

REVIEW ARTICLE

Biosimilars: From Extrapolation into Off Label Use

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Abstract: Background: Biologic drugs have revolutionised the management of many inflammatory conditions. Patent expirations have stimulated development of highly similar but non-identical molecules, the biosimilars. Extrapolation of indications is a key concept in the development of biosimilars. However, this has been met with concerns around mechanisms of action, equivalence in efficacy and immunogenicity, which are reviewed in this article.

Methods: Narrative overview composed from literature search and the authors' experience. Literature search included Pubmed, Web of Science, and online document archives of the Food and Drug Administration and European Medicines Agency.

Results: The concepts of biosimilarity and extrapolation of indications are revisited. Concerns around extrapolation are exemplified using the biosimilar infliximab, CT-P13, focusing on mechanisms of action, immunogenicity and trial design. The opportunities and cautions for using biologics and biosimilars in unlicensed inflammatory conditions are reviewed.

Conclusions: Biosimilars offer many potential opportunities in improving treatment access and increasing treatment options. The high cost associated with marketing approval means that many bio-originators may never become licenced for rarer inflammatory conditions, despite clinical efficacy. Biosimilars, with lower acquisition cost, may improve access for off-label use of biologics in the management of these patients. They may also provide opportunities to explore off-label treatment of conditions where biologic therapy is less established. However, this potential advantage must be balanced with the awareness that off-label prescribing can potentially expose patients to risky and ineffective treatments. Post-marketing surveillance is critical to developing long-term evidence to provide assurances on efficacy as well as safety.

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1. INTRODUCTION

Biologic drugs have revolutionised the management of many immune-mediated inflammatory conditions ranging from rheumatoid arthritis (RA) to inflammatory bowel disease (IBD). These drugs are extremely effective, yet also carry high acquisition costs. In the case of rheumatic diseases, they heralded the development of a market for high cost drugs, previously considered impossible and, in parallel, identified inflammatory diseases as attractive conditions for Industry to invest in [1]. The limited lifespan of patents for these drugs has stimulated programmes, many starting over a decade ago, to develop similar molecules that, whilst not identical to the originator, could be considered to be biological equivalent of a "generic". Such "biosimilars" are defined as a biological agents that are similar in terms of quality, safety and efficacy to an already licensed reference product [2]. To help drive down cost, regulators such as the European Medicines Agency (EMA) and the US Food and Drugs Administration (FDA) have allowed biosimilars to follow an expedited process for approval. Such a process can vastly reduce development costs, which can be passed on to healthcare systems as lower drug cost. Though as a compromise, they are not as extensively investigated as the reference product not only in gaining their licence (of crucial interest to biosimilar companies) but also in post-marketing evaluation for new indications (typically considered not cost-effective for major investment from Industry). This article reviews extrapolation of biosimilar indications and

explores the issues and opportunities presented by biosimilars with a focus on off-label use.

2. BIOSIMILARITY AND EXTRAPOLATION OF INDICATIONS

The prototype class of anti-inflammatory biologic are the anti-tumour necrosis factors (TNF). Both etanercept (a fusion protein comprising two human p75 monoclonal TNF receptors, coupled to a human IgG1 Fc tail) and the monoclonal anti-TNF antibodies (infliximab, adalimumab, golimumab and the PEGylated certolizumab) are large, mainly protein, molecules. They are produced by recombinant DNA techniques using a single clone of cells through a highly refined process. In the manufacturing process, primary amino-acid sequences undergo post-translational modifications such as sialylation, that are affected by the cell line and their environment [3]. This creates specific protein-folding and complex three dimensional structures. Each manufacturer uses a unique cell line and production process, therefore copies cannot be identical to the reference product (RP) [4]. In fact, no two batches of any biologic, even the RP, can be identical [5].

