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The changing landscape of biosimilars in rheumatology

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ABSTRACT

Biosimilars remain a hot topic in rheumatology, and some physicians are cautious about their application in the real world. With many products coming to market and a wealth of guidelines and recommendations concerning their use, there is a need to understand the changing landscape and the real clinical and health-economic potential offered by these agents. Notably, rheumatologists will be at the forefront of the use of biosimilar monoclonal antibodies/soluble receptors. Biosimilars offer cost savings and health gains for our patients and will play an important role in treating rheumatic diseases. We hope that these lower costs will compensate for inequities in access to therapy based on economic differences across countries. Since approved biosimilars have already demonstrated highly similar efficacy, it will be most important to establish pharmacovigilance databases across countries that are adequate to monitor long-term safety after marketing approval.

INTRODUCTION

Biosimilars have been defined extensively elsewhere.^{1–9} In recent years, 20 biosimilar products have come to market, including the first biosimilar monoclonal antibody (mAb) CT-P13 (biosimilar infliximab), which is available in more than 70 countries worldwide.¹⁰ CT-P13 is approved in Europe for treatment of rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis (PsA), psoriasis (Ps), Crohn's disease (CD) and ulcerative colitis (UC). In November 2015, the European Medicines Agency (EMA) recommended marketing approval for SB4 (the first biosimilar etanercept in Europe) for treatment of RA, spondyloarthritis (SpA; axial SpA and non-radiographic axial SpA), PsA and Ps. At the time of writing, only filgrastim-sndz has been approved as a biosimilar in the USA. A Food and Drug (FDA) Arthritis Advisory Committee meeting held in February 2016 to discuss CT-P13 recommended approval of CT-P13 for all indications of the reference product (including extrapolated indications for Ps, PsA and inflammatory bowel disease (IBD)) by a 21 to 3 vote, following strong positive guidance from the agency's briefing document (<http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/UCM484859.pdf>). This further clarifies the FDA position on biosimilar mAbs.

A substantial pipeline of biosimilars is in development, with over 700 products reported to be in preclinical and clinical trials.¹¹ Table 1 presents

molecules under development for use in rheumatic diseases. Data from randomised controlled trials (RCTs) with SB2, SB4 and ZRC-3197 have recently been published,^{12–14} as have been abstracts on several biosimilars of adalimumab.

To provide an update on the status of biosimilars for treatment of rheumatic diseases, a panel of international experts convened in Frankfurt in August 2015 for a round-table meeting. The objectives were to address current regulatory positions and to discuss the requirements for detailed analytical characterisation and specific trial designs for comparing biosimilars with reference products. A key part of the report comprises health-economic considerations, need for value-based medicine and importance of appropriate pharmacovigilance. There is a widespread and very simple expectation among patients, treating physicians and healthcare providers that biosimilars should be highly similar in efficacy and comparable in safety, including immunogenicity, but dissimilar (lower) in price in comparison to their reference products. We also compare and contrast the approach to the regulatory evaluation and approval of biosimilars between Europe, the USA, Canada and Japan. This article summarises topics discussed at the meeting to provide healthcare professionals, patients and other stakeholders with an overview of recent and topical changes in the fast-moving world of biosimilars extending a previous paper.⁶

THE BIOSIMILAR REGULATORY ENVIRONMENT Regulations for biosimilar products are evolving

Regulators have closely followed the small variations in reference products that develop over time with process changes.⁶ Indeed, there is an International Committee on Harmonisation (ICH) guidance regarding variability in manufacture of reference products¹⁵ which has subsequently been applied to biosimilars. Regulatory agencies have described the analysis of biosimilar trials as a paradigm shift in drug development,¹⁶ occurring at variable rates in different countries around the world. To date, 30 applications for biosimilar products have been evaluated in the EU. Of these, 22 biosimilars have been approved in Europe across six classes, 1 rejected and 7 applications withdrawn prior to a regulatory decision. Of the 22 biosimilars approved in Europe across six classes, 2 molecules were subsequently withdrawn. Six biosimilars, including erythropoietin and somatotropin, have also been approved in Japan but, at the time of writing, only one has been formally approved in the USA, with one mAb recommended for

