

# Reviewing the evidence for biosimilars: key insights, lessons learned and future horizons

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## Abstract

Biologic therapies have become central to the long-term management of many chronic diseases, including inflammatory rheumatic diseases. Over recent years, the development and licensing pathways for biosimilars have become more standardized, and several biosimilars have been made available for patients with inflammatory rheumatic diseases, such as RA. Pre-licensing requirements for biosimilars mandate the demonstration of comparability with reference products in terms of clinical activity, safety and immunogenicity, whereas post-marketing surveillance and risk minimization requirements are set in place to ensure that long-term, real-world safety data are collected to assess biosimilars in clinical practice. These measures should provide a foundation for physician confidence in biosimilars, which can be established further through clinical experience. Biosimilars may help to fill an unmet need by improving patient access to effective biologic treatments for chronic diseases. Greater access may result in additional clinical benefits, with appropriate use of biologic therapies according to treatment guidelines being associated with improved outcomes and the potential for reduced costs of care. Key challenges for the integration of biosimilars into everyday practice include questions about interchangeability, switching and automatic substitution. Several switching studies have shown that biosimilars can be used in place of reference products while maintaining efficacy and safety. Additional ongoing studies and registries may help to optimize the process of switching, and different funding models are examining the optimal mechanisms to ensure effective uptake of these new treatments.

**Key words:** biologics, immunogenicity, interchangeability, rheumatologic biosimilars, risk minimization, switching

### Rheumatology key messages

- Biosimilar licensing is based on robust non-clinical and clinical evaluation of comparability with reference products.
- The NOR-SWITCH study has shown that switching to biosimilars does not affect clinical outcomes in chronic diseases.
- Biosimilars may enable improved access to biologic treatments for chronic diseases, such as RA.

## Introduction

The availability of biologic agents has affected the treatment algorithm for many chronic diseases, including inflammatory rheumatic diseases [1, 2]. For example, biologic DMARDs (bDMARDs) are well recognized as a crucial component of long-term therapy for RA [1],

providing clinically meaningful benefits in pain and function for patients who do not respond to traditional DMARDs [2]. However, access to these biologic treatments for RA remains uneven [3], with availability primarily being limited by financial constraints [4].

Biosimilars can help to fulfil an unmet need by providing a new threshold for patient access to effective biologic treatments for chronic diseases [5, 6]. Greater access may result in additional clinical benefits, with potentially earlier and more appropriate use of biologic therapies, which are associated with better outcomes. As a result, both direct and indirect costs of care for chronic diseases may be improved [6, 7]. Within Europe, the European Medicines Agency (EMA) has licensed a number of

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Submitted 22 November 2016; revised version accepted 12 June 2017

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biosimilar products, including epoetin-alfa, etanercept, filgrastim, follitropin-alfa, infliximab, insulins, interferons and somatotropin [8]. Within the USA, the US Food and Drug Administration (FDA) has licensed biosimilars of filgrastim and infliximab [9, 10].

This review examines the integration of biosimilars into everyday clinical practice in Europe, focusing on the management of inflammatory rheumatic diseases. As well as considering the regulatory framework, pharmacovigilance and post-marketing safety monitoring, the challenges of switching and interchangeability are reviewed. The important question of how biosimilars may affect patient access to biologic treatments is also discussed.

### Comparability of biosimilars: how similar is similar?

As described earlier in this supplement, the EMA defines a biosimilar as “a biological medicine that is developed to be similar to an existing biological medicine (reference product)” [11]. The EMA regulatory framework sets out requirements for demonstrating biosimilarity, with the goal of ensuring that any minor differences between biosimilars and reference products do not affect effectiveness or safety [11]. Owing to the size and complexity of biologic products, such as antibodies and soluble receptors, minor differences are inevitable for different batches of the same biologic product, and non-identity is an accepted facet of biotechnology production processes [6, 12, 13]. For biosimilars, functional and structural aspects must be as similar as possible to reference products, with consistency being demonstrated in pharmacokinetics (PK), efficacy and safety, including risk of immunogenicity [6, 11, 14].

Non-clinical studies for biosimilars typically include *in vitro* receptor-binding assays or cell-based assays to establish comparability in reactivity [15]. If comparability is not demonstrated in these studies, the EMA advises additional animal studies, which should be focused on the outcomes that are most likely to answer questions that were not resolved by the non-clinical studies. These may include tests of pharmacodynamics (PD) activity and non-clinical dose toxicity (e.g. antibody titres, cross-reactivity and neutralizing capacity) [15]. In all cases, the EMA advises that drug developers give ongoing consideration to the use of emerging technologies so that the best current technologies are used for assessment. Certain non-clinical studies, such as safety, pharmacology, reproductive and developmental toxicity and carcinogenicity studies, are not required if a high level of similarity between the reference product and biosimilar has been demonstrated in structural and functional characterization studies [15]. With respect to clinical studies, a step-wise approach to clinical comparability is required. Specifically, the EMA suggests that biosimilar comparability testing should begin with PK and, if feasible, PD studies, followed by clinical efficacy and safety [15]. In certain cases, confirmatory PK/PD studies for demonstrating clinical biosimilar comparability may be required [15].

