Heine O, Turner M, Rebollo Laserna F, Lorenz A. Erythropoiesis-stimulating agents for the treatment of chemotherapy induced anemia: comparisons from real-world clinical experience. J Blood Med. 2014;5:43-48.
71. Trotta F, Belleudi V, Fusco D, et al. Comparative effectiveness and safety of erythropoiesis-stimulating agents (biosimilars vs originators)in clinical practice: a population-based cohort study in Italy. BMJ Open. 2017;7(3):e011637.
72. Food and Drug Administration. Real World Evidence. 2018. Available from: https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence Accessed 25 May 2018.
73. Trifirò G, Gini R, Barone-Adesi F, Beghi E, Cantarutti A, Capuano A, Carnovale C, Clavenna A, Dellagiovanna M, Ferrajolo C, Franchi M, Ingrasciotta Y, Kirchmayer U, Lapi F, Leone R, Leoni O, Lucenteforte E, Moretti U, Mugelli A, Naldi L, Poluzzi E, Rafaniello C, Rea F, Sultana J, Tettamanti M, Traversa G, Vannacci A, Mantovani L, Corrao G. The Role of European Healthcare Databases for Post-Marketing Drug Effectiveness, Safety and Value Evaluation: Where Does Italy Stand? Drug Saf. 2019 Mar;42(3):347-363.
74. Ingrasciotta Y, Sultana J, Giorgianni F, Menditto E, Scuteri A, Tari M, et al. Analgesic drug use in elderly persons: A population-based study in Southern Italy. Plos One. 2019, 14(9):e0222836.
75. Viola E, Trifirò G, Ingrasciotta Y, Sottosanti L, Tari M, Giorgianni F, et al. Adverse drug reactions associated with off-label use of ketorolac, with particular focus on elderly patients. An analysis of the Italian pharmacovigilance database and a population based study. Expert Opin Drug Saf. 2016, 15(sup2):61-67.
76. Oppelt KA, Kuiper JG, Ingrasciotta Y, Ientile V, Herings RMC, Tari M, et al. Characteristics and Absolute Survival of Metastatic Colorectal Cancer Patients Treated With Biologics: A Real-World Data Analysis From Three European Countries. Front Oncol. 2021, 11:630456.
77. Ingrasciotta Y, Isgrò V, Ientile V, Tari M, Trifirò G, Guarneri C. Are Patients with Psoriasis and Psoriatic Arthritis Undertreated? A Population-Based Study from Southern Italy. J Clin Med. 2021 Jul 31;10(15):3431.
78. Jin Y, Desai RJ, Liu J, Choi NK, Kim SC. Factors associated with initial or subsequent choice of biologic disease modifying antirheumatic drugs for treatment of rheumatoid arthritis. Arthritis Res Ther. 2017, 19(1):159.

79. Desai RJ, Solomon DH, Jin Y, Liu J, Kim SC. Temporal Trends in Use of Biologic DMARDs for Rheumatoid Arthritis in the United States: A Cohort Study of Publicly and Privately Insured Patients. J Manag Care Spec Pharm. 2017, 23(8):809-685.
80. Ingrasciotta Y, Sultana J, Giorgianni F, Fontana A, Santangelo A, Tari DU, Santoro D, Arcoraci V, Perrotta M, Ibanez L, Trifirò G. Association of individual non-steroidal anti-inflammatory drugs and chronic kidney disease: a population-based case control study. PLoS One. 2015 Apr 16;10(4):e0122899.
81. Ingrasciotta Y, Sultana J, Giorgianni F, Caputi AP, Arcoraci V, Tari DU, Linguiti C, Perrotta M, Nucita A, Pellegrini F, Fontana A, Cavagna L, Santoro D, Trifirò G. The burden of nephrotoxic drug prescriptions in patients with chronic kidney disease: a retrospective population-based study in Southern Italy. PLoS One. 2014 Feb 18;9(2):e89072.
82. Marcianò I, Ingrasciotta Y, Giorgianni F, et al. Pattern of use of biosimilar and originator somatropin in italy: a population-based multiple databases study during the years 2009–2014. Front Endocrinol (Lausanne). 2018;9:95.
83. Bazelier MT, Eriksson I, de Vries F, Schmidt MK, Raitanen J, Haukka J, et al. Data management and data analysis techniques in pharmacoepidemiological studies using a pre-planned multidatabase approach: a systematic literature review. Pharmacoepidemiol Drug Saf. 2015;24(9):897–905.
84. Coloma PM, Schuemie MJ, Trifirò G, Gini R, Herings R, Hippisley-Cox J, et al. Combining electronic healthcare databases in Europe to allow for large-scale drug safety monitoring: the EUADR Project. Pharmacoepidemiol Drug Saf. 2011;20(1):1–11.
85. Trifirò G, Coloma PM, Rijnbeek PR, Romio S, Mosseveld B, Weibel D, et al. Combining multiple healthcare databases for postmarketing drug and vaccine safety surveillance: why and how? J Intern Med. 2014;275(6):551–61.
86. Hammond IW, Gibbs TG, Seifert HA, Rich DS. Database size and power to detect safety signals in pharmacovigilance. Expert Opin Drug Saf. 2007;6(6):713–21.
87. Trifirò G, Massari M, Da Cas R, Menniti Ippolito F, Sultana J, Crisafulli S, Giorgi Rossi P, Marino M, Zorzi M, Bovo E, Leoni O, Ludergnani M, Spila AS, ITA-COVID-19: RAAS inhibitor group. Renin-angiotensin-aldosterone system inhibitors and risk of death in patients hospitalised with COVID-19: a retrospective Italian Cohort Study of 43,000 Patients. Drug Saf. 2020;43(12):1297–308.
88. Ferroni E, Giorgi Rossi P, Spila Alegiani S, Trifirò G, Pitter G, Leoni O, Cereda D, Marino M, Pellizzari M, Fabiani M, Riccardo F, Sultana J, Massari M, ITA-COVID Working Group. Survival of hospitalized COVID-19 patients in Northern Italy: a populationbased cohort study by the ITA-COVID-19 Network. Clin Epidemiol. 2020;12:1337–46.
89. Alegiani SS, Crisafulli S, Rossi PG, Mancuso P, Salvarani C, Atzeni F, Gini R, Kirchmayer U, Belleudi V, Kurotschka PK, Leoni O, Ludergnani M, Ferroni E, Baracco S, Massari M, Trifirò G, ITA-COVID-19 Network. Risk of COVID-19 hospitalization and mortality in rheumatic patients treated with hydroxychloroquine or other conventional DMARDs in Italy. Rheumatology (Oxford). 2021.
90. Viola A, Muscianisi M, Macaluso FS, Ventimiglia M, Cappello M, Privitera AC, Magnano A, Pluchino D, Magrì G, Ferracane C, Mocciaro F, Garufi S, Giuffrida E, Costantino G, Fiocco G, Grova M, Guida L, Alibrandi A, Orlando A, Fries W, "Sicilian Network for Inflammatory Bowel Disease (SN-IBD)" Ustekinumab in Crohn's disease: real-world

