ORIGINAL PAPER

Assessment of patients affected by rheumatoid arthritis eligible for biotechnological agents and evaluation of their healthcare resource utilization and related costs

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SUMMARY

Objective. To provide estimates of patients with rheumatoid arthritis (RA) eligible for biotechnological therapy and to evaluate their healthcare costs.

Method. An observational analysis was performed based on data-linkage between administrative databases of selected Italian Regional/Local healthcare departments. Data were then re-proportioned to the Italian population. Patients with RA diagnosis defined by discharge diagnosis and/or exemption code during 01/01/2013-31/12/2017 were included. The criteria applied to evaluate the elegibility for biotechnological therapy were:

1) methotrexate (MTX)-treatment failure ≥6 months and start of a different conventional-synthetic disease-modifying antirheumatic drugs (csDMARD);
2) corticosteroid ≥6 months with dosage ≥7.5 mg/die;
3) MTX-contraindication (therapy or hospitalization for renal damage/interstizial lung disease/hepatic failure).

Mean annual costs per patient included drugs, hospitalizations, outpatient services.

Results. Data re-proportioned to the Italian population estimated 318,328 RA patients: 43,361 with, 274,967 without biotechnological agents. Among the latter, 26,487(9.6%) patients met ≥1 criteria applied for eligibility: 1,896 had MTX-treatment failure and started another csDMARD; 15,833 received corticosteroid ≥7.5 mg/die; 7,788 had MTX-contraindication. Regarding patients fulfilling two criteria, 107 had MTX-treatment failure followed by another csDMARDs and corticosteroid ≥7.5 mg/die, 53 were treated with another csDMARDs after MTX-treatment failure and also presented MTX-contraindication, 810 had corticosteroid ≥7.5 mg/die and MTX-contraindication. Mean total annual costs for patients estimated eligible for biotechnological therapy was € 3,132, of which € 177 related to drugs indicated for RA and € 2,955 related to other direct costs.

Conclusions. According to our estimates, around 10% RA patients not currently treated with biotechnological agents are eligible for such therapies, highlighting a trend of under-use in clinical practice for RA management.

Key words: *Biotechnological therapy, real-world, rheumatoid arthritis, under-treatment.*

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INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory systemic auto-immune disorder with a progressive course which affects primarily the synovial membrane of the joints, although extraarticular manifestations are often present as well (1). The Global Burden of Disease (GBD) 2010 study gave an estimation of the significant clinical burden of RA (2): of the 291 diseases analysed in the GBD study, RA was ranked as the 42nd and 74th highest contributor of global disability (calculated as years of life lived with disability) and overall burden (calculated as disability-adjusted life years), respectively (2).

RA is one of the most common chronic inflammatory conditions (3). Its global prevalence stands at around 0.24%-1% (2, 4). This estimate is likely to increase over the next decades because of the progressive ageing of the population. In Italy, RA prevalence is estimated approximately at

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0.41%-0.48% (5). RA poses a great economic burden on patients, families and healthcare systems. These costs are set to increase further in the coming years particularly in countries like Italy, where the elderly population is expected to increase (6).

The clinical manifestations of RA are heterogeneous, and can lead to a limitation in the range of motion and impaired function of the affected joints (7). Currently, there is no cure for RA, and the available treatments aim to prevent structural progression of damage, control inflammation and rapidly reach a low disease activity state or remission (8). Therefore, an early initiation of RA therapy upon diagnosis is required to get control of the disease and achieve optimal outcomes. While the short-term use of glucocorticoids can offer a fast control of inflammation to reduce pain and swelling in case of acute flares, the mainstay of RA treatments relies on the Disease Modifying Anti-Rheumatic Drugs (DMARDs), that are able to control the inflammatory course for longer periods (8). DMARDs can be categorized in conventional synthetic (cs), biological (b) and targeted synthetic (ts) (9).

