ARD Online First, published on October 3, 2017 as 10.1136/annrheumdis-2017-211937

Consensus-based recommendations for the use of biosimilars to treat rheumatological diseases

Jonathan Kay,[1] Monika M Schoels,[2] Thomas Dörner,[3] Paul Emery,[4] Tore K Kvien,[5] Josef S Smolen,[2,6] Ferdinand C Breedveld,[7] on behalf of the Task Force on the Use of Biosimilars to Treat Rheumatological Diseases

Handling editor David S Pisetsky

► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/annrheumdis-2017-211937).

For numbered affiliations see end of article.

Correspondence to
Professor Jonathan Kay, Division of Rheumatology, Department of Medicine, UMass Memorial Medical Center and University of Massachusetts Medical School, Worcester, MA 01605, USA;
jonathan.kay@umassmemorial.org

JK and MMS contributed equally.

Received 15 June 2017
Revised 20 July 2017
Accepted 12 August 2017

ABSTRACT

The study aimed to develop evidence-based recommendations regarding the evaluation and use of biosimilars to treat rheumatological diseases. The task force comprised an expert group of specialists in rheumatology, dermatology and gastroenterology, and pharmacologists, patients and a regulator from ten countries. Four key topics regarding biosimilars were identified through a process of discussion and consensus. Using a Delphi process, specific questions were then formulated to guide a systematic literature review. Relevant English-language publications through November 2016 were searched systematically for each topic using Medline; selected papers and pertinent reviews were examined for additional relevant references; and abstracts presented at the 2015 and 2016 American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) annual scientific meetings were searched for those about biosimilars. The experts used evidence obtained from these studies to develop a set of overarching principles and consensus recommendations. The level of evidence and grade of recommendation were determined for each. By the search strategy, 490 references were identified. Of these, 29 full-text papers were included in the systematic review. Additionally, 20 abstracts were retrieved from the ACR and EULAR conference abstract databases. Five overarching principles and eight consensus recommendations were generated, encompassing considerations regarding clinical trials, immunogenicity, extrapolation of indications, switching between bio-originators and biosimilars and among biosimilars, and cost. The level of evidence and grade of recommendation for each varied according to available published evidence. Five overarching principles and eight consensus recommendations regarding the evaluation and use of biosimilars to treat rheumatological diseases were developed using research-based evidence and expert opinion.

INTRODUCTION

Treatment with biological agents (biologics) has dramatically improved the outcome for patients with inflammatory diseases. However, the high cost of these medications has limited access for many patients.[1] To make effective biologics more widely available, biosimilars of products that no longer are protected by patent have been developed and have been made available to patients at costs lower than those of the bio-originator. In the European Union (EU), the USA, Japan and other countries, biosimilars of adalimumab, etanercept, infliximab and rituximab have been approved, and those for which the bio-originator no longer is protected by patent have been marketed.

Over the past decade, several publications have examined the scientific, legal and regulatory aspects of biosimilar development.[1–6] However, little has been published to guide healthcare providers in critically evaluating and differentiating the scientific data available for each of these molecules. Thus, a multidisciplinary group was convened to develop consensus, at an international level, among patients and physicians regarding the evaluation and use of biosimilars to treat rheumatological diseases.

METHODS

Participants

An international multidisciplinary task force on biosimilars was convened in 2016, consisting of 25 experts from eight European countries, Japan and the USA (17 rheumatologists, 1 rheumatologist/regulator, 1 dermatologist, 1 gastroenterologist, 2 pharmacologists, 2 patients with rheumatic diseases as patients' representatives and 1 research fellow). The objective was to develop an evidence-based and consensus-based statement about the use of biosimilars to treat inflammatory diseases by identifying and critically appraising evidence in the literature. This statement was intended both to guide clinicians and to serve as a framework for future educational efforts.

Experts' consensus

In August 2016, a steering committee consisting of six rheumatologists and one research fellow, all of whom were members of this task force, held a preliminary meeting in Vienna, Austria. At this meeting, they identified four key topics for further discussion by the task force: issues related to clinical trials of biosimilars, extrapolation of indications, immunogenicity of biosimilars compared with their bio-originators, and switching between bio-originators and biosimilars and among biosimilars. Using a Delphi process, specific questions were formulated about these subjects to guide a systematic literature review (SLR), which was then performed to identify relevant publications through November 2016.