For each marketed indication, approval for the RP relies on clinical trials to demonstrate efficacy, safety and immunogenicity. In contrast, biosimilar approval does not require the manufacturer to re-establish efficacy, but is instead based on the demonstration that there are no clinically meaningful differences from the RP. This involves comprehensive comparison firstly of structure and function through complex analytical and in vitro studies, then in vivo animal studies and, finally, abridged clinical studies of pharmacokinetics, pharmacodynamics, immunogenicity, safety and efficacy [2, 6, 7].

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Table 1. Approval status of proposed biosimilars of infliximab, etanercept, adalimumab, and rituximab, as of November 2017.

	Biosimilar	EMA approval status	FDA approval status
Infliximab	CT-P13	Remsima/Inflectra Approved Sept 2013	Inflectra Approved Apr 2016
	SB2	Flixabi Approved May 2016	Renflexis Approved Apr 2017
	PF-06438179	NS	N/A
	BOW015	NS	NS
	ABP710	NS	NS
Adalimumab	ABP501	Solymbic Approved Jan 2017	Amjevita Approved Sept 2016
	BI 695501	Cyltezo Approved Nov 2017	Cyltezo Approved Aug 2017
	SB5	Imraldi Approved Jun 2017	NS
	CHS-1420	NS	NS
	GP2017	NS	NS
	M923	NS	NS
	BCD-057	NS	NS
	PF-06410293	NS	NS
Etanercept	SB4	Benepali Approved Jan 2016	NS
	GP2015	Erelzi Approved Jun 2017	Erelzi Approved Aug 2016
	CHS-0214	NS	NS
	HD203	NS	NS
	LBEC0101	NS	NS
	ENIA11 (TuNEX)	NS	NS
Rituximab	CT-P10	Truxima Approved Dec 2016	NS
	GP2013	Rixathon Approved Jun 2017	NS
	ABP798	NS	NS
	PF-05280586	NS	NS
	BCD-020	NS	NS

NS, not submitted; N/A, not applicable.

Once biosimilarity has been established in one indication, the drug may be approved for additional indications held by the RP without comparative clinical trials. Extrapolation of indication is integral to the concept of biosimilarity. It reduces the number and size of clinical trials required, thereby decreasing financial cost and, potentially, increasing access [7]. It is however worth noting that the dramatic cost reductions and improved access for small-

molecule generics were due to automatic substitution at the pharmacy level [8]. This is not currently the case for biosimilars in most regions. Full “interchangeability” requires additional standards that are currently lacking, as each biosimilar is compared only to the RP, without any evaluation of potential swapping between two or more biosimilars for the same RP.

The concept of biosimilar extrapolation is not new. Regulation was less complex for biosimilar recombinant human protein analogues, such as epoetin and filgrastim, where each mechanism of action is mediated by the same receptor [9]. In contrast, mAbs are much more complex molecules; comprising Fab and Fc regions, each with considerable diversity and variable mechanisms of action. The Fab region can neutralise soluble TNF (sTNF) and remove them from the immune pathway. They can also bind to transmembrane TNF (tmTNF) and activate intracellular signalling resulting in apoptosis or cytokine suppression [10, 11]. The Fc region has the ability to bind to specific receptors, leading to potential effector functions such as antibody-dependent cellular cytotoxicity, complement-dependent cytotoxicity, and antibody-dependent cellular phagocytosis. Binding to the neonatal Fc receptor (FcRn) also protects the mAb from proteolytic degradation [12].

3. CONCERNS AROUND EXTRAPOLATION

The biosimilar infliximab CT-P13 was the first to be licensed in the US and EU (see Table I for other biosimilars). Comprehensive comparative analyses were supported by two clinical trials demonstrating that pharmacokinetics (PK), efficacy, safety and immunogenicity were comparable in ankylosing spondylitis (AS) and RA [13-16]. Extension studies also demonstrated unaffected safety, efficacy and immunogenicity when switched from the RP [17, 18]. In the US and EU, CT-P13 indication was then extrapolated to all RP indications for psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis [19, 20]. This was however met with much controversy for several reasons.