Accordingly to the latest European League Against Rheumatism (EULAR) guidelines (10), methotrexate (MTX), which is considered as the *anchor drug* for RA, or another csDMARD in case of MTX contraindications, is recommended as first line treatment. Therapy adjustments should then be made if a low disease activity/remission are not achieved after 6 months, or if no improvement is observed after 3 months from therapy initiation. Patients with associated poor prognostic factors that at this time-point do not respond to the first csDMARDs strategy, or patients that had at least 2 previous treatment failures with different csDMARD should receive also a bDMARD therapy (10).

Over the past decades, the increasing understanding of RA pathogenesis and the underlying mechanisms paved the way to the development of bDMARDs, that positively revolutionized RA management (11). bDMARDs showed indeed to be able to target pivotal proteins of the RA pathogenetic network, providing a valid therapeutic alternative for patient not responding to traditional therapies.

The increasing number of therapeutic options for RA demands more evidence from routine clinical practice to provide insight on the prescription patterns in the real-world rheumatology practice. Larger and more in-depth analyses are also needed to assess their therapeutic appropriateness.

In the Italian context, the analysis of administrative databases, depicting the real-world practice, can represent a useful tool for healthcare professionals to evaluate the implementation of evidence-based recommendations in clinical practice and reduce any potential deviations detected.

Although guidelines recommend to switch treatment in RA patients with an inadequate response to conventional drugs, international studies conducted in real-world settings highlighted that this may not always occur in everyday clinical practice (12, 13).

To investigate if this trend also applies to the Italian context, this study aims to estimate the number of patients with a diagnosis of RA who are eligible for a biotechnological therapy according to the EULAR recommendation (14), but are not actually treated with such drugs in an Italian real-world setting. Moreover, we conducted an economic analysis to estimate the direct healthcare costs for the Italian National Health Service (INHS) associated with RA patients treated with or eligible for biotechnological therapy.

MATERIALS AND METHODS

Data source

An observational retrospective cohort study was conducted by using the administrative databases of a pool of Italian Regional/Local Healthcare departments from Lombardy, Veneto and Apulia Regions. Data were then re-proportioned to the Italian population. To perform the analysis, the following databases were used: demographic database which contains patients' demographic data; pharmaceuticals database providing

data on prescription as Anatomical-Therapeutic Chemical code (ATC), number of packages, number of units per package, and prescription date; hospitalization database which includes all hospitalization data as the discharge diagnosis codes classified according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM); exemption database, which provides exemption code and date of exemption.

In each database, the patient code was used to create an electronic link with all the other databases. To guarantee patients' privacy, an anonymous univocal numeric code was assigned to each subject included in the study, in full compliance with the European General Data Protection Regulation (GDPR) (2016/679). No identifiers related to patients were provided to the authors. All the results of the analyses were produced as aggregated summaries, which could not be associated with the individual patients, either directly or indirectly. An informed consent was not required for using encrypted retrospective information for research purposes. According to the Italian law (15), the local Ethics Committee of the departments involved in the study was notified of the study and approved it. The study followed the REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) guidelines (16).

Study population

The analysis herein included all patients who were diagnosed with RA ascertained for the presence of hospitalization discharge diagnosis with ICD-9-CM code 714 and/or an active exemption code 006 from January 1st, 2013 to December 31st, 2017. The accuracy of the exemption code for RA identification was previously validated by Carrara et al. (17) and its use is in line with other studies following a similar methodology (18, 19). Patients not treated with biotechnological drugs were considered eligible for this therapy if they met at least one of the following criteria (Table I):

1) use of MTX for at least 6 months, then switch to a different csDMARD;
2) corticosteroid treatment for at least 6 months at a dosage ≥7.5 mg/die;
3) contraindication to MTX therapy, defined as patients in therapy or hospitalized for renal damage (ICD-9-CM codes: 580-589), interstitial lung disease (ICD-9-CM codes: 510-519) or hepatic failure (ICD-9-CM codes: 570-573). The criteria applied were developed based on the guidelines in force during the analysis and were refined and validated by a pool of clinicians specialized in rheumatology.

Table I - Criteria applied to identify RA patients eligible for biotechnological therapies.