outcomes from the Sicilian network for inflammatory bowel diseases. JGH Open. 2021;5(3):364–70.
91. Naldi L, Cazzaniga S, Di Mercurio M, Grossi E, Addis A, Psocare study centres. Inequalities in access to biological treatments for psoriasis: results from the Italian Psocare registry. Br J Dermatol. 2017;176(5):1331–8.
92. Caporali R, Sarzi-Puttini P, Atzeni F, Gorla R, Filippini M, Marchesoni A, Favalli EG, Bobbio-Pallavicini F, Montecucco C. Switching TNF-alpha antagonists in rheumatoid arthritis: the experience of the LORHEN registry. Autoimmun Rev. 2010;9(6):465–9.

CHAPTER 6.
SUMMARY OF THE THESIS

6.1. Summary

The world's population in the older ages is increasing and 1.5 billions of persons over 65 years are expected by 2050. As the proportion of the world's elderly population continues to increase, the burden of chronic diseases increases as well. As elderly patients are often excluded from randomized clinical trials (RCTs) evaluating efficacy and safety of new drugs, such exclusions may impair the generalizability of RCT results in real-world settings. Evidences from real-world show that the uptake of biologics, as well as biosimilars, is continuously growing; therefore, it is imperative to monitor the pattern of use and the post-marketing benefit-risk profile of these drugs in real-world settings, especially in elderly. The increasing amount of healthcare databases offers the opportunity to generate a constantly updated picture on drug use, including biologics, in clinical practice and to provide a better insight on the risks of those medications in geriatric population.

The general objective of the research described in the present thesis was to obtain an overview of the real-world use of analgesics and biologics approved for the treatment of immune-mediated inflammatory diseases (IMIDs) (**Chapter 2**) in elderly. Moreover, the post-marketing monitoring of the benefit-risk profile of biologics (**Chapter 3**) as well as the interchangeability and switching practices between originators and biosimilars was investigated (**Chapter 4**).

Real-world use of analgesics and biologics among elderly

In a population study-based study conducted using a General Practice (GP) database in the Caserta Local Health Unit (LHU) (Caserta district, Campania region in Italy), that is the Arianna database, we found that almost 9% of elderly persons received analgesic drugs, mostly non-opioid analgesics than opioid analgesics and, among opioid analgesics, weak opioids were more commonly used than strong opioids (**Chapter 2.1**). In terms of inappropriate analgesic use, 9% of all elderly users were prescribed ketorolac/indomethacin inappropriately, since these drugs should not be prescribed to elderly persons. It is known that abuse of opioids in Italy is not common as in the United States. Indeed, this was in line with results from the study presented in **Chapter 2.2**, a cross-national study comparing the baseline characteristics and the pattern of use of drugs (e.g., anti-inflammatory drugs and disease-modifying anti-rheumatic drugs (DMARDs)) for the treatment of rheumatoid arthritis (RA) in Caserta Local Health Unit (LHU) versus the United States. The study showed a higher use of traditional non-steroidal anti-inflammatory drugs (NSAIDs) and COX-2 inhibitors at baseline among Italian patients with RA, compared to U.S. patients. On the contrary, we found that half of RA patients from U.S. had received at least one dispensing for opioids before the RA diagnosis date, in line the widespread misuse and over-use of opioids in U.S., leading to a large number of overdose-related deaths. Moreover, although RA therapy has made major advances over the past few decades, especially with the introduction of biologics as a treatment option for RA patients, most of the patients included in the study were found to be initially treated with anti-inflammatory drugs or conventional DMARDs rather than biologics. Interestingly, the treatment escalation was less frequent in old RA patients than in young adult patients: compared to 6% of young adult RA patients, only 1% of elderly RA patients from U.S. was treated with biologics, with or without conventional DMARDs, while only 1% of RA patients from Italy received biologic dispensing, without any statistically significant differences observed in the two age groups. This result was in line with other previous studies

showing that old RA patients may be less aggressively treated than they should be. The low use of biologic drugs in elderly was confirmed in the cohort study presented in **Chapter 2.3**. The study was conducted in the context of the VALORE project, funded by the Italian Medicines Agency, using claims databases from Lazio region (covering a total population of almost 6 million inhabitants), during the years 2010-2020 and it focused on elderly users of biologic drugs approved for the treatment of inflammatory bowel disease (IBD), including Crohn's disease (CD) and ulcerative colitis (UC). The prevalence of elderly users of biologic drugs showed a growing trend during the study period (from 0.4*1,000 inhab. in 2010 to 1.3*1,000 inhab. in 2020), but it was lower than prevalence of use observed including both young and old users in Lazio Region (0.9-1.7*1,000 inhab.) (**Chapter 3.3**). In general, adherence and persistence to biologics during the first year of treament was high (>80%) without any statistically significant difference between CD and UC (**Chapter 2.3**). On the contrary, switching between different biologics was not frequent (7.3%) during the first year.

Concerning the use of biologics for the treatment of IMIDs, the VALORE project network presented in **Chapter 3.3** showed an increasing use of biologics in 13 Italian regions over a period of 10 years, with a slightly heterogeneity across regions, in line with the increased use of several biologics over the years reported by the national reports on medicine use in Italy. This could be related to the marketing of several biological drugs (e.g., secukinumab, vedolizumab), including biosimilars, in more recent years as well as the extensions of the approved indications for use for many frequently prescribed biologics (e.g., adalimumab), thus expanding the number of patients eligible for the biological treatments. Indeed, we identified more than 140,000 biologic users with a cumulative 507,745 PYs of exposure. Mostly, were TNFα inhibitors users (82%), followed by interleukin inhibitors (26%), and selective immunosuppressants (12%). As regards specific age groups, more than 10,000 (7%) biologic users were aged < 18 years and more than 46,000 (32%) were aged >65 years. Among elderly patients, 8,886 (6.2% of total biologic users) were aged >80 years.