Although TNF may play a pivotal role in the immune pathway of all six disease indications, it is clear that various mechanisms of action are not of equal importance in each condition. Reverse signalling via tmTNF binding is thought to be an important mechanism of action in IBD [11]. This is supported by the fact that etanercept, which binds less avidly to tmTNF, is effective in rheumatic indications but not in IBD [21]. Another mechanism of action thought to be relevant in IBD is natural killer (NK) cell induced target cell lysis, although this had been contested [22, 23]. Compared to its RP, CT-P13 had reduced binding to NK cell FcγRIIIa (low affinity immunoglobulin γ Fc region receptor IIIa) and for this reason was not approved for IBD in Canada [24].

Concern around immunogenicity is another suggested reason to limit extrapolation, as anti-drug antibodies (ADAs) can affect safety and efficacy [25]. For example, a minor change in the manufacturing process of epoetin was thought to have caused autoantibodies to endogenous erythropoietin and the dramatically increased incidence of pure red cell aplasia - a rare but potentially fatal condition [26]. Similarly, infliximab ADA positive Crohn's patients were much more likely to experience infusion reactions [27].

Comparing immunogenicity is difficult, for example ADA was reported in up to 61% in Crohn's disease [27], but varied significantly depending on concomitant medication [28]. However, there do seem to be situations where the frequency of ADAs differs from one disease to another, possibly due to the immunological background underlying the inflammatory process. For example, around 48% of RA patients developed ADAs to infliximab at 30 weeks, compared with 23-27% of AS patients [13, 15].

Lastly, there were concerns around having RA as the disease model to demonstrate comparability between CT-P13 and the RP. Unlike biomarker endpoints used in biosimilar studies of recombinant human protein analogues, mAb trials rely on less sensitive clinical outcomes due to their complex mechanisms of action. A large treatment-placebo effect difference is therefore necessary to reliably demonstrate equivalence. Of the six infliximab indications, RA was associated with one of the smallest placebo-adjusted response [29, 30]. It may therefore not be the most sensitive clinical model to detect a potential difference in efficacy between CT-P13 and its RP. Similarly for immunogenicity, the population with the

highest immune response should be used to provide the best sensitivity in detecting differences [31]. RA studies reported less infliximab ADA development [30, 32] compared with Crohn's disease [27] or psoriasis [33]. In summary, the RA studies of efficacy and immunogenicity equivalence did not exclude the possibility that CT-P13 and its RP are different in extrapolated indications, where differences may be more easily detected. Experts therefore argued that dedicated clinical trials were needed for each indication and many clinicians hesitated to use biosimilars even when regulatory approval for extrapolation was granted [34-36]. It was only with subsequent real world data and confirmatory studies that practice began to change [37, 38]. This highlights the need to have additional post-market monitoring to develop long-term evidence to provide assurances on efficacy as well as safety.

4. OPPORTUNITIES FROM BIOSIMILARS

Controversies aside, the dawn of biosimilar mAbs presents many potential opportunities as a result of their reduced cost [39]. The most obvious is the hope to increase drug access or to reinvest savings for other health resources. Take for example biosimilar filgrastim (a granulocyte colony-stimulating factor) which was launched in late 2008. With their reduced cost, funding agencies in the UK updated guidelines which saw use of both RP and biosimilar filgrastim increase by over 100% in the subsequent six years [40]. A significant number of these patients may not have otherwise received the drug.

In 2008, the then named National Institute for Clinical Excellence (NICE) rejected RP infliximab for AS on the grounds of cost-effectiveness [41]. The cost of biosimilar infliximab and its impact on the RP cost, meant that in 2016 NICE reissued guidance that recommended infliximab if the patient is started on the least expensive product [42]. This increased access to TNF inhibition therapy, and also increased the number of treatment options for these patients.