Name	Definition
MTX failure	use of MTX for at least 6 months, then switch to a different csDMARD
CS ≥7.5 mg/die	corticosteroid treatment for at least 6 months, with a dose ≥7.5 mg/die
MTX contraindication	contraindication to MTX therapy, defined as patients on therapy or hospitalized for renal damage, interstizial lung disease or hepatic failure.
Sensitivity analysis	
CS ≥5 mg/die	corticosteroid treatment for at least 6 months, with a dose ≥5 mg/die

csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; CS, corticosteroid; MTX, methotrexate; RA, rheumatoid arthritis.

Study variables

Patients were identified as treated with biotechnological therapies if they had a prescription for the following agents indicated for RA at the time of the analysis: abatacept (ATC code: L04AA24), adalimumab (ATC code: L04AB04), anakinra (ATC code: L04AC03), certolizumab (ATC code: L04AB05), etanercept (ATC code: L04AB01), golimumab (ATC code: L04AB06), infliximab (ATC code: L04AB02), rituximab (ATC code: L01XC02), tocilizumab (ATC code: L04AC07). csDMARDs analysed were: MTX (ATC code: L01BA01), leflunomide (ATC code: L04AA13), sulfasalazine (ATC code: A07EC01), cyclosporine (ATC code: L04AD01), azathioprine (ATC code: L04AX01), chloroquine (ATC code: P01BA01), hydroxychloroquine (ATC code: P01BA02). Corticosteroids analysed

belonged to ATC code: H02. The mean daily dose was calculated as the sum of total dosage prescribed in a prescription divided by the days covered by such prescription.

Sensitivity analysis

Corticosteroids at a low-dose of 7.5 mg/die were recommended in combination with csDMARDs as bridging therapy and should be gradually tapered within maximum 6 months. If they could not be completely stopped within this time frame, the DMARD therapy might have to be considered a failure. In the guidelines in force during the analysis (14), the term *low-dose* was changed in *short-term*, leaving to physicians the decision about the dose regimens. Therefore, we decided to conduct a sensitivity analysis considering a corticosteroid dosage ≥5 mg/die instead of ≥7.5 mg/die for at least 6 months (Table I).

Direct healthcare costs analysis

The mean annual direct healthcare costs per patient based on resource consumption were estimated in terms of drugs, hospitalizations, and outpatient services. The healthcare cost analysis was performed from the perspective of the Italian National Health Service (INHS), with costs reported in Euros (€). Drug costs were evaluated using the INHS purchase price. Hospitalization costs were determined using Diagnosis Related Group (DRG) tariffs, which represent the reimbursement levels by the INHS to healthcare providers.

Since in general costs are not normally distributed, Generalized Linear Models (GLM) were assessed in order to evaluate the correlation between costs and use of biotechnological therapies, considering age, male gender and biosimilar formulation as confounding variables. A gamma distribution and an identity link function (in order to retrieve non transformed costs) were applied; post estimation tests included residuals analysis and check for influential observations.

Statistical analysis

Categorical variables were expressed as frequencies and percentages. Percentages of patients eligible for biotechnological therapy are referred to proportion of patients with one or more criteria among patients not treated with this therapy. All statistical analyses were performed using STATA SE, version 12.0.

RESULTS

Data re-proportioned to the Italian population in 2017 (N=60,589,445) estimated in this analysis a total of 318,328 patients affected by RA. According to the estimation, as showed in Figure 1, 43,361 of them