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Table 1 Biosimilars for rheumatic diseases for which data have been published in peer-reviewed journals or presented at international scientific meetings

Reference product	Biosimilar molecules
Adalimumab	ABP501
	BI 695501
	CHS-1420
	GP-2017
	M923
	SB5
Etanercept	ZRC-3197
	CHS-0214
	GP2015
	HD203
Infliximab	SB4*
	BOW015†
	CT-P13*‡
	PF-06438179
Rituximab	SB2
	CT-P10
	GP2013
	PF-05280586

*Approved by EMA and multiple other countries.

†Approved in India.

‡Recommended for approval by FDA.

EMA, European Medicines Agency; FDA, Food and Drug Administration.

approval.¹⁷ Recent congressional testimony by Janet Woodcock, Director FDA Center for Drugs Evaluation and Research indicated 59 proposed biosimilars for 18 different reference products were enrolled in the agency's Biosimilar Product Development Program.¹⁸

EMA first developed guidelines for approval of biosimilars using an abbreviated registration process in 2005 and 2006; these have been updated and revised several times over the intervening decade, and a specific guideline for mAbs was adopted in 2013.^{19–22} Of specific interest to rheumatologists is the 2013 European Public Assessment Report (EPAR) for CT-P13,²³ which allowed extrapolation of this biosimilar infliximab to all indications for which the reference product is approved, despite RCTs conducted only in AS and RA. For naming of biosimilars, EMA recommends the use of trademarks.

In the USA, there are now eight FDA guidance documents addressing biosimilars.^{24–31} A draft guidance on Clinical Pharmacology Data in 2014 added a requirement for comparison between multiple lots of the biosimilar with both US and ex-US licensed reference products. Draft guidance on Reference Product Exclusivity (2014) prevents application for and approval of a biosimilar until 4 years and 12 years following initial approval of the reference product, respectively. The most recent guidance document on labelling (2015) designates biosimilars using the proper name with a four-letter suffix and includes data only for the reference product.³⁰ This is suggested to facilitate traceability, pharmacovigilance and collection of real-world data through registries. US FDA has indicated that guidance regarding interchangeability will not be issued yet and has asked for commentary as they expect review of such applications to require a similar amount of time as would a new Biologics License Application. Thus, substitution of a biosimilar for the reference product, without

knowledge of the prescribing physician, is not expected soon in the USA.

In Canada, guidelines for biosimilar approval are laid out in the 2010 Submission Requirements for Subsequent Entry Biologics and refer specifically to EMA guidelines.⁴ Japanese biosimilar guidelines were published in 2009 and require that a biosimilar product be developed on the basis of data that demonstrate its comparability with the reference product in terms of quality, safety and efficacy, or other relevant data.^{5 32 33} Other countries follow WHO guidelines for evaluation of similar biological products,³ although Brazilian authorities omit information about conduct of RCTs from their guidelines.³⁴

Regulatory requirements have evolved, and there is now a high bar set for both reference and biosimilar products. In Finland—where biosimilars other than mAbs have been available since 2008—the position of Finnish Medicines Agency (Fimea) states that evidence of adverse events related to moving from a reference product to a biosimilar is yet to emerge and, in the opinion of Fimea, the theoretical basis for such fears is weak.³⁵ The risk of adverse effects with use of a biosimilar can be expected to be similar to those associated with changes in the manufacturing process of any reference biologic product.³⁶ Many medical societies and other interested organisations have issued position statements, which indicate that harmonisation across countries is emerging regarding the development and acceptance of biosimilars.