The European Union (EU) regulatory framework has enabled several biosimilar products to be licensed in the area of rheumatic diseases: infliximab (CT-P13: Remsima<sup>®</sup>/Inflectra<sup>®</sup>; SB2: Flixabi<sup>®</sup>) [16–18] and etanercept (Benepali<sup>®</sup>) [19], and a number of other biosimilars are in development (Table 1). In clinical studies, these biosimilar products have demonstrated PK equivalence to their reference products [37–39], as well as equivalent efficacy and comparable safety and immunogenicity [40–45]. An upcoming milestone in this therapeutic area is the projected expiry of patent protection for adalimumab in the EU in April 2018 [46].

The next-generation biologics (sometimes referred to as biobetter agents) aim to build on the available biologic agents by providing enhanced attributes [47–49]. Indeed, these next-generation biologics can be defined as having the same target as the originator but improved characteristics, such as PD or PK [50]. If these agents do indeed deliver improvements over available drugs, we can look forward to even greater choices in this therapeutic area.

### Assessment and monitoring of biosimilars

#### Pre-licensing safety assessments, including immunogenicity

In addition to efficacy and PK testing, safety assessments are a key element of the pre-licensing of biosimilars and should involve sufficient patient data to enable the biosimilars and the reference product to be compared [51, 52]. In particular, there has been concern about the possibility of original drugs and their biosimilars differing in immunogenicity; any level of post-translational modification to the antibody structure could affect patterns of immunogenicity [51]. EMA guidance states that non-clinical immunogenicity findings do not predict potential immunogenic responses to biologics in humans [15]. As a result, clinical immunogenicity testing is a crucial component of the safety evaluation of biosimilars, including detection of anti-drug antibodies (ADAs) [15, 51, 52].

Immunogenicity with the infliximab biosimilar Remsima<sup>®</sup> appears to be similar to that observed with the reference product [41–43, 53]. In a phase III study comparing Remsima<sup>®</sup> with its reference product, the incidence of ADAs was very slightly higher for Remsima<sup>®</sup> (ADAs detected in 25.4 and 25.8% of patients for Remsima<sup>®</sup> and the reference product, respectively, at week 14) [41]. In this instance, the incidence of ADAs appeared to increase over time but did not appear to affect efficacy or safety [41]. In a phase III, randomized study comparing the etanercept biosimilar Benepali<sup>®</sup> with the etanercept reference product in patients with refractory RA, Benepali<sup>®</sup> was associated with a significantly lower incidence of ADAs compared with the etanercept reference product (0.7 and 13.1% of patients, respectively, tested positive for ADAs at least once up to week 24;  $P < 0.001$ ) [40]. The ADAs appeared early and did not

**TABLE 1** Biosimilars of infliximab, etanercept and adalimumab, licensed or in development for rheumatic diseases

Reference product	Biosimilar	Biosimilar manufacturer	Highest development status
Infliximab	Remsima <sup>®</sup> (CT-P13) [16]	Celltrion	Licensed in EU
	Inflectra <sup>®</sup> [17]	Hospira	Licensed in Canada, USA
	Inflimab <sup>®</sup> (BOW015) [20]	Epirus	Licensed in India
	Flixabi <sup>®</sup> /Renflexis <sup>®</sup> (SB2) [21, 22]	Samsung Bioepis/Biogen	Licensed in EU and Korea
	PF-06438179 [23]	Pfizer/Sandoz	Phase III
Etanercept	ABP710 [24]	Amgen	Phase I/II
	Benepali <sup>®</sup> /Brenzys <sup>®</sup> (SB4) [19, 25]	Samsung Bioepis/Biogen	Licensed in EU, Korea
	Davictre <sup>®</sup> (HD203) [26]	Hanwha/Merck	Licensed in Korea
	GP-2015 [27]	Sandoz	Filed in USA
Adalimumab	CHS-0214 [28]	Coherus/Baxalta	Phase III
	Exemptia <sup>®</sup> (ZRC-3197) [29]	Zydus	Licensed in India
	ABP501 [30]	Amgen	Filed in USA
	BI695501 [31]	Boehringer Ingelheim	Phase III
	GP-2017 [27]	Sandoz	Phase III
	CHS-1420 [32]	Coherus	Phase III
	M923 [33]	Momenta/Baxalta	Phase III
	SB5 [34]	Samsung Bioepis/Biogen	Phase III
	PF-06410293 [35]	Pfizer	Phase III
Rituximab [36]	ABP 798	Amgen	Phase III
	AcellBia	Biocad	Licensed in Russia
	CT-P10	Celltrion/Hospira	Phase III
	Reditux	Dr Reddy's Laboratories	Licensed in Bolivia, Chile, India, Peru
	Maball	Hetero group	Licensed in India
	MabTas	Intas Biopharmaceuticals	Licensed in India
	JHL1101	JHL Biotech	Phase I
	MabionCD20	Mabion	Phase III
	PF-05280586	Pfizer	Phase I/II
	Kikuzubam	Probiomed	Licensed in Bolivia, Chile, Mexico, Peru
	GP2013	Sandoz	EU application submitted
	HLX01	Shanghai Henlius Biotech	Phase III
	TL011	Teva	Phase I/II
	Rituximab	Zenotech Laboratories	Licensed in India

Information current as of October 2016. EU: European Union; USA, United States of America.

affect efficacy or safety, which was consistent with the reference product, and so were considered to have no bearing on establishing biosimilarity [40]. In response to questions regarding the interpretation of these results [54], the authors commented that there was no correlation between ADA incidence and safety profile, and suggested that differences in product aggregates, impurities and glycosylation for Benepali<sup>®</sup> compared with the etanercept reference product may have resulted in the lower incidence of ADAs with Benepali<sup>®</sup> in this study [55].