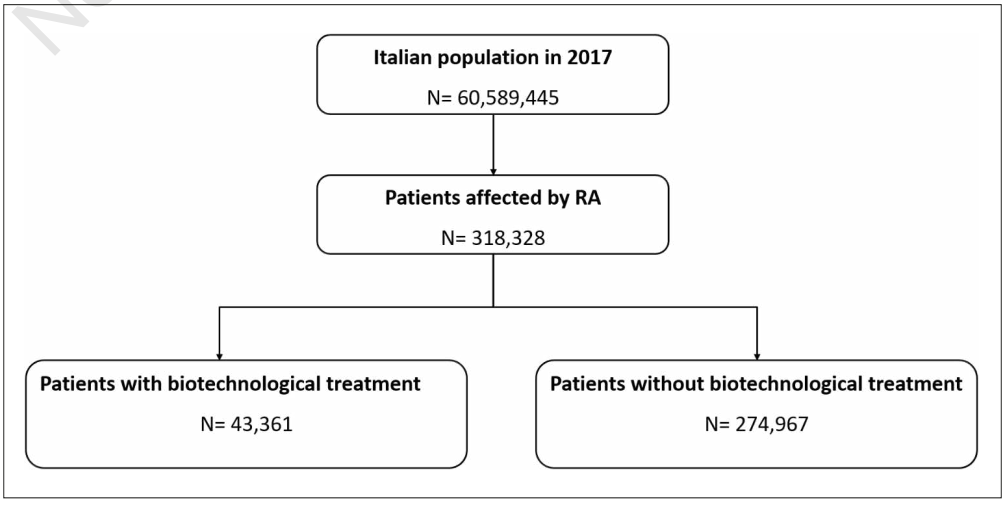

Figure 1 - Flowchart of the study population. Notes: data re-proportioned to the Italian population. RA, rheumatoid arthritis.