Clinical trial design for biosimilar products

As part of the stepwise process to demonstrate biosimilarity and gain regulatory approval for a biosimilar, EMA, FDA and other regulatory agencies require a pharmacokinetic/pharmacodynamic (PK/PD) study in humans and at least one RCT to demonstrate equivalent efficacy and immunogenicity and comparable safety of the biosimilar and its reference product. Thus, an equivalence trial design should be employed, conducted in a sensitive population of patients with a disease for which the reference product is licensed, and immunogenicity should be compared in this trial. In contrast, the PK/PD study may be conducted in healthy volunteers as well as in patients. Use of healthy volunteers for PK/PD studies is becoming more common, since they provide a more homogenous population in which variability introduced by diseases is not present. However, there may be differences in the development of anti-drug antibodies (ADAbs) between healthy volunteers and patients, for biosimilars and for reference products. For biosimilars that can be administered either by subcutaneous or intravenous routes, new guidance from FDA states that the PK study should be performed using a single subcutaneous injection, since this route is considered to be more likely than intravenous administration to uncover potential differences in immunogenicity between the biosimilar and the reference product.²

The RCT to confirm biosimilarity should be designed with an equivalence margin based on the difference in the primary end point between active treatment and placebo derived from a meta-analysis of prior RCTs of the reference product. The clinical trials of the first infliximab biosimilar, CT-P13, evaluated efficacy and safety at 14 weeks, 30 weeks and 54 weeks.^{37 38} In the phase 3 PLANETRA trial, which compared CT-P13 to reference infliximab in patients with RA, 95% CIs for the difference between treatments for primary and secondary end points fell within the prespecified equivalence margin of $\pm 15\%$.³⁷ Comparability of CT-P13 with reference infliximab was also demonstrated in the PLANETAS PK/PD trial in AS, with an equivalence margin of 80–125% based on 90% CIs.³⁸

Subsequent RCTs conducted for other biosimilars—such as those that compared the infliximab biosimilar SB2 and etanercept biosimilar SB4 with their respective reference products—have confirmed highly similar efficacy and comparable safety.^{12 13} However, the RCT comparing SB4 with reference etanercept found this biosimilar to have less and transient immunogenicity, mainly between week 4–8, and fewer injection site reactions than the reference product. Consequently, EMA recently recommended SB4 for marketing approval with full extrapolation of indications. An issue for clinicians in evaluating these data is the absence of the SB2 or SB4 phase 1 data from the published literature, and sponsors are encouraged to share these results with the regulatory authorities and more fully with the public in order to support the abbreviated clinical development of biosimilars. In general, the authors recommend that physicians consult individual EPARs and the FDA Purple Book (online) to obtain more information about the comparability programmes conducted with biosimilar products.

CHALLENGES REMAINING IN CLINICAL PRACTICE

Switching

With respect to transitioning or switching between a reference product and a biosimilar, several considerations are relevant for clinical practice. The absence from many regulatory guidelines of requirements for multiple switching between reference and biosimilar products may be seen as a gap in our understanding. Of note, we often do not see studies in the public domain that address manufacturing changes of a reference product, even though post-translational differences occurred. It is left to the regulators to require such studies, which remain confidential between sponsors and FDA, although EMA does issue a notification. Drift may occur at any time, but there is no need for additional trials as long as batches remain within the predefined specifications for the product.

Most RCTs investigating transitioning to a biosimilar have incorporated only one randomised switch from the reference product to the biosimilar that occurs after assessment of the primary end point. Currently several efforts are underway to collect real-world data about transitioning.¹⁰ One example is the NOR-SWITCH study, supported financially by the Norwegian government. NOR-SWITCH was designed as a non-inferiority study over 12 months to evaluate maintenance of efficacy as well as adverse event monitoring following transitioning from reference to biosimilar infliximab, compared with maintaining treatment with the reference product in patients with RA, SpA, PsA, Ps and IBD. Eligible patients on stable treatment for at least 6 months were randomised to either continue

treatment with reference infliximab or to transition to CT-P13. The primary end point of this study is disease worsening. Enrolment was completed in June 2015; 498 patients were randomised. Those who complete 12 months' treatment are then asked to participate in an open-label follow-up study during which all patients will receive the biosimilar for 26 weeks. Results from this study are expected to be available at the end of 2016.³⁹