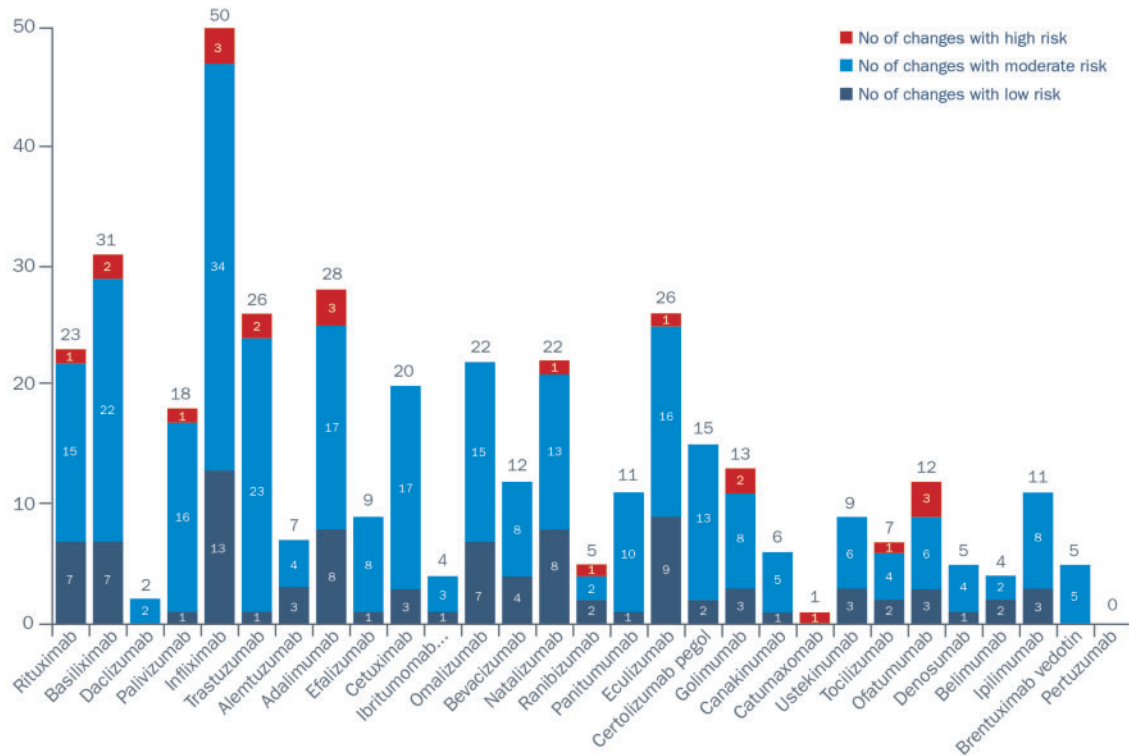
It is challenging to compare immunogenicity results across studies because of differences in assays, patient populations and the timing of testing [56]. In addition, immunogenicity assessments can be affected by previous exposure to a reference product or similar biologic therapeutic, co-administration of other drugs and the underlying disease [57]. The results with Remsima<sup>®</sup> and Benepali<sup>®</sup> suggest that immunogenicity for biosimilars must be considered on a case-by-case basis. This is in

line with EMA recommendations, which recommend focusing on any differences in immunogenicity that translate into clinically meaningful changes in safety or efficacy [58]. In addition, monitoring of immunogenicity and any link with clinical activity is a crucial component of post-marketing pharmacovigilance [51].

#### Post-marketing pharmacovigilance and risk management

Biologic products vary over time as a result of modifications to the manufacturing process. This applies to both originator products and biosimilars [59]. Indeed, results from a study that investigated the number and types of manufacturing changes for originator mAbs according to the European Public Assessment Report reported 404 manufacturing changes authorized by the EMA from 29 European Public Assessment Report reports [59]. Of these, 22 were categorized as high-risk, 286 as moderate-risk and 96 as low-risk manufacturing changes

**Fig. 1** Number of manufacturing changes for monoclonal antibodies in their European Public Assessment Reports according to risk category



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(Fig. 1). However, although the EMA has significant experience of process changes for originator mAbs, manufacturers of biosimilars are required to implement pharmacovigilance or risk management plans to assess potential product risks proactively after the biosimilar is made available, including the following [51, 60]: safety profile; how any risks will be prevented or minimized; plans for studies and other activities to gain more knowledge about the safety and efficacy of the medicine; risk factors for developing adverse reactions; and measuring the effectiveness of risk minimization measures.