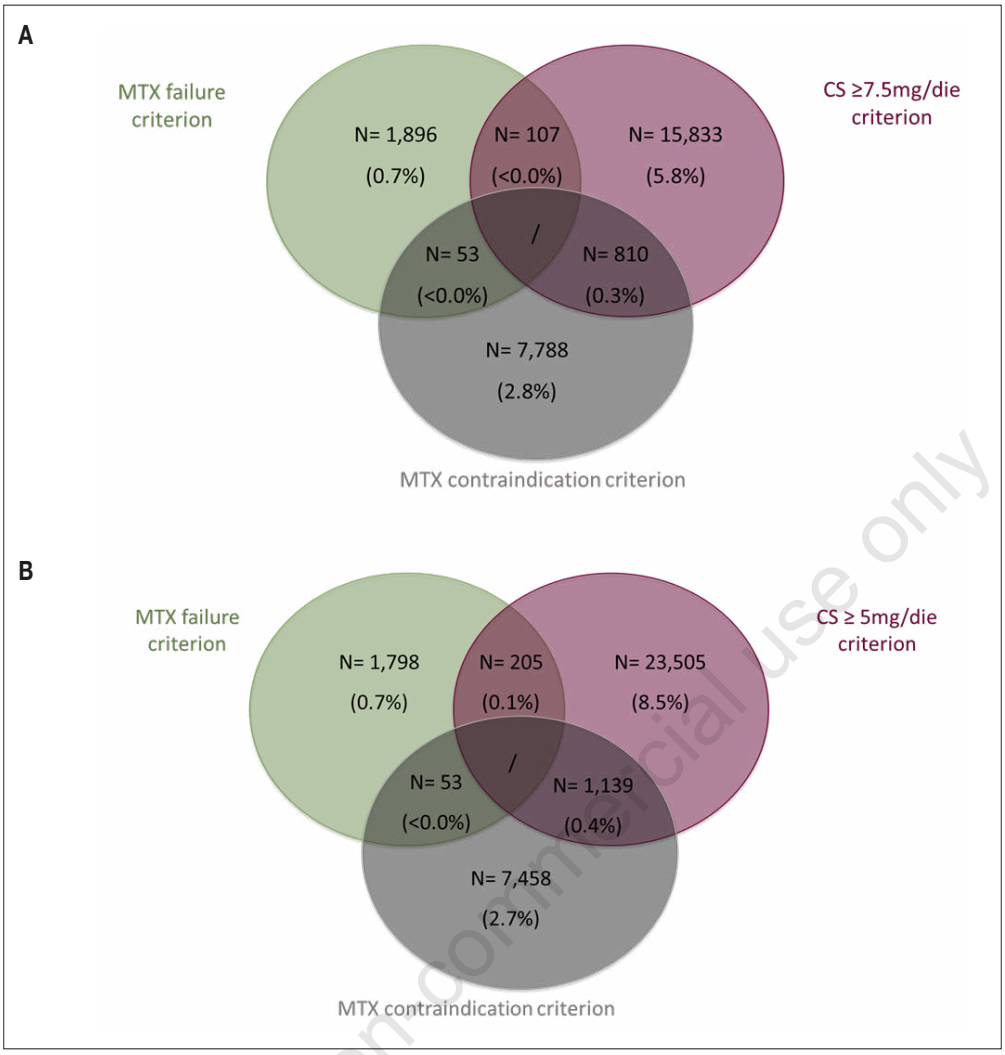

Figure 2
Distribution of patients eligible for biotechnological therapy according to criteria applied (a) and to sensitivity analysis (b). Notes: data re-proportioned to the Italian population. Percentages referred to proportion of patients with 1 or more criteria among patients not treated with biotechnological therapy (N=274,967). CS, corticosteroid; MTX, methotrexate.

were treated with biotechnological treatments, while 274,967 were not prescribed with these drugs. Among the latter, 26,487 (9.6%) patients were estimated to be eligible for biotechnological therapy, and their distribution according to the criteria applied is reported in Figure 2a. The demographic characteristics (re-proportioned) for patients with one criterion of eligibility and for patients receiving biotechnological agents are reported in Table II. As to patients who met one criterion of eligibility, 1,896 (0.7%) (mean age 64.4, 24.4%male) used MTX for at least 6 months, then switched to a different csDMARD (MTX failure criterion), 15,833 (5.8%) (mean age 68.7, 31.1% male) were on a corticosteroid ≥7.5 mg/die for at least 6 months(CS ≥7.5 mg/die criterion) and 7,788 (2.8%) (mean age 72.4, 35.1% male) had MTX contraindication (MTX contraindication criterion). As to patients fulfilling two of the criteria applied, 107 (<0.0%) used MTX for at least 6 months, then switched to a different csDMARD and were treated also with a corticosteroid ≥7.5 mg/die for at least 6 months (MTX failure and CS ≥7.5 mg/die criteria), 53 (<0.0%) were treated with another csDMARDs after MTX treatment for at least 6 months and also presented MTX contraindication (MTX failure and MTX contraindication criteria), 810 (0.3%) were on a corticosteroid ≥7.5 mg/die for at least 6 months and had MTX contraindication (CS ≥7.5 mg/die and MTX contraindication criteria).

A similar trend was also observed in the sensitivity analysis in which the criterion CS ≥7.5 mg/die was replaced by a corticosteroid dosage ≥5 mg/die for at least 6 months (CS ≥5 mg/die criterion). In this analysis, eligible patients re-proportioned to Italian population were estimated to be 34,158, representing 12.4% of patients without biotechnological treatment. Among them, as reported in Figure 3, 1,798 (0.7%) patients met the MTX failure criterion, 23,505 (8.5%) the CS ≥5 mg/die criterion and 7,458 (2.7%) the MTX contraindication criterion (Figure 2b). In the same analysis, patients presenting two criteria were distributed as follow: 205 (0.1%) satisfied MTX failure and CS ≥5 mg/die criteria; 53 (<0.0%) MTX failure and MTX contraindication criteria; 1,139 (0.4%) CS ≥5 mg/die and MTX contraindication criteria.

While patients receiving biotechnological therapy were mainly found in the age ranges between 60-69 (27.4%) and 50-59 (24.5%), patients with one eligibility criterion were mostly aged between 70-79 (28.2% for MTX failure criterion and 32.3% for CS ≥7.5 mg/die criterion) or over 80 (35.8% for MTX contraindication criterion) (Table II). Overall, among eligible patiens, the most common age range among women was 70-79 (21.6%) followed by 80-89 (12.8%) and 60-69 (15.4%), while

Table II - Demographic characteristics of RA patients meeting one eligibility criterion for biotechnological therapy and RA patients treated with biotechnological therapies, as estimated in Italy.