Post-marketing monitoring of the benefit-risk profile of biologics

Since biologics are large molecules, more complex than traditional small chemically synthesized molecules, their complexity may result in a degree of variability in molecules of the same active substance, particularly across different batches of the medicine. Therefore, some safety issues, such as the risk of infection, administration-site reactions or immunogenicity, may arise during therapy with biologics. In **Chapter 3.1**, we provided an overview of the characteristics and potential challenges in the safety profile assessment of biologics, incliding biosimilars, with a focus on the post-marketing setting. In this review, we highlight that spontaneous reporting system and healthcare databases may represent valid instruments for post-marketing surveillance of biologics. Moreover, in **Chapter 3.2**, we provided an overview of the safety and potential drug-drug interactions of immunosuppressive drugs for the treatment of IBD in elderly patients, showing that

the use of thiopurine may increase the risk of malignancies such as lymphomas, non-melanoma skin cancers and urinary tract cancers raising concerns about their use in elderly; while, evidences showed that use of tumour necrosis factor (TNF) inhibitor, was associated with higher rate of opportunistic infection, such as pneumonia, sepsis, candidiasis orherpes zoster, compared with

younger IBD patients. Concerning drug-drug interactions, evidences from literature don't show specific differences between young and old IBD patients.
In **Chapter 3.3** we highlight the potential of a multi-database healthcare network to estimate the number of drugs that could be monitored for surveillance of a range of safety outcomes with different background incidence rates. Specifically, the study showed that the distributed multi-database network had enough statistical power to adequately detect even weak associations between biologics approved for IMIDs and specific safety outcomes of interest. For instance, for SARSCoV-2 infection, 12,439 person-years (PYs) of exposure to any biologic would be required to detect a weak (IRR 1.5) association, which would allow investigation of nine of the 15 individual biologics aprroved for the treatment of IMIDs.

Since previous Italian population-based studies showed that 20% of users of either biosimilar or originator erythropoiesis-stimulating agents (ESAs) for the treatment of chronic kidney disease (CKD)- and cancer-related anemia were "non-responsive", irrespective of the type of ESA (originator or biosimilars), we explored the potential predictors of ESAs hyporesponsiveness in anaemic patients with CKD or cancer, in the general population from two Italian LHUs (**Chapter 3.4**). The study confirmed that type of dispensed ESA (biosimilar or originator) was not a predictor of ESA hyporesponsiveness in CKD patients; while inflammatory condition (as high levels of C-reactive protein) was a predictor of ESA hyporesponsiveness (confirmed by literature); on the other hand, we found that concomitant use of high dosage of angiotensin-converting enzyme inhibitors/angiotensin II-receptor blockers and of iron preparations could be protective factors against ESA hyporesponsiveness.

Interchangeability and switching practices of biologics originators and biosimilars
Althought biosimilars have established similarity to the reference product in terms of safety and efficacy according to the guidelines and procedures provided for by the European Medicines Agency (EMA) and Food and Drug Administration (FDA), interchangeability of biosimilars and reference products still represents an important concern from a scientific and regulatory perspective because of the risk of immunogenicity by switching between originator and biosimilars, which may cause a lack of effect and toxicity. In **Chapter 4.1**, we provided an overview of the different positions of regulatory authorities on the interchangeability and automatic substitution of biosimilars and reference products, as well as evidences from RCTs and real-world. Specifically, we summarized that the FDA defines a biological product as interchangeable with the reference product if it is a biosimilar and it can be expected to produce the same clinical result as the reference product in any given patient. EMA does not include any recommendation on interchangeability and automatic substitution, but it should be decided by each national competent authority. Specifically in Italy, the most recent position paper on biosimilars of the Italian Medicines Agency took a position in favor of biosimilar and reference product interchangeability, without mentioning automatic substitution between originators and biosimilars. The multi-Regional cohort study presented in **Chapter 4.2** showed that switching between ESAs originators and biosimilars and viceversa is frequent (15.5%) in CKD and cancer patients, as confirmed by other previous drug utilisation Italian studies. The switch was more common toward an originator ESA than a biosimilar (82% vs. 18%) and simple switch was more common (62.2% of the switchers) than multiple (23.5%) or backward switch (14.3%). We found

that severity of CKD, history of comorbidities or concomitant drugs use, previous bood transfusions as well as type of ESA dispensed to naïve patients were potential predictors of switching in both CKD and cancer patients.

Concerning the safety and effectiveness of the switch between originator and biosimilars, our large-scale Italian multi-database study, conducted in the context of a project funded by Italian Health Ministry using fully anonymised data from four Italian centres (i.e. Lazio and Tuscany Regions, and Caserta and Palermo Local Health Units), confirmed that switching versus non-switching during the first 2 years of treatment in CKD patients was not associated with any effectiveness and safety outcomes (**Chapter 4.3**). Specifically, switching from originator ESA α to biosimilars was effective and safe when compared with switching from a biosimilar, as confirmed by evidences from RCTs and real-world studies (**Chapter 4.1**).

Finally, a multi-database population-based study, through the building of an Italian claims database network from 5 Italian regions (covering almost 8 million inhabitants) explored direct healthcare costs of CKD patients treated with ESAs and the potential savings achievable by increasing the use of biosimilars and preventing inappropriate ESA use (**Chapter 4.4**). We found that more than 50% of total costs of CKD stage I-V were attributable to hospitalizations, while in dialysis the highest cost was attributable to dialysis procedure. ESA-related yearly mean cost was 17% of total yearly costs in CKD stage I-III, decreasing to 13%-6% in stage IV-V and in dialysis, respectively. Only 15% of all ESA users included in the study cohort received a biosimilar as a first epoetin, in contrast with the current position of the Italian Medicines Agency, which recommends prescribing biosimilars to treat naive patients. We demonstrated that if 25% of originator ESA users were treated with a biosimilar, the annual cost-savings of the total ESA treatment cost would range from 8% to 11%, depending on the CKD stage. Moreover, we found that 9% of our study cohort started inappropriately (based on hemoglobin levels) ESA treatment, increasing to 62.0% during the first year of maintenance therapy. Hypothesizing prevention of the first inappropriate ESA dispensing, the total yearly cost-savings would amount to over €35,000, increasing to over €167,000 eliminating the inappropriate dispensing during maintenance therapy. Therefore, the prevention of inappropriate ESA use in CKD may represent the best strategy to reduce the risk of renal function deterioration, thus delaying dialysis entry and reducing direct healthcare costs CKD.