For IBD, the UK Royal College of Physicians' annual audit of biologics suggested that the introduction of biosimilar infliximab could half the annual cost of treatment [43]. This would save the health services an estimated £90 million per year if all patients were switched to a biosimilar [44]. The 2016 audit, which captured the introduction of biosimilar infliximab in 2015, reported the largest annual increase in the absolute number of biologic-treated patients; 22% of patients were prescribed biosimilar infliximab [45]. In addition to licenced indications, biosimilars may also improve access to biologics for other unlicensed inflammatory conditions.

5. OFF-LABEL USE OF BIOSIMILARS

Many of the issues of biosimilars discussed so far have focused on considerations of regulatory agencies. However, these agencies do not have authority over the use of drugs outside of their licenced indications. Health care professionals can prescribe drugs "off-label" to treat (typically rare) conditions other than those formally approved. There are several reasons why off-label prescribing exists [46]. The most pertinent, in the case of biologics, is related to their cost.

For any biologic, obtaining approval for a new indication requires extensive and costly clinical studies. In the US, licence approval requires two randomised, placebo-controlled clinical trials that demonstrate both efficacy and safety in the disease for which the indication is being sought [47]. If a disease is uncommon, such trials will be difficult to conduct and, even if approved, the revenue may not offset costs in obtaining approval. Consequently, there are many inflammatory diseases which share common pathological pathways but may never receive licence as an indication. Of course, biosimilar development and usage may be very different in Asia and the third world countries, where regulatory requirements for biosimilar approval vary and are less stringent.

There are many instances where biologics have been successful in treating unlicensed inflammatory diseases [48]. Indeed some off-label uses are integral to disease management and recommended in guidelines. For example infliximab for Behçet's disease [49] or rituximab in refractory lupus, lupus nephritis [50, 51] and ANCA associated vasculitis (AAV) [52, 53]. Greater accessibility to biologics may improve management of patients with such unlicensed indications. For example in AAV, rituximab is non-inferior to cyclophosphamide for remission induction [54, 55] with preferable qualities with respect to fertility and infection concerns. However, the cost-effectiveness of rituximab had been raised as a concern [56]. The emergence of rituximab biosimilars will undoubtedly improve care for patients with AAV or other conditions where rituximab is as effective as cyclophosphamide.

Reduced biologic costs may also promote further controlled trials to generate higher quality evidence, such as for inflammatory myositis [57]. Additionally, more opportunities may open up to explore off-label treatment of conditions where biologic therapy is less established, such as TNF inhibition for polymyalgia rheumatica [58] or giant cell arteritis [59, 60]. However, it is worth noting that biosimilar manufacturers will be unlikely to seek approval for additional indications. Once licensed, a biosimilar needs to go through the same approval process as the RP for additional indications. If the RP were to obtain new indications, extrapolation of indications in the biosimilar no longer applies.

There is concern that if a drug can be used off-label, patients have less incentive to enrol in trials where they may receive a placebo. This may reduce opportunity to develop rigorous data and could explain why most off-label studies are anecdotal reports [48]. Most importantly, unregulated off-label prescribing can potentially expose patients to risky and ineffective treatments [61]. Therefore off-label use must be applied with the same level of caution as for the RP [62]. Post-market monitoring is essential to develop long-term evidence and provide assurances on efficacy as well as safety.

6. PHARMACOVIGILANCE

Given the nature of biologics and their production, the model used for drug safety monitoring of small-molecule generics is inadequate. Pharmacovigilance systems need to be able to distinguish between adverse events associated with the biosimilar from those of its RP. Therefore, the UK's Medicines and Healthcare products Regulatory Agency (MHRA) recommends that all biologics, including biosimilars, are prescribed by brand name rather than International Non-proprietary Name [63, 64].