Early transition data from the PLANETAS extension study showed comparable rates of serious treatment emergent adverse events (TEAEs) between maintenance and transition groups (4.4% vs 4.8%), but fewer patients experienced more than one TEAE during the 2nd year with continuation of CT-P13 compared with those transitioning to CT-P13 (48.9% vs 71.4%)—predominantly due to more mild/moderate events.⁴⁰ These data were published in abstract form in sufficient detail to allow analysis of comparability for safety, as illustrated by statistical considerations (table 2). On the other hand, in the long-term extension of the Japanese study of CT-P13, 41 of 43 ADAb-negative patients remained negative and 10 ADAb-positive patients became negative after transitioning from reference product to CT-P13 or having the CT-P13 dose escalated (Y Tanaka, *et al.* Evaluation of safety and efficacy of CT-P13 in patients with rheumatoid arthritis when CT-P13 is continued throughout the extension study and switched from the reference drug innovator infliximab. manuscript submitted). ADAb positivity and hypersensitivity reactions during the 2nd year of both PLANETRA and PLANETAS did not differ significantly between patients exposed to both reference and biosimilar as compared with those who received only the biosimilar over 2 years. Recent studies have demonstrated that the binding specificity of ADAb to reference infliximab and CT-P13 is identical: the same epitopes are recognised on both mAbs.^{43 44}

Although close analytical similarity of the critical attributes of a biosimilar with its reference product suggests that clinical differences will be unlikely, RCTs for biosimilars, which typically enrol fewer than 600 participants, are underpowered to identify unexpected rare adverse events.⁴⁵ Thus, careful postmarketing pharmacovigilance is important for both biosimilars and reference products.

With respect to the naming of biosimilars, many have debated the need for these agents to be named differently from their reference products to inform, document switches and facilitate pharmacovigilance.⁴⁶ WHO has suggested that each international non-proprietary drug name be followed by a four-letter suffix to identify each brand^{3 47 48} recently endorsed by FDA in their 2015 draft guidance.³⁰ To date, EMA has required brand

Table 2 Limitations of safety data derived from trials: statistical reminders when interpreting regulatory trials for reference and biosimilar products

Test	Uses and interpretation	Example	
Bonferroni correction ⁴¹	When you perform a hypothesis test in statistics, a p value helps you determine the significance of your results. The more often you repeat a test in a study, the more likely it is to show a positive result by chance (a false positive). The simplest way to compensate for this is to limit comparisons to only the most clinically relevant and critical outcome. If multiple comparisons are needed, the measure of statistical confidence (traditionally taken to be $p \leq 0.05$) needs to be adjusted downwards. The Bonferroni correction is the simplest method for this.	Number of tests	Bonferroni's adjusted p value
		2	0.025
		3	0.0167
		4	0.0125
		10	0.005
The 'rule of 3' ⁴²	In statistical analysis, the 'rule of 3' states that if a certain event did not occur in a sample with n subjects, then you can approximate that the upper limit of 95% CI=maximum risk=3/n. When n is greater than 30, this is a good approximation to results from more sensitive tests.	For example, if a drug was studied in 900 patients, you could be 95% certain that any unreported toxicity should occur at a rate of <1 in 300 (<3/900). To exclude less frequent events requires larger trial sizes and emphasises the importance of pharmacovigilance reporting.	

naming which in practice has worked well: a survey of 13 790 biologic entries in the EUdravigilance system showed >96% ability to track the biosimilar.⁴⁹ In the future it is expected that biosimilars and reference products will be substituted back and forth repeatedly as will biosimilars of the same reference product.^{2 10 28} There will be a need to introduce new ways to track and document which products a patient receives—for example patient passports or similar traceability methods. Such strategies for drug monitoring and immunogenicity assessments before and after switching will facilitate mandated as well as voluntary pharmacovigilance. Accumulated experience with biosimilars of smaller therapeutic proteins than mAbs have not indicated a safety risk of switching between reference products or biosimilars.⁵⁰