6.2. Samenvatting

Het deel van De wereldbevolking wordt steeds ouder, en tegen 2050 worden 1,5 miljard 65-plussers verwacht. Naarmate het aandeel van de ouderen in de wereldbevolking blijft toenemen, neemt ook de last van chronische ziekten toe. Aangezien oudere patiënten vaak worden uitgesloten van gerandomiseerde klinische onderzoeken (RCT's) die de werkzaamheid en veiligheid van nieuwe geneesmiddelen evalueren, kunnen dergelijke uitsluitingen de generaliseerbaarheid van RCT-resultaten in de praktijk verminderen. De praktijk toont aan dat het gebruik van biologische geneesmiddelen, evenals biosimilars, voortdurend groeit; daarom is het absoluut noodzakelijk om het gebruikspatroon en het post-marketing baten-risicoprofiel van deze geneesmiddelen in de praktijk te controleren, vooral bij ouderen. De toenemende hoeveelheid zorgdatabases biedt de mogelijkheid om een constant actueel beeld te krijgen in de klinische praktijk van het medicijngebruik, inclusief biologische geneesmiddelen en tevens een beter inzicht te geven in de risico's van genoemde medicijnen bij de geriatrische populatie.

Het doel van dit proefschrift was het verkrijgen van een overzicht van het gebruik in de praktijk van analgetica en biologische geneesmiddelen die goedgekeurd zijn voor de behandeling van immuungemedieerde inflammatoire ziekten (IMID's) (hoofdstuk 2) bij ouderen. Bovendien werd de post-marketing monitoring van het baten-risicoprofiel van biologische geneesmiddelen (hoofdstuk 3) en de uitwisselbaarheid en overstappraktijken tussen originators en biosimilars onderzocht (hoofdstuk 4).

Gebruik in de praktijk van analgetica en biologische geneesmiddelen bij ouderen
In een op bevolkingsonderzoek gebaseerd onderzoek dat is uitgevoerd met behulp van een huisartsendatabase in de Caserta Local Health Unit (LHU) (district Caserta, regio Campania in Italië), de Arianna-database, ontdekten we dat 9% van de ouderen niet-opioïde pijnstillers kregen, (hoofdstuk 2.1). Wat betreft oneigenlijk gebruik van analgetica, kreeg 9% van alle oudere gebruikers ketorolac/indomethacine op oneigenlijke wijze voorgeschreven, aangezien deze geneesmiddelen niet aan ouderen mogen worden voorgeschreven. Het is bekend dat het gebruik van opioïden in Italië niet zo frequent is , zoals in de Verenigde Staten. Dit was inderdaad in overeenstemming met de resultaten van de studie gepresenteerd in hoofdstuk 2.2, een cross-nationale studie waarin de baselinekenmerken en het gebruikspatroon van geneesmiddelen (bijv. ontstekingsremmende geneesmiddelen en disease-modifying anti-rheumatic drugs (DMARD's)) voor de behandeling van reumatoïde artritis (RA) in Caserta Local Health Unit (LHU) versus de Verenigde Staten. De studie toonde een hoger gebruik van traditionele niet-steroïde anti-inflammatoire geneesmiddelen (NSAID's) en COX-2-remmers bij aanvang bij Italiaanse patiënten met RA, in vergelijking met Amerikaanse patiënten. Integendeel, we ontdekten dat de helft van de RA-patiënten uit de VS ten minste één keer opioïden had ontvangen vóór de diagnosedatum van RA, in lijn met het wijdverbreide misbruik en overmatig gebruik van opioïden in de VS, wat leidde tot een groot aantal overdosisgerelateerde sterfgevallen. Bovendien, hoewel RA-therapie de afgelopen decennia grote vooruitgang heeft geboekt, vooral met de introductie van biologische geneesmiddelen als behandelingsoptie voor RA-patiënten, bleken de meeste patiënten die in het onderzoek waren opgenomen aanvankelijk te worden behandeld met ontstekingsremmende geneesmiddelen of conventionele geneesmiddelen. DMARD's in plaats van biologische geneesmiddelen. Interessant is dat de escalatie van de behandeling minder vaak voorkwam bij oude RA-patiënten dan bij jongvolwassen patiënten:

vergeleken met 6% van de jongvolwassen RA-patiënten werd slechts 1% van de oudere RA-patiënten uit de VS behandeld met biologische geneesmiddelen, met of zonder conventionele DMARD's, terwijl alleen 1% van de RA-patiënten uit Italië ontving biologische toediening, zonder dat er statistisch significante verschillen werden waargenomen in de twee leeftijdsgroepen. Dit resultaat was in lijn met andere eerdere onderzoeken die aantoonden dat oude RA-patiënten mogelijk minder agressief worden behandeld dan zou moeten. Het lage gebruik van biologische geneesmiddelen bij ouderen werd bevestigd in de cohortstudie gepresenteerd in Hoofdstuk 2.3. De studie werd uitgevoerd in de context van het VALORE-project, gefinancierd door het Italiaanse Geneesmiddelenbureau, met gebruikmaking van databases met claims uit de regio Lazio (met een totale bevolking van bijna 6 miljoen inwoners), in de jaren 2010-2020 en was gericht op oudere gebruikers van biologische geneesmiddelen die zijn goedgekeurd voor de behandeling van inflammatoire darmaandoeningen (IBD), waaronder de ziekte van Crohn (CD) en colitis ulcerosa (UC). De prevalentie van oudere gebruikers van biologische geneesmiddelen vertoonde een stijgende trend tijdens de onderzoeksperiode (van 0,4*1.000 inw. in 2010 naar 1,3*1.000 inw. in 2020), maar was lager dan de waargenomen gebruiksprevalentie bij zowel jonge als oude gebruikers in de regio Lazio (0,9-1,7*1.000 inw) (hoofdstuk 3.3). In het algemeen was de therapietrouw en persistentie van biologische geneesmiddelen tijdens het eerste jaar van de behandeling hoog (>80%) zonder enig statistisch significant verschil tussen CD en UC (Hoofdstuk 2.3). Integendeel, het wisselen tussen verschillende biologische geneesmiddelen kwam het eerste jaar niet vaak voor (7,3%).