	Eligible patients			Treated patients
	MTX failure	CS ≥7.5 mg/die	MTX contraindication	
N	1,896	15,833	7,788	43,361
Mean Age	64.1	68.7	72.4	56.3
Male n (%)	463 (24.4)	4,931 (31.1)	2,732 (35.1)	9,852 (22.7)
Age range distribution n (%)				
<40	62 (3.3)	427 (2.7)	187 (2.4)	6,016 (13.9)
40-49	205 (10.8)	1,068 (6.7)	401 (5.1)	6,043 (13.9)
50-59	409 (21.6)	2,243 (14.2)	685 (8.8)	10,636 (24.5)
60-69	454 (23.9)	3,489 (22.0)	1,513 (19.4)	11,873 (27.4)
70-79	534 (28.2)	5,118 (32.3)	2,216 (28.5)	7,271 (16.8)
≥80	231 (12.2)	3,489 (22.0)	2,786 (35.8)	1,522 (3.5)

CS, corticosteroid; MTX, methotrexate; RA, rheumatoid arthritis. Notes: data re-proportioned to the Italian population.

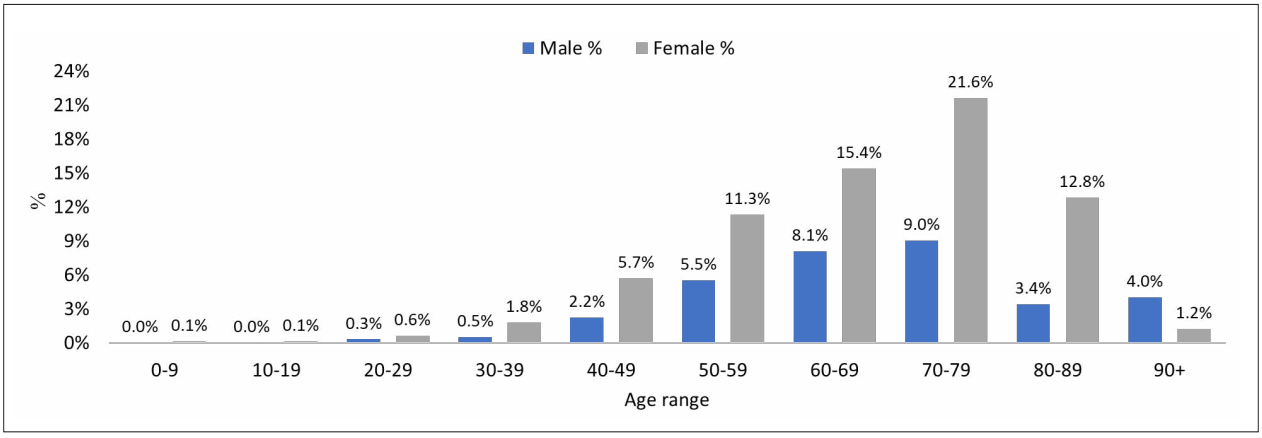

Figure 3 - Distribution of patients eligible for biotechnological therapy per gender and age. Notes: data re-proportioned to the Italian population.