Extrapolation of indications

Extrapolation across clinical indications has a basis in pre-existing scientific and regulatory principles and practice.⁵¹ At present EMA and US labels for a biosimilar are the same as for the reference product and do not include information about the biosimilar itself. The only way for prescribers to obtain such information is through publications or regulatory agency documents such as EPARs and FDA Purple Book. In the case of tumour necrosis factor inhibitors (TNFis) with multiple clinical indications, no biosimilar is likely to be studied across all relevant diseases, provided they share the same mechanism of action. While no head-to-head trials between different TNFis exist, it is clear that all mAb-based TNFis, despite differences in their molecular characteristics, have efficacy across the same indications; therefore a molecularly correctly developed biosimilar mAb is expected to also have that quality. Although preclinical analytical structural and functional data and toxicology with the currently approved CT-P13 indicated biosimilarity in all respects, this was ultimately confirmed only in RCTs conducted in AS and RA, but not PsA, Ps or IBD. In Japan, CT-P13 was tested in RA but approval also included Ps, PsA and IBD.⁵² Furthermore, dose increases from 3 mg/kg to 10 mg/kg and treatment intervals varying from every 4–8 weeks were allowed.^{53 54} Conversely, in Canada the theoretical

pathophysiological mechanism of disease was identified as a point to consider in support of indication extrapolation; and CT-P13 was approved in PsA and Ps but not in CD or UC, although this is again under review.^{55–57} In the USA, the FDA Arthritis Advisory Committee recently recommended approval of CT-P13 across all clinical indications approved for infliximab. Regulatory agencies have in general offered similar conclusions regarding extrapolation, with the exception of Canada (table 3)^{1 4 5 28 59} but there exists variability between society positions.⁶⁰

Disease type, genetics, administered dose and background therapy can affect immunogenicity. Similar to other TNFis, it has been observed that ADABs were more frequent in patients with RA than patients with AS with both infliximab reference product and biosimilar, despite use of methotrexate (MTX) in RA.^{37 38 61} This suggests that RA is an important trial indication to obtain insights into immunogenicity.

Many of the concerns raised with regard to extrapolation appear to be hypothetical,¹⁰ and will likely not be problematic in the long term. All biosimilars will require postmarketing surveillance to track ongoing safety and immunogenicity. In the EU, postmarketing surveillance is a task performed by the individual member states; therefore, national programmes and required safety data may vary—we have yet to better understand requirements mandated in Canada and the USA. Overall, compatibility and consistency of these databases should be a major objective, so that safety signals can be detected in a timely fashion. To ensure proper assessment of all aspects, it may be wise to also include batch numbers of all biologics in registries, so that the variability among biosimilars and reference products can be compared.

BIOSIMILARS AND ACCESS TO HEALTHCARE

Experience in oncology

Oncologists in the EU have had access to biosimilar products for over 8 years. These have transformed care by increasing access to treatment.⁶² At the outset, many learned societies suggested cautious use of biosimilars (especially in extrapolated or paediatric populations). Based on evidence this cautious approach was