In contrast to the requirements for non-biologic products, additional safety post-marketing monitoring requirements for biosimilars are mandated in view of their abbreviated approval pathway, which may not have enabled the collection of extensive, long-term safety data (Table 2) [51, 60, 61]. For example, a condition of the licensing of Remsima® in Europe was a mandatory post-marketing programme, including multiple registries that will continue up to the year 2026 [62, 63]. Examples of a post-marketing risk management plan and a post-authorization study programme are shown in Tables 3 and 4, respectively [51, 60, 61, 64]. The plan should lay out safety information acquired, any

safety concerns and gaps in knowledge to be addressed in the post-authorization programme.

#### Nomenclature and traceability

The World Health Organization has previously recommended that the standard international non-proprietary name (INN) system be used for biosimilars to enable physicians and regulatory authorities to recognize the active ingredient easily [65]. This approach is used within Europe, whereby a biosimilar that is designed to be identical to a reference product does not have a different INN [11, 65]. In contrast, FDA guidance for industry indicates that biosimilar products submitted under the Public Health Service Act should have a non-proprietary name that includes a four-letter suffix to distinguish the biosimilar from the reference product; for example, the biosimilar filgrastim has the non-proprietary name filgrastim-sndz in the USA [66].

Although emphasizing to clinicians and patients that biosimilars and reference products are to be seen as the same, the policy of using the same name could pose challenges for traceability [67]. Consistent pharmacovigilance systems are required that enable capture of both product (brand

**TABLE 2** Example of risk minimization measures

Risk identified	Risk minimization measure	Objective and rationale	Description
Serious infections (including opportunistic infections, tuberculosis, <i>Legionella</i> , <i>Listeria</i> , parasitic infection)	Patient alert card	To provide information to patients to make them aware that, during treatment with Benepali <sup>®</sup> , there is an increased risk of acquiring serious infections or that existing infections may get worse	Patient alert card will be provided to Benepali <sup>®</sup> prescribing physicians for distribution to patients receiving Benepali <sup>®</sup> This card provides important safety information for patients, including information relating to infections
Worsening heart failure (worsening of congestive heart failure in adult patients)	Patient alert card	To provide adequate information to patients to make them aware of the increased risk of worsening of heart failure during treatment with Benepali <sup>®</sup>	Patient alert card will be provided to prescribing physicians for distribution to patients receiving Benepali <sup>®</sup> This card provides important safety information for patients, including information relating to heart failure
Potential for medication errors (pre-filled pen)	Educational material for healthcare professionals and patients	To alert patients and healthcare professionals to the risk of medication errors in patients using a pre-filled pen	A mock pre-filled pen device for practice will be provided to healthcare professionals An educational programme will be provided to healthcare professionals and patients
Potential for pediatric off-label use	Educational material/patient alert card	To remind patients and healthcare professionals that Benepali <sup>®</sup> is not indicated for children under the age of 18 years	Warnings will be inserted in the patient alert card An educational programme will be provided to healthcare professionals and patients

Summary of information from [61]. Example shown is for a biosimilar etanercept (Benepali<sup>®</sup>).

**TABLE 3** Safety risk management requirements for biosimilars in Europe

Module	Details	Required for biosimilars
Module S1	Epidemiology of the indication(s) and target population(s)	No
Module SII	Non-clinical part of the safety specification	Yes
Module SIII	Clinical trial exposure	Yes
Module SIV	Populations not studied in clinical trials	Yes
Module SV	Post-authorization experience	Yes
Module SVI	Additional EU requirements for the safety specification	Yes
Module SVII	Identified and potential risks	Yes
Module SVIII	Summary of the safety concerns	Yes

Adapted from EU's new pharmacovigilance legislation: considerations for biosimilars. *Drug Saf* 2014;37:9–18. Calvo B, Zuñiga L, © 2013 [51]. With permission of Springer. With additional information from [60]. EU: European Union.

name) and batch manufacturing information in relationship to individual dispensed medications, as well as the transfer of exposure details to the relevant pharmacovigilance programmes [67]. Accordingly, European legislation requires that, for all reports of adverse drug reactions, all appropriate measures should be taken to identify the brand name and

batch number, as well as the INN [51]. Although national traceability regulations and local procedures for monitoring the dispensing of biologics currently vary, post-marketing studies and monitoring programmes for licensed biosimilars should assist in facilitating traceability in the short and medium term [67].