As with all new medicines, biosimilars have a 'black triangle' for usually two years post-approval to encourage reporting of suspected adverse drug reactions (ADR). The MHRA's Yellow Card scheme in the UK requires such reports to provide the brand name and batch number to aid traceability [65]. This information should also be provided to patients to help more accurate reporting. In the US, similar post-approval safety surveillance is performed using voluntary reporting systems. There is also a system of active surveillance using retrospective analysis of medical records and drug event monitoring using patient surveys [66].

The EMA also recommends that all biosimilar manufacturers should participate in existing pharmacoepidemiological studies, such as registries that have been set up primarily to monitor safety [67]. The British Society for Rheumatology (BSR) recommends that all patients using biosimilars should be registered with the BSR biologics register [68].

CONCLUSION

The emergence of biosimilars heralds an exciting time for the management of inflammatory diseases. Extrapolation of indication is integral to the concept of biosimilar development. The consequent cost reductions will improve access, increase treatment options, and help resource reallocation to research in hitherto low

volume but high-impact diseases. The use of biosimilars should, however, be approached with similar levels of caution as with their RP and robust mechanisms should be in place for efficacy assessments and pharmacovigilance.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

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REFERENCES

- [1] Ioannidis JP, Karassa FB, Druyts E, *et al.* Biologic agents in rheumatology: unmet issues after 200 trials and \$200 billion sales. *Nat Rev Rheumatol* 2013; 9: 665-73.
- [2] World Health Organization. Guidelines on evaluation of monoclonal antibodies as similar biotherapeutic products (SBPs) 2016 [cited 2017 May]. Available from: (http://www.who.int/biologicals/biotherapeutics/similar_biotherapeutic_products/en/)
- [3] McCamish M, Woollett G. The state of the art in the development of biosimilars. *Clin Pharmacol Ther* 2012; 91: 405-17.
- [4] Calo-Fernandez B, Martinez-Hurtado JL. Biosimilars: company strategies to capture value from the biologics market. *Pharmaceuticals (Basel)* 2012; 5: 1393-408.
- [5] Al-Sabbagh A, Olech E, McClellan JE, *et al.* Development of biosimilars. *Semin Arthritis Rheum* 2016; 45: S11-8.
- [6] Food and Drug Administration. Scientific Considerations in Demonstrating Biosimilarity to a Reference Product 2015 [cited 2017 May]. Available from: (<https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm290967.htm>)
- [7] European Medicines Agency. Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues 2015 [cited 2017 May]. Available from: (http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000408.jsp)
- [8] Blackstone EA, Joseph PF. The economics of biosimilars. *Am Health Drug Benefits* 2013; 6: 469-78.
- [9] Curigliano G, O'Connor DP, Rosenberg JA, *et al.* Biosimilars: Extrapolation for oncology. *Crit Rev Oncol Hematol* 2016; 104: 131-7.
- [10] Sedger LM, McDermott MF. TNF and TNF-receptors: From mediators of cell death and inflammation to therapeutic giants - past, present and future. *Cytokine Growth Factor Rev* 2014; 25: 453-72.
- [11] Van den Brande JM, Koehler TC, Zelinkova Z, *et al.* Prediction of antitumour necrosis factor clinical efficacy by real-time visualisation of apoptosis in patients with Crohn's disease. *Gut* 2007; 56: 509-17.
- [12] Kuo TT, Baker K, Yoshida M, *et al.* Neonatal Fc receptor: from immunity to therapeutics. *J Clin Immunol* 2010; 30: 777-89.
- [13] Park W, Hrycaj P, Jeka S, *et al.* A randomised, double-blind, multicentre, parallel-group, prospective study comparing the pharmacokinetics, safety, and efficacy of CT-P13 and innovator infliximab in patients with ankylosing spondylitis: the PLANETAS study. *Ann Rheum Dis* 2013; 72: 1605-12.
- [14] Park W, Yoo DH, Jaworski J, *et al.* Comparable long-term efficacy, as assessed by patient-reported outcomes, safety and pharmacokinetics, of CT-P13 and reference infliximab in patients with ankylosing spondylitis: 54-week results from the randomized, parallel-group PLANETAS study. *Arthritis Res Ther* 2016; 18: 25.
- [15] Yoo DH, Hrycaj P, Miranda P, *et al.* A randomised, double-blind, parallel-group study to demonstrate equivalence in efficacy and safety of CT-P13 compared with innovator infliximab when coadministered with methotrexate in patients with active rheumatoid arthritis: the PLANETRA study. *Ann Rheum Dis* 2013; 72: 1613-20.
- [16] Yoo DH, Racewicz A, Brzezicki J, *et al.* A phase III randomized study to evaluate the efficacy and safety of CT-P13 compared with reference infliximab in patients with active rheumatoid arthritis:

- 54-week results from the PLANETRA study. *Arthritis Res Ther* 2016; 18: 82.
- [17] 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: 346-54.
- [18] 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: 355-63.
- [19] European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP) Assessment report: Inflectra (infliximab) 2013 [cited 2017 May]. Available from: (http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002778/WC500151490.pdf)
- [20] Food and Drug Administration. CT-P13 (infliximab biosimilar) briefing document for the arthritis advisory committee 2016 [cited 2017 May]. Available from: (<https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/UCM484860.pdf>)
- [21] Van den Brande JM, Braat H, van den Brink GR, *et al.* Infliximab but not etanercept induces apoptosis in lamina propria T-lymphocytes from patients with Crohn's disease. *Gastroenterology* 2003; 124: 1774-85.
- [22] Moroi R, Endo K, Kinouchi Y, *et al.* FCGR3A-158 polymorphism influences the biological response to infliximab in Crohn's disease through affecting the ADCC activity. *Immunogenetics* 2013; 65: 265-71.
- [23] Louis E, El Ghoul Z, Vermeire S, *et al.* Association between polymorphism in IgG Fc receptor IIIa coding gene and biological response to infliximab in Crohn's disease. *Aliment Pharmacol Ther* 2004; 19: 511-9.
- [24] Health Canada. Inflectra 2016 [cited 2017 May]. Available from: (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/sbd-smd/drug-med/sbd_smd_2014_inflectra_159493-eng.php)
- [25] Moots RJ, Xavier RM, Mok CC, *et al.* The impact of anti-drug antibodies on drug concentrations and clinical outcomes in rheumatoid arthritis patients treated with adalimumab, etanercept, or infliximab: Results from a multinational, real-world clinical practice, non-interventional study. *PLoS One* 2017; 12: e0175207.
- [26] Schellekens H. Immunologic mechanisms of EPO-associated pure red cell aplasia. *Best Pract Res Clin Haematol* 2005; 18: 473-80.
- [27] Baert F, Noman M, Vermeire S, *et al.* Influence of immunogenicity on the long-term efficacy of infliximab in Crohn's disease. *N Engl J Med* 2003; 348: 601-8.
- [28] Sands BE, Anderson FH, Bernstein CN, *et al.* Infliximab maintenance therapy for fistulizing Crohn's disease. *N Engl J Med* 2004; 350: 876-85.
- [29] St Clair EW, van der Heijde DM, Smolen JS, *et al.* Combination of infliximab and methotrexate therapy for early rheumatoid arthritis: a randomized, controlled trial. *Arthritis Rheum* 2004; 50: 3432-43.
- [30] Lipsky PE, van der Heijde DM, St Clair EW, *et al.* Infliximab and methotrexate in the treatment of rheumatoid arthritis. Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. *N Engl J Med* 2000; 343: 1594-602.
- [31] World Health Organization. Guidelines on evaluation of similar biotechnological products (SBPs) 2009 [cited 2017 May]. Available from: (http://www.who.int/biologicals/areas/biological_therapeutics/BIO_THERAPEUTICS_FOR_WEB_22APRIL2010.pdf)
- [32] Maini R, St Clair EW, Breedveld F, *et al.* Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. ATTRACT Study Group. *Lancet* 1999; 354: 1932-9.
- [33] Reich K, Nestle FO, Papp K, *et al.* Infliximab induction and maintenance therapy for moderate-to-severe psoriasis: a phase III, multicentre, double-blind trial. *Lancet* 2005; 366: 1367-74.
- [34] Fiorino G, Girolomoni G, Lapadula G, *et al.* The use of biosimilars in immune-mediated disease: A joint Italian Society of Rheumatology (SIR), Italian Society of Dermatology (SIDeMaST), and Italian Group of Inflammatory Bowel Disease (IG-IBD) position paper. *Autoimmun Rev* 2014; 13: 751-5.
- [35] Danese S, Fiorino G, Michetti P. Viewpoint: knowledge and viewpoints on biosimilar monoclonal antibodies among members of the European Crohn's and Colitis Organization. *J Crohns Colitis* 2014; 8: 1548-50.