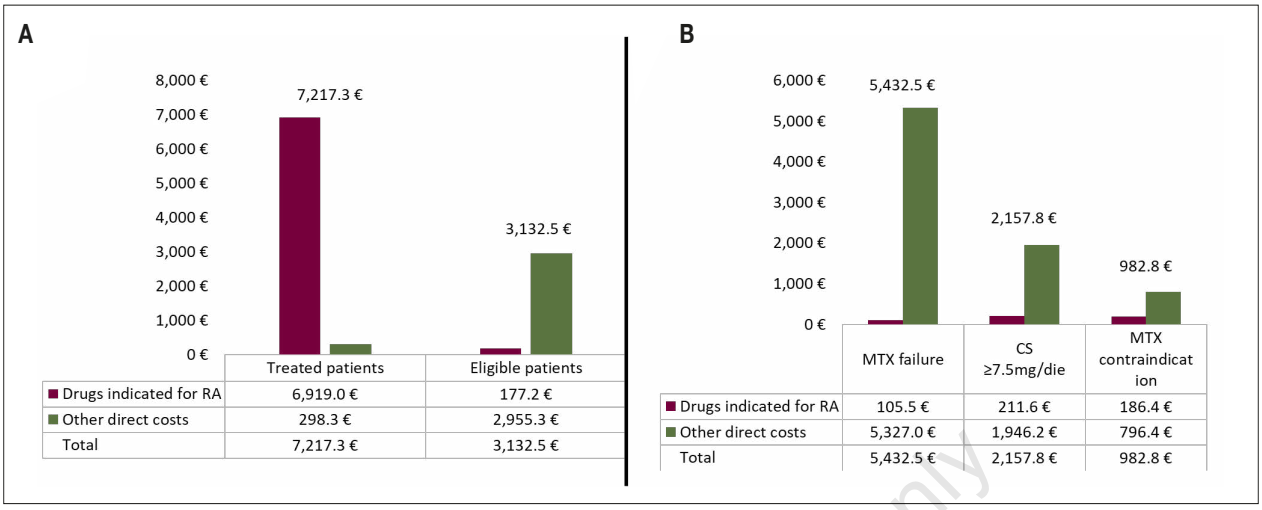

Figure 4 - Mean annual costs for patients treated with biotechnological therapy or eligible for biotechnological therapy (a) and stratified by elegibility criteria (b). Notes: data re-proportioned to the Italian population. Other costs include other drugs, hospitalizations, outpatient services. RA, rheumatoid arthritis.

among men the most common age ranges were 70-79, 60-69 and 50-59 (9.0%, 8.1% and 5.5%, respectively) (Figure 3).

The mean total annual healthcare cost (Figure 4a) for RA patients treated with biotechnological therapy was estimated to be € 7,217, of which € 6,919 for drugs indicated for RA and € 298 for other direct costs. For patients eligible for such therapy, the estimated total annual expenditure was € 3,132, of which € 177 for drugs indicated for RA and € 2,955 for other direct costs. Figure 4b shows the mean annual costs for patients stratified by eligibility criteria, which reached € 5,432 for patients with the MTX failure criterion, € 2,158 for patients with the CS ≥7.5 mg/die criterion and € 983 for the MTX contraindication criterion. For patients who met each criterion, the other direct costs were the main determinant of the total expenditure.

Since eligible patients were generally older than those receiving biotechnological drugs, a GLM analysis was conducted taking into account potentially confounding variables. As reported in Table III, direct costs other than drugs indicated for RA were estimated to decrease significantly when using biotechnological drugs (€ 89.6, p=0.027) and to increase with age (€ 19.3, p<0.001).

Table III - Generalized linear models for direct costs other than drugs indicated for RA.

	€	95% CI		p value
Use of biotechnological therapy	–89.6	–169.0	–10.2	0.027
Age	19.3	17.1	21.5	<0.001
Male gender	–53.3	–132.8	26.2	0.189
Biosimilar formulation	137.0	–40.6	314.6	0.130
Intercept	*176.1*	*8.0*	*344.2*	*0.040*

DISCUSSION

Over the past 30 years, the availability of biotechnological treatments has transformed the management of RA. These drugs have proven to be highly effective in slowing disease progression and reducing RA symptoms, thus improving the quality of life of affected individuals (20-22). However, Italy is in the lowest positions in Europe in terms of access to biotechnological therapies (23, 24).

This study gave an estimation of RA patients at a National level who are eligible for biotechnological therapy, yet are not currently treated with these agents. To assess eligibility, 3 criteria were applied that reflected the recommendations reported in the EULAR guidelines concerning biotechnological drugs initiation in RA patients (14). Our estimation showed that

out of 274,967 AR patients who were not treated with biotechnological therapies, from 26,487 up to 34,158 patients were eligible for such therapies, thus highlighting a trend of under-prescription in this patient population in Italy.