Wat betreft het gebruik van biologische geneesmiddelen voor de behandeling van IMID's, toonde het in hoofdstuk 3.3 gepresenteerde VALORE-projectnetwerk een toenemend gebruik van biologische geneesmiddelen in 13 Italiaanse regio's over een periode van 10 jaar, met een lichte heterogeniteit tussen regio's, in lijn met het toegenomen gebruik van verschillende biologische geneesmiddelen door de jaren heen gerapporteerd door de nationale rapporten over medicijngebruik in Italië. Dit kan te maken hebben met het recent op de markt brengen van verschillende biologische geneesmiddelen (bijv. secukinumab, vedolizumab), waaronder biosimilars, evenals met uitbreidingen van de goedgekeurde indicaties voor gebruik van de vaker voorgeschreven biologische geneesmiddelen (bijv. adalimumab), waardoor het aantal patiënten dat in aanmerking komt voor de biologische middelene toeneemt. We hebben inderdaad meer dan 140.000 biologische gebruikers geïdentificeerd met een cumulatieve blootstelling van 507.745 PY's. Meestal betrof het gebruikers van TNFα-remmers (82%), gevolgd door interleukineremmers (26%) en selectieve immunosuppressiva (12%). Wat specifieke leeftijdsgroepen betreft, werden meer dan 10.000 (7%) biologische gebruikers < 18 jaar geïndentificeerd en meer dan 46.000 (32%) > 65 jaar. Van de oudere patiënten waren 8.886 (6,2% van de totale biologische gebruikers) ouder dan 80 jaar.

Monitoring van het baten-risicoprofiel van biologische geneesmiddelen

Aangezien biologische geneesmiddelen grote moleculen zijn, complexer dan traditionele kleine chemisch gesynthetiseerde moleculen, kan hun complexiteit resulteren in een zekere mate van variabiliteit in moleculen van dezelfde werkzame stof, met name tussen verschillende batches van het geneesmiddel. Daarom kunnen er tijdens de behandeling met biologische geneesmiddelen enkele veiligheidsproblemen optreden, zoals het risico op infectie, reacties op

de toedieningsplaats of immunogeniciteit. In hoofdstuk 3.1 hebben we een overzicht gegeven van de kenmerken en potentiële uitdagingen bij de beoordeling van het veiligheidsprofiel van biologische geneesmiddelen, inclusief biosimilars, met een focus op de post-marketing setting. In dit review benadrukken we dat spontane rapportagesystemen en zorgdatabases valide instrumenten kunnen zijn voor postmarketingsurveillance van biologische geneesmiddelen. Bovendien hebben we in hoofdstuk 3.2 een overzicht gegeven van de veiligheid en mogelijke geneesmiddelinteracties van immunosuppressiva voor de behandeling van IBD bij oudere patiënten, waaruit blijkt dat het gebruik van thiopurine het risico op maligniteiten zoals lymfomen, niet-melanoom huidkankers en urinewegkankers kan verhogen, wat aanleiding geeft tot bezorgdheid over het gebruik ervan bij ouderen; terwijl bewijzen aantoonden dat het gebruik van tumornecrosefactor (TNF) -remmer gepaard ging met een hoger percentage opportunistische infecties, zoals longontsteking, sepsis, candidiasis of herpes zoster, in vergelijking met jongere IBD-patiënten. Met betrekking tot geneesmiddelinteracties laten bewijzen uit de literatuur geen specifieke verschillen zien tussen jonge en oude IBD-patiënten.
In hoofdstuk 3.3 belichten we het potentieel van een zorgnetwerk met meerdere databases om het aantal geneesmiddelen in kaart te brengen dat zou kunnen worden gecontroleerd voor surveillance van een reeks veiligheidsresultaten met verschillende achtergrondincidentiecijfers. De studie toonde met name aan dat het gedistribueerde netwerk met meerdere databases voldoende statistische kracht had om zelfs zwakke associaties tussen biologische geneesmiddelen die zijn goedgekeurd voor IMID's en specifieke veiligheidsresultaten van belang adequaat te detecteren. Voor SARSCoV-2-infectie zou bijvoorbeeld 12.439 persoonsjaren (PY's) van blootstelling aan een biologisch middel nodig zijn om een zwakke (IRR 1.5) associatie te detecteren, wat het mogelijk zou maken om 9 van de 15 individuele biologische geneesmiddelen te onderzoeken die zijn goedgekeurd voor de behandeling van IMID's.

Omdat eerdere Italiaanse populatie-gebaseerde studies hebben aangetoond dat 20% van de gebruikers van ofwel biosimilar ofwel originator erytropoëse-stimulerende middelen (ESA's) voor de behandeling van chronische nierziekte (CKD) en kankergerelateerde anemie "niet-reagerend" waren, ongeacht het type ESA (originator of biosimilars), onderzochten we de mogelijke voorspellers van hyporeactiviteit van ESA's bij anemische patiënten met CKD of kanker, in de algemene populatie van twee Italiaanse LHU's (hoofdstuk 3.4). De studie bevestigde dat het type afgegeven ESA (biosimilar of originator) géén voorspeller was van ESA-hyporesponsiviteit bij CKD-patiënten; terwijl een ontstekingsaandoening (als hoge niveaus van C-reactief proteïne) wél een voorspeller was van ESA-hyporesponsiviteit (bevestigd door de literatuur). Tevens werd aangetoond dat gelijktijdig gebruik van hoge doseringen van angiotensine-converterende enzymremmers/angiotensine II-receptorblokkers en van ijzerpreparaten beschermende factoren zouden kunnen zijn tegen ESA-hyporesponsiviteit.

Uitwisselbaarheid en overstappraktijken van biologische originators en biosimilars
Hoewel biosimilars overeenkomsten hebben aangetoond met het referentieproduct wat betreft veiligheid en werkzaamheid volgens de richtlijnen en procedures van het Europees Geneesmiddelenbureau (EMA) en de Food and Drug Administration (FDA), vormt de uitwisselbaarheid van biosimilars en referentieproducten nog steeds een belangrijk zorgpunt vanuit een wetenschappelijk en regelgevend perspectief; vanwege het risico op immunogeniciteit