- [36] Danese S, Gomollon F, Governing B, *et al.* ECCO position statement: the use of biosimilar medicines in the treatment of inflammatory bowel disease (IBD). *J Crohns Colitis* 2013; 7: 586-9.
- [37] 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: 26-34.
- [38] British Society of Gastroenterology. BSG Guidance on the Use of Biosimilar Infliximab CT-P13 in Inflammatory Bowel Disease 2016 [cited 2017 May]. Available from: (http://www.bsg.org.uk/images/stories/docs/clinical/guidance/bsg_infliximab_guidance_16.pdf)
- [39] Mulcahy AW, Predmore Z, Mattke S. The Cost Savings Potential of Biosimilar Drugs in the United States 2014 [cited 2017 May]. Available from: (https://www.rand.org/content/dam/rand/pubs/presspectives/PE100/PE127/RAND_PE127.pdf)
- [40] IMS institute. Delivering on the Potential of Biosimilar Medicines: The Role of Functioning Competitive Markets 2016 [cited 2017 May]. Available from: (http://www.imshealth.com/files/web/IMSH%20Institute/Healthcare%20Briefs/Documents/IMS_Institute_Biosimilar_Brief_March_2016.pdf)
- [41] NICE. Adalimumab, etanercept and infliximab for ankylosing spondylitis. 2008.
- [42] NICE. TNF-alpha inhibitors for ankylosing spondylitis and non-radiographic axial spondyloarthritis 2016 [cited 2017 May]. Available from: (<https://www.nice.org.uk/guidance/ta383/resources/tnfalpha-inhibitors-for-ankylosing-spondylitis-and-nonradiographic-axial-spondyloarthritis-82602848027077>)
- [43] White C. Infliximab biosimilars are safe, effective, and cheap, UK audit shows. *BMJ* 2016; 354: i5084.
- [44] Hawkes N. Biosimilar versions of anti-TNF drugs could save NHS money, drug company claims. *BMJ* 2015; 351: h5337.
- [45] Royal College of Physicians. National clinical audit of biological therapies – Annual report 2016 2016 [cited 2017 May]. Available from: (<https://www.rcplondon.ac.uk/projects/outputs/national-clinical-audit-biological-therapies-annual-report-2016>)
- [46] Wittich CM, Burkle CM, Lanier WL. Ten common questions (and their answers) about off-label drug use. *Mayo Clin Proc* 2012; 87: 982-90.
- [47] Stafford RS. Regulating off-label drug use--rethinking the role of the FDA. *N Engl J Med* 2008; 358: 1427-9.
- [48] Furst DE, Fleischman R, Kalden J, *et al.* Documentation of off-label use of biologics in Rheumatoid Arthritis. *Ann Rheum Dis* 2013; 72 Suppl 2: ii35-51.
- [49] Hatemi G, Silman A, Bang D, *et al.* EULAR recommendations for the management of Behcet disease. *Ann Rheum Dis* 2008; 67: 1656-62.
- [50] NHS England. Interim Clinical Commissioning Policy Statement: Rituximab for the treatment of Systemic Lupus Erythematosus in adults 2013 [cited 2017 May]. Available from: (<https://www.england.nhs.uk/wp-content/uploads/2013/09/a13-psa.pdf>)
- [51] Bertias GK, Tektonidou M, Amoura Z, *et al.* Joint European League Against Rheumatism and European Renal Association-European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations for the management of adult and paediatric lupus nephritis. *Ann Rheum Dis* 2012; 71: 1771-82.
- [52] NICE. Rituximab in combination with glucocorticoids for treating anti-neutrophil cytoplasmic antibody-associated vasculitis 2014 [cited 2017 May]. Available from: (<http://www.nice.org.uk/Guidance/TA308>)
- [53] Ntatsaki E, Carruthers D, Chakravarty K, *et al.* BSR and BHPR guideline for the management of adults with ANCA-associated vasculitis. *Rheumatology (Oxford)* 2014; 53: 2306-9.
- [54] Stone JH, Merkel PA, Spiera R, *et al.* Rituximab versus cyclophosphamide for ANCA-associated vasculitis. *N Engl J Med* 2010; 363: 221-32.
- [55] Jones RB, Tervaert JW, Hauser T, *et al.* Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. *N Engl J Med* 2010; 363: 211-20.
- [56] Specks U, Ikle D, Stone JH. Induction regimens for ANCA-Associated Vasculitis. *N Engl J Med* 2013; 369: 1865-6.