TABLE 4 Example of post-authorization development

Safety/efficacy concerns addressed	Study	Location(s)	Study overview	Estimated time lines
All safety concerns, including serious and/or opportunistic infections, cancers, heart failure and injection-site reactions	SB4-G31-RA (NCT01895309)	Europe	Randomized, double-blind study of the efficacy, safety, pharmacokinetics and immunogenicity of Benepali® vs Enbrel® in patients with moderate-to-severe RA despite MTX therapy  The first 52 weeks will compare Benepali® and Enbrel®, and the next 48 weeks constitutes an open-label study switching the Enbrel® arm to Benepali®	100-week switching data reported at EULAR 2016
All safety concerns, including serious and/or opportunistic infections, cancers, heart failure and injection-site reactions	British Society for Rheumatology Register-Rheumatoid Arthritis (BSRBR-RA)	UK	An established nationwide register for patients with rheumatological disorders treated with biologic agents  The register is designed as a national prospective study, the primary purpose of which is to assess long-term toxicity from the use of these agents in routine practice	Final report planned for 2027 Annual interim reports, with PSUR/RMP updates where applicable
All safety concerns, including serious and/or opportunistic infections, cancers, heart failure and injection-site reactions	Rheumatoid Arthritis oBServation of Biologic Therapy (RABBIT)	Germany	Prospective, observational study to evaluate the long-term effectiveness, safety and costs of anti-TNF therapies for RA  Comparison with a cohort of patients with RA treated with non-biologic DMARDs	Final report planned for 2027 Annual interim reports, with PSUR/RMP updates where applicable
All safety concerns, including serious and/or opportunistic infections, cancers, heart failure and injection-site reactions	Anti-Rheumatic Therapies In Sweden (ARTIS)	Sweden	Prospective, observational study to assess the risk of selected adverse events in patients with RA, juvenile idiopathic arthritis and other rheumatic diseases receiving Benepali®	Final report planned for 2027 Annual interim reports, with PSUR/RMP updates where applicable
Long-term safety of biologic treatments for psoriasis	British Association of Dermatologists Biologic Interventions Register (BADBIR)	UK	Nationwide registry to monitor the long-term safety of biologic treatments for psoriasis	Final report planned for 2027 Annual interim reports, with PSUR/RMP updates where applicable

Summary of information from [61]. Example shown is for a biosimilar etanercept (Benepali®). DMARD: disease-modifying anti-rheumatic drug; EULAR: European League Against Rheumatism; PSUR: Periodic Safety Update Report; RA: rheumatoid arthritis; RMP: risk management plan; TNF: tumor necrosis factor.

## Integrating biosimilars into clinical practice

### Switching

Switching is defined as a decision by the treating physician to exchange one medicine for another medicine with the same therapeutic intent in patients who are

undergoing treatment [68, 69]. Several studies (including open-label extensions to randomized controlled studies, observational studies and a randomized study) have examined the impact of using the biosimilar infliximab (Remsima®) in place of the reference product (switching) in patients receiving ongoing treatment for rheumatic diseases or IBD. The PLANETRA open-label extension study recruited 302 patients with RA who completed the

54-week randomized PLANETRA study, and either continued Remsima<sup>®</sup> (n = 158) or were switched from infliximab to Remsima<sup>®</sup> for 1 year of treatment in the extension, which ran from weeks 62 to 102 (n = 144) [70]. Comparable efficacy and tolerability were observed in the patients who switched to Remsima<sup>®</sup> in the extension and the patients who received Remsima<sup>®</sup> for 2 years (in the randomized study and extension) [70]. Likewise, in the PLANETAS open-label extension study in patients with ankylosing spondylitis, switching to Remsima<sup>®</sup> from infliximab from weeks 62 to 102, after 54 weeks of prior treatment, was associated with similar efficacy and tolerability compared with receipt of Remsima<sup>®</sup> throughout [71]. Additional studies in different countries have indicated that switching to Remsima<sup>®</sup> offers clinical efficacy that is comparable to the reference product [72–77]. However, in some observational studies, discontinuation rates for patients switching from infliximab to Remsima<sup>®</sup> have been attributed to a possible nocebo effect [72, 76, 77]. These findings, although suppositional, underscore the need for controlled switching studies in this therapeutic area. More recently, a government-funded, randomized, double-blind, multicenter, phase IV study in Norway (NOR-SWITCH) assessed the safety and efficacy of switching patients from reference infliximab (Remicade<sup>®</sup>) to Remsima<sup>®</sup> [78, 79]. Altogether, 498 patients were recruited into the study, including patients with RA (n = 77), spondyloarthritis (n = 91), PsA (n = 30), ulcerative colitis (n = 93), Crohn's disease (n = 155) and chronic plaque psoriasis (n = 35) who had been treated with Remicade<sup>®</sup> for at least 6 months and who were experiencing stable disease. These patients were randomized (1:1) to switch to Remsima<sup>®</sup> (n = 241) or to continue treatment with Remicade<sup>®</sup> (n = 240) for 52 weeks. Disease worsening (primary end point; worsening in disease-specific composite measures and/or a consensus between investigator and patient leading to major change in treatment) occurred in 29.6% of patients receiving Remsima<sup>®</sup> and in 26.2% of patients receiving Remicade<sup>®</sup> (treatment difference - 4.4%; 95% CI: -12.7% to 3.9%) which confirmed non-inferiority [79]. Evaluations of generic and specific disease measures were similar between the groups, as were the incidence of ADAs (8% Remsima<sup>®</sup>; 7% Remicade<sup>®</sup>), trough drug levels and the incidence of adverse events. An extension to the NOR-SWITCH study is also ongoing, in which eligible patients are followed up for a further 6 months while receiving Remsima<sup>®</sup>, enabling additional comparison of efficacy and safety between patients receiving Remsima<sup>®</sup> for 12 months and patients who have recently been switched [78].