The Medline database was searched for English-language publications about biosimilars; selected papers and pertinent reviews were examined for additional relevant references. Abstracts presented at the 2015 and 2016 American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) annual scientific

To cite: Kay J, Schoels MM, Dörner T, *et al*. *Ann Rheum Dis* Published Online First: [*please include* Day Month Year]. doi:10.1136/annrheumdis-2017-211937

meetings were searched for those about biosimilars. The European public assessment reports for human medicines, published by the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) publications (Drugs@FDA), were reviewed to identify those about biosimilars approved by the EMA and/or the FDA to treat rheumatological diseases, as of December 2016 (online supplementary table S1). The EU clinical trials register and ClinicalTrials.gov databases were queried to identify clinical trials in which a biosimilar was studied in patients with an inflammatory disease. We included publications on biosimilars that were approved to treat rheumatological diseases. During the initial search process, no quality criteria were applied for inclusion, but all relevant studies were later rated using the Oxford Centre for Evidence-Based Medicine Levels of Evidence 1.[7]

The findings of the SLR were communicated to the steering committee members, augmented by two pharmacologists and a rheumatologist/regulator, at a second meeting that was held in Leiden, the Netherlands, in December 2016. Additional presentations were made about the relative immunogenicity of biosimilars to their bio-originators and about regulatory issues related to approval of biosimilars by the EMA. Group discussion followed these talks, during which overarching principles and consensus statements were developed to propose to the entire task force.

On the following day, a consensus conference took place, at which all but two members of the full task force were in attendance. At this face-to-face meeting, a summary of the evidence obtained through the SLR was presented to the entire task force. Subsequently, the proposed overarching principles and consensus statements that had been developed by the augmented steering committee were presented. The task force members deliberated on each statement and modified the wording, if necessary. Each statement was then voted on and high-level agreement was achieved for all statements. The two members of the task force who were absent from the Leiden meeting subsequently voted on each statement by email and their votes were combined with those of the other task force members (table 1). Overarching principles and recommendations were accepted when ≥80% of the experts agreed.

RESULTS

Systematic literature review

The initial search strategy (online supplementary table S2) identified 490 publications in Medline, as of December 2016. After the selection process had been applied, 29 full-text papers were included. From the ACR and EULAR conference abstract databases, 20 abstracts were retrieved (online supplementary figure S1).

Experts' opinion approach

After discussing the results of the SLR, the consensus process was initiated. The full task force agreed on five overarching principles and eight consensus recommendations (table 1).

Table 1 Overarching principles (A–E) and consensus recommendations (1–8) for biosimilars

		Agreement* (%)	Level of evidence†	Grade of recommendation‡
Overarching principles				
A.	Treatment of rheumatic diseases is based on a shared decision-making process between patients and their rheumatologists.	100	5	D
B.	The contextual aspects of the healthcare system should be taken into consideration when treatment decisions are made.	100	5	D
C.	A biosimilar, as approved by authorities in a highly regulated area, is neither better nor worse in efficacy and not inferior in safety to its bio-originator.	88	5	D
D.	Patients and healthcare providers should be informed about the nature of biosimilars, their approval process, and their safety and efficacy.	96	5	D
E.	Harmonised methods should be established to obtain reliable pharmacovigilance data, including traceability, about both biosimilars and bio-originators.	100	5	D
Consensus recommendations				
1.	The availability of biosimilars must significantly lower the cost of treating an individual patient and increase access to optimal therapy for all patients with rheumatic diseases.	100	5	D
2.	Approved biosimilars can be used to treat appropriate patients in the same way as their bio-originators.	100	1b	A
3.	As no clinically significant differences in immunogenicity between biosimilars and their bio-originators have been detected, antidrug antibodies to biosimilars need not be measured in clinical practice.	100	2b	B
4.	Relevant preclinical and phase I data on a biosimilar should be available when phase III data are published.	100	5	D
5.	Since the biosimilar is equivalent to the bio-originator in its physicochemical, functional and pharmacokinetic properties, confirmation of efficacy and safety in a single indication is sufficient for extrapolation to other diseases for which the bio-originator has been approved.	100	5	D
6.	Currently available evidence indicates that a single switch from a bio-originator to one of its biosimilars is safe and effective; there is no scientific rationale to expect that switching among biosimilars of the same bio-originator would result in a different clinical outcome but patient perspectives must be considered.	96	1b	A
7.	Multiple switching between biosimilars and their bio-originators or other biosimilars should be assessed in registries.	100	5	D
8.	No switch to or among biosimilars should be initiated without the prior awareness of the patient and the treating healthcare provider.	91	5	D