This tendency was also found in another Italian study, which investigated the underuse of biotechnological agents in clinical practice for several chronic diseases, RA included, for which these type of drugs are indicated (25). Based on a prevalence of 200,000 RA patients reported in literature (26), in that study a minimum of 43,000 and a maximum of 58,000 patients requiring biotechnological therapies were estimated, yet only 38,000 of them were on biotechnological treatment. Therefore, from a minimum of 5,000 to a maximum of 20,000 patients were calculated as being under treated with regard to these drugs. Over the last few years, several interpretations for this finding have been reported in the literature. The first reason could be related to the variability observed in terms of access to the prescription of biotechnological drugs. In the first social report on RA drafted by the Italian Society of Rheumatology (*Società Italiana di Reumatologia*, SIR) and the National Association of Rheumatic Patients (*Associazione Nazionale Malati Reumatici*, ANMAR) (27), patients who were more often prescribed biotechnological agents were treated in rheumatology centers, which are not evenly distributed across Italian territory, and only a small proportion were followed by general practitioners or rheumatologists. Moreover, the limited access to these therapies could be also a consequence of a delay in the diagnosis of RA. Indeed, the mean time from symptoms onset to confirmed RA diagnosis was estimated to be almost 1 year (27). There could be also economic reasons, since biotechnological agents have the drawback of costing more than the traditional therapy, which could limit their use. As a result, a higher number of patients on this therapy translates into a significant economic burden for the National Healthcare Systems, which should reconcile the need to contain health expenditure and avoid exceeding spending limits with the need to respect the right to health of all patients (28). In this regard, the advent of biosimilars could offer a lower-priced alternative (29). A further cause of biotechnological drugs under-use could be related to a therapeutic strategy different from the *treat-to-target* one claimed by international guidelines due to several reasons including age, presence of comorbidities and drug-related risks (30).

The age distribution revealed that the population eligible for biotechnological therapy included mainly older peole. This is in line with other analyses reporting that younger patients are more likely to be prescribed biotechnological treatments than older ones, and there is a tendency of not prescribing these agents in the elderly (31-33). Nevertheless, our results showed a quite significant proportion of working-age patients being not prescribed this therapy: as a result under-treatment could contribute to worsen the burden placed on them by RA (34).

The economic analysis revealed that while total costs for patients treated with biotechnological drugs were mainly driven by drugs indicated for RA, those estimated for eligible patients were mostly affected by direct costs related to other drugs, hospitalizations and outpatient services. This trend emerged also when looking at patients meeting one of the eligibility criteria. The higher direct costs for patients eligible to the biotechnological therapy could be influenced by the older age observed in the eligibility cohort.

We acknowledge some limitations of the present study. Our cohort of patients reflected real clinical practice, but the results must be interpreted taking into account the limitations related to the observational nature of the study, which was based on data collected from administrative databases. The first one was the lack of clinical information related to the severity of RA in terms of disease activity, prognostic favourable/unfavorable factors and other potential confounders. Secondly, it was not possible to gain information from administrative databases on the reasons behind the underuse of biotechnological drugs, which could

be related to clinical reasons or to different treatment strategies adopted. Moreover, the selected criteria could have over-estimated or under-estimated the number of RA patients eligible for biotechnological therapy in Italy. Finally, our study was based on estimates of the national population from a sample of Italian Regional/Local Healthcare departments which might be not fully representative of the Italian context.

CONCLUSIONS

In this analysis, data collected from administrative databases were re-proprtioned to the Italian population to provide an estimation at the national level of the number of patients affected by RA eligible for the biotechnological therapy. A characterization of these patients in terms of direct healthcare costs was also provided. Our results highlighted the under-treatment of a significant proportion (around 10%-12%) of RA patients who were considered eligible, yet actually did not receive any biotechnological treatments. Given the data source used in the study, we could not investigate the reasons underlying the trend of the underuse of these therapies in clinical practice for RA, which could be economic or organizational or due to prescribing decisions. The high direct healthcare costs for eligible patients could be mainly due to the older age observed in this cohort compared to patients who receive biotechnological therapies.

Disclosure

LS reports personal fees (invited speaker) from Amgen, personal fees (invited speaker) from Eli Lilly, personal fees (invited speaker) from UCB, personal fees (invited speaker) from Abbvie, personal fees (invited speaker) from Roche, personal fees (invited speaker) from BMS. LDE, VP, DS report no conflict of interest.

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