Table 3 Regulatory guidance on extrapolation

Agency	Requirements for extrapolation	Issues precluding extrapolation
Europe ¹	<ul style="list-style-type: none"> ▶ In certain cases, it may be possible to extrapolate therapeutic similarity shown in one indication to other indications of the reference medicinal product. ▶ Case-by-case decision based on the 'totality of evidence'. ▶ Possible safety issues in different subpopulations should also be addressed. 	Justification will depend on, for example, clinical experience, available literature data, whether or not the same mechanisms of action or the same receptor(s) are involved in all indications.
Canada ^{4 58}	<ul style="list-style-type: none"> ▶ Indication of a biosimilar must be the same as its reference product. ▶ Similarity must be demonstrated by comprehensive comparative characterisation. ▶ Type and design of trials using sensitive populations and end points must be capable of detecting changes in the end points chosen. ▶ Consider route of administration; posology and PK/PD profiles in each indication considered. 	<ul style="list-style-type: none"> ▶ Minor differences in active ingredients or mechanism of action. ▶ Differences in pathophysiology of the disease/s. ▶ Differences in clinical experience compared with reference drug.
Australia ⁵⁹	<ul style="list-style-type: none"> ▶ In certain cases, it may be possible to extrapolate therapeutic similarity shown in one indication to other indications of the reference medicinal product. ▶ Possible safety issues in different subpopulations should also be addressed. 	Justification will depend on, for example, clinical experience, available literature data, whether or not the same mechanisms of action or the same receptor(s) are involved in all indications.
Japan ^{5 33}	Extrapolation to the Japanese population should be justified according to the ICH guidelines.	Japanese guideline describes that it may be possible to extrapolate from one indication to other indications of the reference product if the mechanism of action is the same.
USA ²⁸	<ul style="list-style-type: none"> ▶ Use a study population and treatment regimen adequately sensitive. ▶ Sufficient scientific justification for each condition. ▶ Only for conditions of use previously licensed for the reference product. ▶ Demonstration requires detailed information regarding similar mechanism of action between biosimilar and reference product. 	Extrapolation based on totality of the evidence.

PK/PD, pharmacokinetic/pharmacodynamic.

not necessary—the first wave of biosimilar agents have exceeded 5 years' use although they were peptides, not mAbs.^{29 49 63 64} In light of the evidence collected, strong endorsement of use of biosimilars by groups such as the European Organisation for Research and Treatment of Cancer occurred even in 2010.⁶⁵ Confirmation that regulatory measures to control both manufacturing changes of reference products and biosimilars are effective are evident from the experience of the first three classes of biosimilars approved by EMA that do not indicate additional safety risks from switching between reference products and biosimilars. Furthermore, a recent meta-analysis of switching between human recombinant growth factors and granulocyte colony stimulating agents showed no different safety signals in >12 000 patients in 58 clinical trials, as well as across all the individual European pharmacovigilance data.⁶⁶

Biologic therapies are important in oncology, but they are also pinpointed as the reason for escalating global healthcare costs.⁶⁷ Oncology cannot afford the current trajectory of drug pricing.^{68 69} The next generation of biosimilars (trastuzumab, rituximab, cetuximab) will be vital in managing budgets and coping with increasing cancer incidence—putting great pressure on physicians to justify any decision not to switch patients.^{70 71} This experience in oncology is valuable to rheumatologists in considering the introduction of biosimilars into clinical practice.

Health-economic considerations in rheumatology

The expense of biologic agents is a major issue. What should a biologic disease-modifying antirheumatic drug (bDMARD) really cost? How much shareholder value above and beyond the return of investment should society pay? What should subsequently marketed biosimilars cost given that the first has already led to a price reduction?

The QUEST-RA study found huge disparities in disease activity in patients with RA across 25 countries, with average disease activity score in 28 joints (DAS-28) scores ranging from 3.1 (The Netherlands) to 6.0 (Kosovo). Interestingly, there was a strong inverse association between gross domestic product (GDP) and DAS-28, indicating that disease burden is strongly related to country welfare.⁷² More recently, data from the COMORA study revealed that the association between disease activity and socioeconomic status is evident both at an individual level (measured as education) and a country level (measured as GDP).⁷³

Two other groups performed surveys to compare accessibility and criteria regulating reimbursement of bDMARDs, and demonstrated large price differences between countries. Accessibility based on availability, affordability and acceptability varied across countries, again strongly related to GDP—criteria for regulating treatment were stricter in less affluent countries.^{74 75} Real-world utilisation of bDMARDs was assessed in six central and eastern European countries. The number of patients with RA receiving bDMARDs varied significantly: Poland 1.3%, Bulgaria 2.6%, Romania 4.1%, the Czech Republic 4.2%, Hungary 8.4% and Slovakia 10.0%.⁷⁶ These data indicate large inequities in health status, access to bDMARDs and use of regulatory criteria—the relationship between these dimensions and GDP should support the importance of availability of cheaper therapies such as biosimilars provided there is willingness to replace reference products.