- [57] Vermaak E, Tansley SL, McHugh NJ. The evidence for immunotherapy in dermatomyositis and polymyositis: a systematic review. *Clin Rheumatol* 2015; 34: 2089-95.
- [58] Kreiner F, Galbo H. Effect of etanercept in polymyalgia rheumatica: a randomized controlled trial. *Arthritis Res Ther* 2010; 12: R176.
- [59] Cantini F, Niccoli L, Salvarani C, *et al.* Treatment of longstanding active giant cell arteritis with infliximab: report of four cases. *Arthritis Rheum* 2001; 44: 2933-5.
- [60] Andonopoulos AP, Meimaris N, Daoussis D, *et al.* Experience with infliximab (anti-TNF alpha monoclonal antibody) as monotherapy for giant cell arteritis. *Ann Rheum Dis* 2003; 62: 1116.
- [61] Radley DC, Finkelstein SN, Stafford RS. Off-label prescribing among office-based physicians. *Arch Intern Med* 2006; 166: 1021-6.
- [62] American College of Rheumatology. ACR position statement: Biosimilars 2016 [cited 2017 May]. Available from: (<http://www.rheumatology.org/Portals/0/Files/Biosimilars-Position-Statement.pdf>)
- [63] Medicines and Healthcare products Regulatory Agency. Drug Safety Update Feb 2008: Biosimilar products. 2008; 1: 8.
- [64] European Medicines Agency. Guideline on similar biological medicinal products 2014 [cited 2017 May]. Available from: (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/10/WC500176768.pdf)
- [65] Medicines and Healthcare products Regulatory Agency. Drug Safety Update Feb 2009: The Black Triangle Scheme (▼ or ▼*). 2009; 2(11): 7.
- [66] Grampp G, Felix T. Pharmacovigilance Considerations for Biosimilars in the USA. *BioDrugs* 2015; 29: 309-21.
- [67] European Medicines Agency. Guideline on good pharmacovigilance practices (GVP) 2016 [cited 2017 May]. Available from: (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/08/WC500211728.pdf)
- [68] British Society for Rheumatology. BSR Position statement on biosimilar medicines 2015 [cited 2017 May]. Available from: (http://www.rheumatology.org.uk/includes/documents/cm_docs/2015/b/bsr_biosimilars_position_statement_feb_2015.pdf)