door over te schakelen tussen originator en biosimilars, wat een gebrek aan effect en toxiciteit kan veroorzaken. In hoofdstuk 4.1 hebben we een overzicht gegeven van de verschillende standpunten van regelgevende instanties over de uitwisselbaarheid en automatische substitutie van biosimilars en referentieproducten, evenals bewijzen uit RCT's en de praktijk. Concreet kunnen we zeggen dat de FDA een biologisch product definieert als uitwisselbaar met het referentieproduct als het een biosimilar is en kan worden verwacht dat het hetzelfde klinische resultaat oplevert als het referentieproduct bij een bepaalde patiënt. Het EMA bevat geen aanbeveling over uitwisselbaarheid en automatische vervanging, maar hierover moet worden beslist door de nationale bevoegde autoriteit. Met name in Italië werd in het meest recente standpunt over biosimilars van het Italiaanse Geneesmiddelenbureau een standpunt ingenomen ten gunste van de uitwisselbaarheid van biosimilars en referentieproducten, zonder melding te maken van automatische substitutie tussen originators en biosimilars. De multiregionale cohortstudie gepresenteerd in Hoofdstuk 4.2 toont aan dat er vaak wordt gewisseld tussen ESA's originators en biosimilars en vice versa (15,5%) bij CKD- en kankerpatiënten, zoals bevestigd door andere eerdere Italiaanse onderzoeken naar medicijngebruik. De overstap naar een originator-ESA kwam vaker voor dan naar een biosimilar (82% vs. 18%) en een simpele overstap kwam vaker voor (62,2% van de overstappers) dan een meervoudige (23,5%) of achterwaartse overstap (14,3%). We ontdekten dat de ernst van CKD, voorgeschiedenis van comorbiditeiten of gelijktijdig drugsgebruik, eerdere bloedtransfusies en het type ESA dat werd toegediend aan naïeve patiënten, potentiële voorspellers waren van overschakeling bij zowel CKD als kankerpatiënten.

Wat betreft de veiligheid en effectiviteit van de omschakeling tussen originator en biosimilars, overstappen versus niet-overstappen tijdens de eerste 2 jaar van behandeling bij CKD-patiënten was niet geassocieerd met enige effectiviteit en veiligheidsuitkomsten (hoofdstuk 4.3). In het bijzonder was het overschakelen van de oorspronkelijke ESA α naar biosimilars effectief en veilig in vergelijking met het overschakelen van een biosimilar, zoals bevestigd door bewijzen van RCT's en real-world studies (hoofdstuk 4.1).

Tenslotte heeft een bevolkingsonderzoek met meerdere databases, (een Italiaans databasenetwerk voor claims uit 5 Italiaanse regio's (met bijna 8 miljoen inwoners), de directe zorgkosten onderzocht van CKD-patiënten die met ESA's werden behandeld en de mogelijke besparingen die haalbaar zijn door het gebruik van van biosimilars en het voorkomen van ongepast ESA-gebruik (hoofdstuk 4.4). We ontdekten dat meer dan 50% van de totale kosten van CKD stadium IV toe te schrijven waren aan ziekenhuisopnames, terwijl bij dialyse de hoogste kosten te wijten waren aan de dialyseprocedure. De ESA-gerelateerde jaarlijkse gemiddelde kosten waren 17% van de totale jaarlijkse kosten in CKD stadium I-III, en daalden tot respectievelijk 13%-6% in stadium IV-V en in dialyse. Slechts 15% van alle ESA-gebruikers in het onderzoekscohort ontving een biosimilar als eerste epoëtine, in tegenstelling tot het huidige standpunt van het Italiaanse Geneesmiddelenbureau, dat aanbeveelt om biosimilars voor te schrijven voor de behandeling van naïeve patiënten. We hebben aangetoond dat als 25% van de oorspronkelijke ESA-gebruikers zou worden behandeld met een biosimilar, de jaarlijkse kostenbesparingen van de totale ESA-behandelingskosten zouden variëren van 8% tot 11%, afhankelijk van het CKD-stadium. Bovendien ontdekten we dat 9% van ons studiecohort oneingelijk begon (gebaseerd op hemoglobineniveaus) ESA-behandeling, oplopend tot 62,0% tijdens het eerste jaar van onderhoudstherapie. Als we uitgaan van preventie van de eerste

oneingelijke ESA-verstrekking, zou de totale jaarlijkse kostenbesparing meer dan € 35.000 bedragen, oplopend tot meer dan € 167.000, waardoor de ongepaste verstrekking tijdens onderhoudstherapie wordt geëlimineerd. Daarom kan het voorkomen van oneingelijk gebruik van ESA bij CKD de beste strategie zijn om het risico op verslechtering van de nierfunctie te verminderen, waardoor de opname van dialyse wordt vertraagd en de directe gezondheidszorgkosten voor CKD worden verlaagd.

ACKNOWLEDGMENTS

In 2012, I started to work in the Unit of Pharmacology at the University of Messina. I remember the first time I met *Prof. Caputi*. *Prof*, I heard about your expertise in the field of pharmacovigilance and I was fascinated by this field, even if I did not know anything about that. When you introduced me to *Gianluca Trifirò*, you told me that it would go too far from the start.

Gianluca, Prof. Caputi was right! The first time I met you, I thought that you were so young, but in the meantime I was attracted by your enthusiasm in creating a research group at University of Messina, despite all the difficulties. We were three young guys (Francesco, Marco and I) and now we are two research groups at University of Messina and Verona, including almost 15 people. You have been the first one that enthusiastically talked to me about pharmacoepidemiology. You taught me the importance and utility of real-world data, as you always say: "Without data, research does not exist". I would like to thank you because you trusted me, giving me the priviledge to be involved in the coordination of several multi-center pharmacoepidemiology studies, funded by private companies or public institutions, such as Ministry of Health or Italian Medicines Agency. I want to thank you also because you gave me the possibility to educate myself in Boston and in Rotterdam, in two centers of excellence in pharmacoepidemiology research.

I would like to thank my research supervisor, *Prof. Dr. Francesco Mattace Raso*. Thanks for your full availability and help! Without your assistance and dedicated involvement in every step throughout the process, this paper would have never been accomplished and I am extremely grateful for that.

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During my staying in Messina, I also met *Erica*; we shared our apartment for 5 years. *Erica* thanks for your lightness! I cannot forget our "focaccia&birra" days! Even if we currently live in two different cities and we rarely meet , we are the 25 years-old-girls of the past years, when we meet.

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PHD PORTFOLIO

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Promotors:	Prof. F.U.S. Mattace Raso and Prof. G. Trifiro'

1. PHD TRAINING

Research skills

Statistics and methodology

January-March 2020	**EPI 235 Epidemiologic Methods in Health Services Research course** (Harvard T.H. Chan School of Public Health, Boston, MA).
March-June 2020	**Comparative Effectiveness Research course** (Harvard Medical School, Boston, MA).