Budget impact savings

The role of biosimilars in reducing costs and increasing patient access to bDMARDs in rheumatology has been analysed recently.⁷⁷ The budget impact of switching patients to CT-P13

for RA in the UK, Italy, France and Germany is estimated over 5 years to offer savings of €233 million and €433.5 million for 20% and 30% discount scenarios, respectively.⁷⁸ With a 30% discount, an additional 7561 patients could be treated across these four countries and the Netherlands using drug cost savings after 1 year of biosimilar infliximab.⁷⁹ These data are supported by another analysis in Italy, which demonstrated that availability of CT-P13 could lead to cumulative national cost savings of €47 million over 5 years.⁸⁰ In Ireland the total savings over 5 years with use of CT-P13 in RA has been estimated to be €5.3 million.⁸¹ The budget impact of CT-P13 introduction has also been estimated for patients with RA in Bulgaria, the Czech Republic, Hungary, Poland, Romania and Slovakia. Over 3 years, and assuming a 25% discount, savings of €15.3 million could be made in the first scenario, and €20.8 million in the second, allowing treatment of an additional 1200 or 1800 patients across the six countries, respectively.⁸²

In practice, savings are already evident. In Japan CT-P13 has been launched as Infleximab-BS-NK, its price is reduced by 67% compared with reference infliximab⁸³ and in Norway by 69%.⁸⁴ Recent data from South Korea 15 months after introduction of CT-P13 show that a fifth of all infliximab claims were for the biosimilar. More interesting is the indication that the use of TNFi increased overall⁸⁵—suggesting that additional patients are being treated.

In the UK, the National Institute for Health and Care Excellence (NICE) has given guidance to rheumatologists that 'treatment should be initiated with the least expensive drug'⁸⁶ while in Belgium and Germany there is a quota system, which drives physicians to prescribe biosimilars in up to 40% of their patients.⁸⁷ Thus, cost remains an important consideration regarding access to treatment and will drive the implementation of biosimilars.

Country example: Norway

Norway has a tender system where each company offers a price for their product for a time period of 12 months. The least expensive alternative will be recommended, since no study has demonstrated a significant difference in efficacy and safety on a group level among the various TNFis across SpA, PsA, Ps or IBD. This competitive system has helped to reduce prices of bDMARDs in Norway. Biosimilar infliximab was approved in Norway in 2013, priced 33–39% lower than the reference product from 2014. For 2015 prices were further reduced—51–69% lower than the reference product—making biosimilar infliximab the preferred bDMARD for all six indications when initiating a bDMARD or switching to a TNFi in naïve patients.⁸⁴ The cost for the biosimilar infliximab for the 1st year of treatment in RA is about 20% the cost of adalimumab.⁸⁴ Motivated by cost saving many departments in Norway have initiated switching of patients from reference to biosimilar infliximab even before results from the NOR-SWITCH are available. As of September 2015 the total number of departments using infliximab had increased approximately 50% since 2014; 80% with biosimilar infliximab. Recent data from Denmark similarly show that biosimilar infliximab has about 90% of the market since switching was mandated by payers to reduce costs.⁸⁸

The results of the Norwegian tender for 2016 gave some changes—biosimilar infliximab is still the cheapest alternative with a price about 60% lower than Remicade. SB4 (Benepali) was offered at a price which is 47% lower than the regular price of reference etanercept (but is more expensive than certolizumab; personal communication Tore K Kvien).

Better access and health gain

It has been argued that a simple cost saving is not sufficient to justify biosimilar switching—there also needs to be an overall health gain. Clinicians are said to be more willing to use biosimilars if their patients are beneficiaries of the cost savings.⁸⁹ Alternatively, if a biosimilar has no clinically meaningful difference in efficacy or safety with the reference product, then cost saving should be sufficient moral reason to promote its use in a world where medical resources are finite. The availability of biosimilars will allow patients to receive medications that might otherwise be unaffordable to them.