In an open-label extension to the phase III, 52-week randomized study that compared SB4 with reference etanercept, 126 patients continued to receive SB4 (SB4/SB4) and 119 patients switched from reference etanercept to SB4 (etanercept/SB4) for a further 48 weeks [45]. At the end of this open-label treatment period, the efficacy, safety and immunogenicity profiles were again comparable for both SB4/SB4 and etanercept/SB4 groups. Switching from etanercept to SB4 had no detrimental

effects. Of note, there was no decline in efficacy, increase in adverse events or increase in immunogenicity [45].

Against this background, there is a growing body of evidence to support switching from an originator to a biosimilar, with the NOR-SWITCH study providing the first randomized data set in this respect [79]. National and regional registries will probably provide crucial, real-world data on switching to biosimilars. As more biosimilars become available, a key challenge will be the issue of multiple switching, which is not currently covered in regulatory guidelines and has not yet been addressed in clinical studies [6].

### Interchangeability

Interchangeability can be defined as the medical practice of changing one medicine for another that is expected to achieve the same clinical effect in a given clinical setting and in any patients on the initiative, or with agreement of the prescriber [68, 69]. Interchangeability is also a regulatory term used for switching. A biosimilar is defined as being interchangeable with the reference product if biosimilarity has been demonstrated and if it can be expected to produce the same clinical result in any given patient [14]. The term interchangeability is often confused with automatic substitution (see next subsection). The regulatory framework in Europe and post-marketing pharmacovigilance commitments undertaken by manufacturers should provide reassurance to prescribers that an approved biosimilar can be administered safely to their patients, and is therefore interchangeable with the reference product [14].

### Automatic substitution

Substitution is the practice of dispensing one medicine instead of another equivalent and interchangeable medicine at the pharmacy level without consulting the prescriber [68, 69]. Generic small molecules may be dispensed to patients at the pharmacy level through automatic substitution. In contrast, automatic substitution of biosimilars for reference products is not currently recommended in most countries [14]. Within Europe, the EMA notes that guidance on biosimilar substitution is the responsibility of individual member states and should take place only under the guidance of a healthcare professional [80]. Interpretation of this guidance varies across different European markets, with some countries prohibiting automatic substitution at the pharmacy level [14]. In the UK, for example, the National Health Service recommends against automatic substitution for any biologics at the pharmacy level, and leaves the decision on the use of a biosimilar with the prescriber, who must use brand-name prescribing [81]. In contrast, in many other settings, the use of biosimilars has been actively facilitated by national and local tender systems [82, 83], where the manufacturers are invited to tender a price for their product, thus creating open competition.

### Extrapolation of evidence across indications

During the development and licensing of biosimilars, questions have been raised as to whether the demonstration of similar efficacy and safety in one disease justifies indication extrapolation to support licensing of the biosimilar for other diseases [84, 85]. Within the EMA regulatory framework, extrapolation across indications is possible, based on the total evidence of comparability if the reference product's mechanisms of action are consistent across its different indications [84]. If different mechanisms of action across indications are suspected, then additional evidence is required.

In the case of Remsima<sup>®</sup>, for which pre-registration clinical trials focused on RA [41], the EMA license included extrapolation across all licensed indications [62]. Likewise, based on the quality of the evidence, the EMA permitted extrapolation of the PK, efficacy and safety data generated with the etanercept biosimilar Benepali<sup>®</sup> in healthy volunteers and patients with RA to the other adult-licensed indications of the reference product, Enbrel<sup>®</sup> [64]. Within the FDA framework, extrapolation of indications has also been permitted in the case of Inflectra<sup>®</sup> (biosimilar infliximab) [10], and this approach is accepted by other regulatory authorities on a case-by-case basis dependent on sufficient scientific rationale [86, 87]. An increasing number of articles are providing evidence that the extrapolation of the biosimilar infliximab from rheumatic to gastrointestinal indications is both efficient and safe [88].

### Barriers to implementation—healthcare professional and patient opinions

In order for biosimilars to be adopted widely, both prescribers and patients need to be fully aware of their attributes and benefits to be confident in their use. A recent physician Web-based survey of members of the European Crohn's and Colitis Organization indicated high levels of awareness for biosimilar attributes and potential advantages. However, only 24% agreed with extrapolation of use to indications without direct clinical evidence, and 61% stated that they had little or no confidence in using biosimilars in their clinical practice [89]. This last point is interesting and may require further information and education. Indeed, in a more recent survey of US and European physicians, biosimilar awareness was again found to be high, and whereas 47% of respondents stated they felt these agents were sufficiently safe and effective for them to prescribe, 43% said that they required more information on biosimilars [90].