Oral presentations

2019

"In search of predictors of switching between biosimilar and originator epoetins in clinical practice: a multi-Regional cohort study", ICPE 2019 Mid-Year Meeting "Challenges in postmarketing studies of biological: drugs in the era of biosimilars", Rome, 6-9 April 2019

"Validation Of Diagnostic Algorithms To Detect Type 1 Diabetes Mellitus Disease Using Administrative Data From A General Population From Southern Italy" 35 International Conference on Pharmacoepidemiology & Therapeutic Risk Management, Philadelphia, 24-28 August 2019

"Sviluppo premarketing dei biosimilari: l'esempio di pegfilgrastim/filgrastim", XXI AIOM National Conference, Rome, 25-27 October 2019

How much benefits and risks of new oral anticoagulants as observed in pivotal randomized clinical trials can be generalized to a real-world setting from Southern Italy?",
39th National Conference of the Italian Society of Pharmacology, Florence, 20-23 November 2019

"Il Progetto VALORE: VALutazione post-marketing del profilo beneficio-rischio dei farmaci biologici Originator e biosimilari tramite la costituzione di un network unico multiregionale per l'analisi integrata dei

dati provenienti da banche dati sanitarie, sorveglianze attive e REgistri clinici", XL National Conference of the Italian Society of Hospital Pharmacy, Genova, 21-24 November 2019

2020 *"The VALORE Project"*, Webinar "World Biosimilar Congress Europe 2020", Festival of Biologics, 2-4 November 2020

"VALORE: risultati preliminari del progetto nazionale VALORE", Webinar "Presentazione del Rapporto farmaci in Toscana 2020", 15 December 2020

2021 *"Real-world characteristics and use of disease-modifying anti-rheumatic drugs in patients with rheumatoid arthritis: a cross-national study"*, 40th National Conference of the Italian Society of Pharmacology, Webinar, 9-13 March 2021

"A multi-Regional distributed database network for post-marketing surveillance of biological drugs: the VALORE Project", Webinar "6th symposium on the role of the real world evidence to support regulatory decision making: post-marketing surveillance of biologics in real world setting: which strategies?", 22 September 2021

"The VALORE Project", Webinar "World Biosimilar Congress Europe 2021", Festival of Biologics, Basel, 9-11 November 2021

"Un network multiregionale per la sorveglianza postmarketing dei farmaci biologici in oncoematologia: il progetto VALORE", Conference "Farmaci in ematologia e oncologia: biologici, medicina di precisione e strumenti nel real world setting", Verona, 30 November 2021

"Un network multiregionale per la sorveglianza post-marketing dei farmaci biologici: il progetto VALORE", Conference "Presentazione del Rapporto sui farmaci in Toscana 2021", Florence, 15 December 2021

Seminars and workshop

2019 *"a) Introduction to Pharmacoepidemiology; b) Advanced Topics in Pharmacoepidemiology"*, 2019 ICPE Mid-Year Meeting

	"*a) Pharmacoepidemiologic Considerations for Biologics and Biosimilars; b) Comparative Effectiveness Research: Real-World Evidence in Health Technology Assessment; c) Pharmacovigilance and Signal Detection; d) Advanced Pharmacoepidemiology*", 2019 International Conference of Phamacoepidemiology and Therapeutic Risk Management
Teaching	
2019-2020	Research Project Director for the thesis "Comparisons of risk management of biosimilars between USA and Europe" at the International Master programme "Eu2P - European programme in Pharmacovigilance and Pharmacoepidemiology" (www.eu2p.org), year 2019-2020, University of Bordeaux
2019-2021	Teaching at the II level University Master Programmes on pharmacoepidemiology at Univesity of Messina, Padova, and Università degli Studi della Campania "Luigi Vanvitelli", Naples
2022	Teaching at the II level University Master Programme at Univesity of Verona
	Teaching at online FAD course "Farmaci biotecnologici e biosimilari: uso appropriato - WP3 Progetto Valore"
Others	
2013-current	Member of national and international scientific societies in the fied of pharmacoepidemiology and pharmacovigilance (e.g. *Italian Society of Pharmacology, Italian Association of Epidemiology, International Society of Pharmacoepidemiology, International Society of Pharmacovigilance*)
2021- current	Member, as a Review Editor, of the Editorial Board of Frontiers in Pharmacology (Pharmacoepidemiology section) (IF: 5,810)
2022	Member of the Local Organizing Committee for the 21st Annual Meeting of the International Society of Pharmacovigilance (ISoP) "A new Era of Pharmacovigilance: challenges and opportunities" – Verona, 20-23 Septemebr 2022

ABOUT THE AUTHOR

Ylenia Ingrasciotta was born in Caltagirone (Italy) on the 11th of July 1986. After finishing secondary school at *Liceo Classico "Ruggero Settimo"* in Caltanissetta in 2005, she started to study Pharmaceutical Chemistry and Tecnology at University of Catania, where she obtained her Master's degree in 2011. Since 2012, she studied to obtain her Postgraduate degree cum laude in Medical Pharmacology in 2017 at University of Catania. In 2018, she completed her Master of Science degree on "Pharmacovigilance, pharmacoepidemiology and pharmacoeconomics: assessment using real world data", at University of Messina. She was also a teaching assistant of this Master's course for 2 editions. In 2019, she started to work as a PhD student at the Department of Internal Medicine of the Erasmus University Medical Center (The Netherlands). In 2020, she was a Visiting Research Fellow at the Division of Pharmacoepidemiology and Pharmacoeconomics at the Brigham and Women's Hospital and Harvard Medical School in Boston. Currently, she is also the CEO of the Academic Spin-Off "INnovative Solutions for medical Prediction and big data Integration in REal world setting - INSPIRE SRL" of the University of Messina.

Aside the research that is presented in this thesis, she is working as a pharmacoepidemiologist at the Department of Biomedical and Dental Sciences and Morphofunctional Imaging of the University of Messina since January 2012. She has been involved in several multi-center pharmacoepidemiology studies using different Italian claims and general practice databases. In particular, she worked firstly, on a multi-center project funded by the Italian Ministry of Health, aimed at evaluating the prescribing pattern, effectiveness and safety of some first generation biologics, including biosimilars (e.g. erythropoiesis-stimulating agents, granulocyte colony-stimulating factors, somatropin), through a network of claims databases from different Italian regions and Local Health Units. She's currently actively involved in the coordination of an Italian multi-regional project, known as the VALORE project, funded by the Italian Drug Agency and evaluating the comparative post-marketing benefit-risk profile of biological drugs, both originators and biosimilars, in dermatology, rheumatology, gastroenterology and onco-hematology, using real world data from an Italian network of databases (from 16 Italian regions, covering more than 54 million of inhabitants), active surveillance and clinical registries.