Physicians therefore need to be aware of costs to their patients and wider societal implications of delaying biosimilar use without very good reason. Assuming a conservative 30% price discount for biosimilar infliximab, this would represent cost savings in Europe of more than €530 million every year. If the 50% price reductions seen in the Nordic nations are achieved across the EU, the potential savings to reinvest in better health-care could exceed €880 million annually.⁸⁸

Physicians are reminded by WHO of their responsibility to the community when prescribing medicines with the lowest cost to patients and their communities.⁹⁰ Costs should also be taken into consideration when developing treatment recommendations.⁹¹ In 2014, three of the four top-selling global therapies were bDMARDs—all TNFis. If even one of these agents becomes significantly cheaper, the changing pattern of use becomes a serious consideration for affordable care. The 2013 update of the European League Against Rheumatism recommendations for use of DMARDs and bDMARDs highlight in their overarching principles that medicinal costs should be considered when prescribing these therapies.⁹² Similarly, the 2015 American College of Rheumatology guidelines raise cost as an important issue.⁹³

DISCUSSION

Biosimilars have entered clinical practice, and they are already changing access to therapies in rheumatology.⁹⁴ Although mAbs may be more complex than some biologics used in oncology, there are many parallels. Biosimilars offer the potential to reduce acquisition costs of bDMARDs, removing current inequity in their use between countries with high and low GDPs.⁷⁴ Harmonisation of regulatory guidance and recommendations on the use of biosimilars may help guide physicians' decisions. Rheumatologists will be at the forefront of the use of biosimilar mAbs, in terms of recommendations for use but also design and analyses of RCTs. In the UK, NICE concluded that there was no compelling evidence to distinguish between TNFis on the basis of clinical effectiveness when making recommendations—prompting a broader appraisal of the use of all bDMARDs.⁸⁶

For patients, biosimilars will increase affordability of treatment options and improve accessibility. Understandably, evidence-based information is needed to inform choices.⁹⁵ Patients should be kept informed about which products they are receiving, and should not be transitioned without their knowledge. Reduced costs are important but heterogeneous healthcare systems may lead to substantial price differences between countries which will require attention as resources for improved care of our patients become limited.

Pharmacovigilance remains the key to incorporating biosimilars into clinical practice and requires collection of safety data across nations to detect even small safety signals. Sponsors are required to submit a risk-management plan (RMP) to EMA

Box 1 Group recommendations for the future

- ▶ Pay close attention to which biosimilar product is being prescribed and used.
- ▶ Prescribe using the proper name or trade name with suffix.
- ▶ Contribute to local and international pharmacovigilance efforts (registries).
- ▶ Conduct quality pharmacovigilance to monitor long-term safety, with harmonisation of data collection across registries.
- ▶ Encourage transparency in drug characterisation.

when applying for marketing authorisation, and to FDA at the time of final approval. RMPs in general lay out information on a product's safety profile, including how risks will be prevented or minimised and plans for further studies to gain additional knowledge.⁹⁶ They are resubmitted during periodic safety update reports. An example can be found in the EPAR for Remsima/Inflectra.^{23 97} Similarly, the RMP for the infliximab reference product specified data collection across several registries, including ARTIS, BIOBADASER, BSRBR, RABBIT, BADBIR, ENCORE, OPUS, the paediatric IBD registry, PSOLAR and likely CORRONA. With biosimilars also come new insights into the immunogenicity of bDMARDs, with potentially broader use of ADAb testing in clinical practice.

It remains an academic responsibility to guide implementation of biosimilars into clinical practice while simultaneously continuing to search for improved therapeutic approaches and treatment sequences. More than 40 biosimilar candidates are in development for use in rheumatic diseases, and this group will continue to carefully monitor data relating to their efficacy and safety. It will be important to share information with clinicians and patients as more biosimilars are introduced (box 1).

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