In a similar vein, patients have a need for education regarding biosimilars. Awareness of biosimilars is low among patients, with gaps in knowledge being notable for efficacy, safety and access to these agents [91]. Important issues relating to practical management, such as pharmacovigilance, interchangeability, switching and substitution, are causes of scepticism and anxiety among patients with rheumatic and musculoskeletal diseases [92]. It is not surprising, as previously noted, that switching to a biosimilar has been associated with a

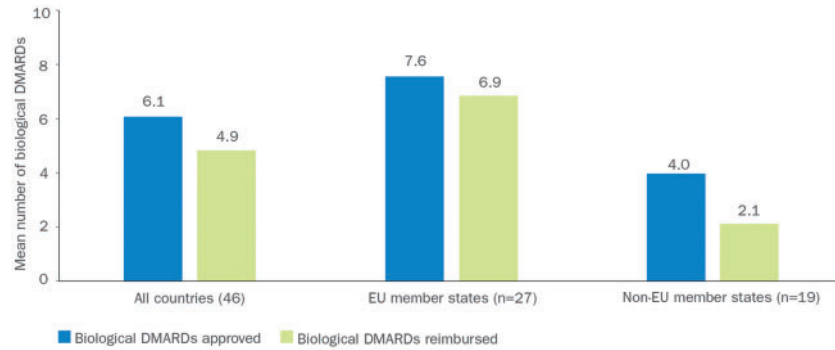
possible nocebo effect [72, 76, 77]. The possibility that secondary inefficacy or adverse effects are inappropriately attributed to the switch is a cause for concern. Overall, the need for patient and physician education and for effective communication between physician and patient are issues that need to be addressed in order for biosimilars to be integrated effectively into clinical practice.

### Access to implementation—access to treatments

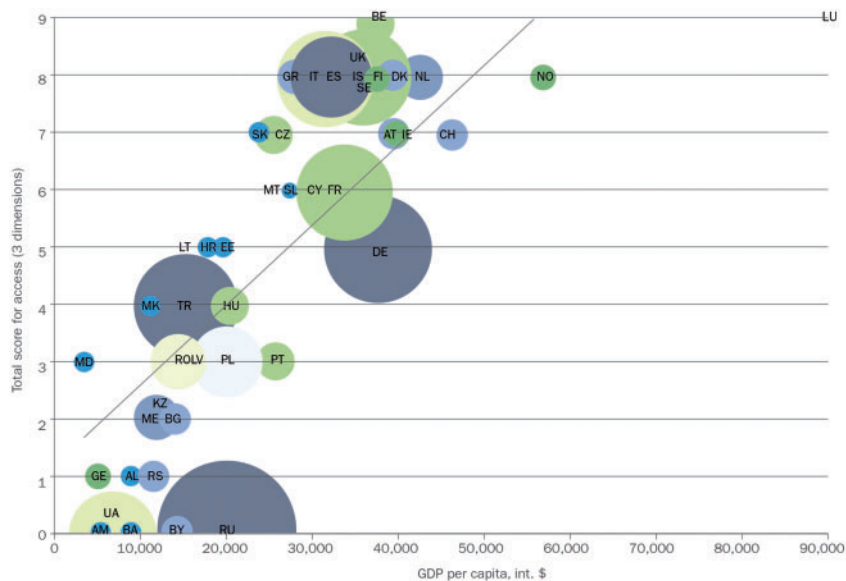
Access to bDMARDs varies considerably across Europe and is dependent on national and local guidelines, levels of funding and differing approaches to healthcare management [3, 4, 93]. In a study of 46 European countries published in 2015, access to bDMARDs differed by country, with 22% of the countries (10/46) having no reimbursement of any of the bDMARDs assessed [3]. Across all of the 46 countries, the mean (s.d.) number of bDMARDs reimbursed was 4.9 (3.3), and this varied according to EU member states and non-EU member states (Fig. 2) [3]. Further analyses of three dimensions of access (acceptability, affordability and availability) indicated a strong correlation between higher socio-economic status, assessed as gross domestic product per capita, and access to bDMARDs (Fig. 3) [3]. The study estimated that, in total, 320 million people with RA in the European region (~40%) would have severe restrictions on their access to bDMARDs [3]. Barriers to access appeared to be primarily financial and administrative, but may also have been related to prescribing restrictions, which means that countries with lower socio-economic status have higher eligibility barriers for access to biologic treatments [4]. Among the countries in which bDMARDs were reimbursed (n = 36), clinical criteria were in place to regulate the initiation of treatment in all countries, whereas 39% (14/36) had regulations affecting stopping or maintaining treatment and 53% (19/36) provided guidance on switching between treatments [4]. In more than half of the countries (56%; 20/36), a DAS-28 of  $\geq 3.2$  was required to initiate bDMARD treatment, and 61% of countries (22/36) required the failure of more than one traditional DMARD before bDMARD treatment could be started [4]. Of note, non-EU member states tended to have eligibility criteria for access to bDMARDs that were more stringent than recommendations from the EULAR [4]. A composite eligibility score indicated that one-third of all countries had highly restricted access to bDMARDs for RA [4].

An important consideration for chronic diseases, such as RA, is that earlier intervention generally results in substantially improved outcomes. Treatment of RA, with effective treatments, may provide a unique opportunity to change the course of RA early: after the start of symptoms but before radiographic damage occurs [94]. In countries with spending limitations, early treatment may be less likely, and cost pressure may prevent patients from receiving optimal doses or continuing with appropriate treatments [95]. Budget impact analyses and feedback from countries where biosimilar products are being used suggest that substantial cost savings are possible,



**Fig. 2** Approval and reimbursement of biologic DMARDs in Europe

The mean number of bDMARDs approved and reimbursed varied across the 46 European countries in this study, with a different profile being observed for EU member states compared with non-EU member states. Data taken from [3]. bDMARDs: biologic DMARDs; EU: European Union.