She has also coordinated several observational studies funded by pharmaceutical companies, including: studies on the pattern of anti-osteoporosis drugs, antidiabetic drugs or new oral anticoagulants use, and analgesic drug use in elderly persons, using two claims databases of Caserta and Palermo (Southern Italy); a multi-center pharmacoutilization study in collaboration with the University of Bremen (Germany) and with PHARMO Institute for Drug Outcomes Research (Netherlands), aimed at exploring the real world use of biologics for the treatment of colorectal cancer patients.

On behalf of the INSPIRE academic Spin-Off, she is also involved in some international studies on the safety sssessment of SARS-CoV-2 vaccines in EU Member States using electronic health care datasources in the context of "Covid Vaccine Monitor" project, funded by the European Medicines Agency.

LIST OF PUBLICATIONS

Manuscrips included in this thesis:

Real-world use of biologics and analgesics among elderly

Ingrasciotta Y, Sultana J, Giorgianni F, Menditto E, Scuteri A, Tari M, Tari DU, Basile G, Trifiro' G. Analgesic drug use in elderly persons: A population-based study in Southern Italy. PLoS One. 2019 Sep 19;14(9):e0222836. doi: 10.1371/journal.pone.0222836

Ingrasciotta Y, Jin Y, Foti SS, Landon JE, Tari M, Mattace-Raso F, Kim SK, Trifirò G. Real-world patient characteristics and use of disease-modifying anti-rheumatic drugs in patients with rheumatoid arthritis: a cross-national study [*Submitted for pubblication*]

Ingrasciotta Y, Isgrò V, Ientile V, Tanaglia M, L'Abbate L, Belleudi V, Poggi F, Fiore ES, Trifirò G, Mattace-Raso F. Real-world use of biologics among elderly patients with inflammatory bowel disease [*To be submitted*]

Monitoring of the benefit-risk profile of biologics

Ingrasciotta Y, Cutroneo PM, Marcianò I, Giezen T, Atzeni F, Trifirò G. Safety of Biologics, Including Biosimilars: Perspectives on Current Status and Future Direction. Drug Saf. 2018 Nov;41(11):1013-1022. doi: 10.1007/s40264-018-0684-9

Ingrasciotta Y, Grova M, Crispino F, Isgró V, Calapai F, Macaluso FS, Mattace-Raso F, Trifiró G, Orlando A. Safety and potential interaction of immunosuppressive drugs for the treatment of inflammatory bowel disease in elderly patients. Minerva Gastroenterol (Torino). 2021 May 31. doi: 10.23736/S2724-5985.21.02919-3

Trifirò G, Isgrò V, **Ingrasciotta Y**, Ientile V, L'Abbate L, Foti SS, Belleudi V, Poggi F, Fontana A, Moretti U, Lora R, Sabaini A, Senesi I, Sorrentino C, Puzo MR, Padula A, Fusco M, Giordana R, Solfrini V, Puccini A, Rossi P, Del Zotto S, Leoni O, Zanforlini M, Ancona D, Bavaro V, Garau D, Ledda S, Scondotto S, Allotta A, Tuccori M, Gini R, Bucaneve G, Franchini D, Cavazzana A, Biasi V, Spila Alegiani S, Massari M; VALORE Project Collaborators. Large-Scale Postmarketing Surveillance of Biological Drugs for Immune-Mediated Inflammatory Diseases Through an Italian Distributed Multi-Database Healthcare Network: The VALORE Project. BioDrugs. 2021 Nov;35(6):749-764. doi: 10.1007/s40259-021-00498-3

Ingrasciotta Y, Lacava V, Marcianò I, Giorgianni F, Tripepi G, D' Arrigo G, Chinellato A, Ugo Tari D, Santoro D, Trifirò G. In search of potential predictors of erythropoiesis-stimulating agents (ESAs) hyporesponsiveness: a population-based study. BMC Nephrol. 2019 Sep 14;20(1):359. doi: 10.1186/s12882-019-1554-0. Erratum in: BMC Nephrol. 2020 Jul 9;21(1):262

Interchangeability and switching practices of biologics originators and biosimilars

Trifirò G, Marcianò I, **Ingrasciotta Y**. Interchangeability of biosimilar and biological reference product: updated regulatory positions and pre- and post-marketing evidence. Expert Opin Biol Ther. 2018 Mar;18(3):309-315. doi: 10.1080/14712598.2018.1410134

Ingrasciotta Y, Belleudi V, Trotta F, Addis A, Fontana A, Chinellato A, Ientile V, Tari DU, Roberto G, Pastorello M, Scondotto S, Cananzi P, Traversa G, Davoli M, Rossi M, Trifirò G; Italian Biosimilars Network (I-BioNetwork). In Search of Predictors of Switching Between Erythropoiesis-Stimulating Agents in Clinical Practice: A Multi-Regional Cohort Study. BioDrugs. 2020 Feb;34(1):55-64. doi: 10.1007/s40259-019-00385-y

Belleudi V, Trotta F, Addis A, **Ingrasciotta Y**, Ientile V, Tari M, Gini R, Pastorello M, Scondotto S, Cananzi P, Traversa G, Davoli M, Trifirò G; Italian Biosimilar Network (ItaBioNet). Effectiveness and Safety of Switching Originator and Biosimilar Epoetins in Patients with Chronic Kidney Disease in a Large-Scale Italian Cohort Study. Drug Saf. 2019 Dec;42(12):1437-1447. doi: 10.1007/s40264-019-00845-y

Ingrasciotta Y, Sultana J, Formica D, Ientile V, Aiello A, Chinellato A, Tari DU, Gini R, Pastorello M, Scondotto S, Cananzi P, Traversa G, Rossi M, Santoro D, Trifirò G; Italian Biosimilars Network (I-BioNetwork). Direct healthcare costs of chronic kidney disease management in Italy: What cost-savings can be achieved with higher biosimilar uptake and more appropriate use of erythropoiesis-stimulating agents? Pharmacoepidemiol Drug Saf. 2021 Jan;30(1):65-77. doi: 10.1002/pds.5152