**Fig. 3** Access to biologic DMARDs according to gross domestic product per capita

Analysis based on GDP in dollars in 44 countries. The size of the bubbles is proportional to the population size of the country. Reproduced from: Putrik P, Ramiro S, Kvien TK *et al.* Inequalities in access to biological and synthetic DMARDs across 46 European Countries. *Ann Rheum Dis* 2014;73:198–206, © 2014 [3]. With permission from BMJ Publishing Group Ltd. AL: Albania; AM: Armenia; AT: Austria; BA: Bosnia and Herzegovina; bDMARD: biologic DMARD; BE: Belgium; BG: Bulgaria; BY: Belarus; CH: Switzerland; CY: Cyprus; CZ: Czech Republic; DE: Germany; DK: Denmark; EE: Estonia; ES: Spain; FI: Finland; FR: France; GDP: gross domestic product; GE: Georgia; GR: Greece; HR: Croatia; HU: Hungary; IE: Ireland; IS: Iceland; IT: Italy; KZ: Kazakhstan; LT: Lithuania; LU: Luxembourg; LV: Latvia; MD: Moldova; ME: Montenegro; MK: Macedonia; MT: Malta; NL: The Netherlands; NO: Norway; PL: Poland; PT: Portugal; RO: Romania; RS: Serbia; RU: Russia; SE: Sweden; SK: Slovakia; SL: Slovenia; TR: Turkey; UA: Ukraine; UK: United Kingdom.

particularly when biosimilar substitution is favoured, which could enable many more patients to receive treatment [96, 97]. Changes to European prescribing practices and regulations are necessary to take advantage of the potential benefits of biosimilar products and to harmonize

treatment within EU member states. However, alternative strategies before attempting bDMARD implementation need to be considered. These include a treat-to-target (or tight control) approach for example, combination of conventional synthetic DMARDs (csDMARDs) [98–101],

following inadequate response to csDMARD monotherapy [102, 103]. Once bDMARDs are introduced, it is important also to consider strategies to reduce costs [104, 105].

## Discussion and future directions

Biosimilars offer an important opportunity to improve patient access to effective biologic treatments, thereby not only enhancing the individual patient experience, but also contributing to a reduction in long-term care costs for chronic diseases [6, 7]. Inequity in the access to biologic treatment across European countries could be reduced by better access, with treatment of a greater number of patients at a more cost-effective level. Indeed, several cost-minimization analyses have shown these agents to be cost effective in this context, with biosimilars appearing to exert downward pressure on pricing [96, 97, 106–109]. For example, in Central and Eastern Europe, the introduction of CT-P13 has resulted in a 20–60% reduction in the cost of infliximab [110], and a 69% discount was offered for CT-P13 vs that offered for Remicade® for its national supply in Norway in 2015 [111].

Against this background, the development and licensing process for biosimilars has been shown to be effective and robust, with biologic similarity resulting in consistency with respect to efficacy and safety. Although small in number, switching studies have so far shown that consistent efficacy and safety can be achieved when switching between reference products and biosimilars. Crucially, the real-world experience that is being proactively gathered through post-marketing studies (including the NOR-SWITCH study) and patient registries will add to our knowledge concerning biosimilars, and may further enhance confidence in the use of these products in clinical practice.

There are many stakeholders with various attitudes to important questions, such as switching and interchangeability, and issues are becoming more complex as more biosimilars become available. Interchanging is not standard practice in Europe at present, and this may affect the uptake of biosimilars in some markets. Experience with different pricing and tender systems may be valuable to facilitate the use of biosimilars while leaving the decision for prescription with the physician. Specific mechanisms for tracing the use of specific biosimilars are essential, which must take into account differing approaches to their nomenclature in Europe and the USA.

In the future, biosimilars are expected to play an important role in providing patients with access to effective biologic treatment at the appropriate time during their disease course. Mechanisms are in place to monitor biosimilar effectiveness and safety in clinical practice, and evidence is growing regarding how patients may be switched safely to these treatments. An important issue for future clinical practice will be how to approach multiple switching, as the number of biosimilars increases.

## Acknowledgments

The authors would like to acknowledge the editorial support provided by inVentiv Health Medical Communications. Philip Ford and Frances Gambling from inVentiv Health Medical Communications wrote the drafts of the article based on input from all authors, and styled the article per journal requirements. Biogen reviewed and provided feedback on the article to the authors. The authors had full editorial control of the article and provided their final approval of all content. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval to the version to be published.

*Funding:* This work was supported by Biogen, who provided funding for medical writing and editorial support in the development of this article.

*Disclosure statement:* T.U. has received consultancy fees from AbbVie, Biogen, Bristol-Myers Squibb, Eli Lilly, MSD, Pfizer, Roche and UCB. G.L.G. has received honoraria/served a consultant for AbbVie, Novartis, Orion Pharma, Boehringer Ingelheim and Pfizer.

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