*Agreement indicates percentage of experts who approved the recommendation during the final voting round of the consensus meeting.
†1a: systematic review of randomised clinical trials (RCTs); 1b: individual RCT; 2a: systematic review of cohort studies; 2b: individual cohort study (including low-quality RCT; eg, <80% follow-up); 3a: systematic review of case–control studies; 3b: individual case–control study; 4: case-series (and poor quality cohort and case–control studies); 5: expert opinion without explicit critical appraisal, or based on physiology, bench research or 'first principles'.
‡A: based on consistent level 1 evidence; B: based on consistent level 2 or 3 evidence or extrapolations from level 1 evidence; C: based on level 4 evidence or extrapolations from level 2 or 3 evidence; D: based on level 5 evidence or on troublingly inconsistent or inconclusive studies of any level.

RECOMMENDATIONS

Five main topics related to biosimilars were identified: considerations regarding clinical trials, immunogenicity, extrapolation of indications, switching between bio-originators and biosimilars and among biosimilars, and cost. Within each of these areas, key issues were identified that form the basis for the overarching principles and consensus recommendations described here (table 1). We present the overarching principles and consensus statements in the sequence listed in table 1, followed by an explanatory discussion of each.

Overarching principles

Treatment of rheumatic diseases is based on a shared decision-making process between patients and their rheumatologists

A fundamental principle underlying the treatment of all diseases is that informed patients share in making decisions about therapy with their healthcare providers. For the rheumatic diseases, the rheumatologist is obliged to educate the patient both about the disease process and about appropriate treatment options. Once informed, the patient can then engage the healthcare provider in a dialogue in which personal preferences, treatment goals, and the potential risks and benefits of each treatment option are discussed and evaluated relative to one another. Such a discussion should result in optimal treatment of the disease process and empower patients to remain in control of their health.

The contextual aspects of the healthcare system should be taken into consideration when treatment decisions are made

The structure of healthcare systems varies in different countries. In some countries, the government oversees the healthcare system and serves as a single payer to cover the costs of medical treatment for its citizens. In other countries, such as the USA, a variety of systems are in place to support access to healthcare: some patients are covered by government-supported insurance plans, others purchase private insurance coverage, and some have no health insurance coverage at all. In single-payer systems, the payer often supports the cost of medications. However, in countries in which coverage for healthcare expenses is provided by a variety of systems, there often is a similar range of approaches to subsidise the cost of medications. Among those individuals who have prescription coverage, the proportion of the drug acquisition cost that is subsidised varies. Although only a small monetary copayment is required of some patients, others are expected to pay 20% or more of the cost of medications. This can place a significant burden on some individuals and may make necessary treatment inaccessible to some. These contextual aspects must be considered when choosing appropriate drug therapy for a given patient, since lower drug costs increase affordability.

A biosimilar, as approved by authorities in a highly regulated area, is neither better nor worse in efficacy and not inferior in safety to its bio-originator

A biosimilar is a replica of a biopharmaceutical that has met criteria for biosimilarity, according to a defined pathway established to demonstrate equivalent pharmacokinetics (PK), pharmacodynamics (PD) and efficacy and comparable safety and immunogenicity, and has been reviewed and approved by a regulatory authority in a highly regulated area. Many such regulatory agencies are members or observers of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH).[8] ICH aims to recommend guidelines and requirements for approval of pharmaceutical products to achieve harmonisation among regulatory agencies worldwide.

The EMA defines a biosimilar as 'a biological medicinal product that contains a version of the active substance of an already authorised' bio-originator, for which 'similarity to the reference product in terms of quality characteristics, biological activity, safety and efficacy' has been demonstrated.[9] In the USA, a biosimilar is defined in the Biologics Price Competition and Innovation Act of 2009 as a biological product that is 'highly similar to the reference product notwithstanding minor differences in clinically inactive components' and that 'there are no clinically meaningful differences between the reference product and the biologic product in terms of the safety, purity and potency of the product'.[10] In 2005, the EMA proposed a pathway by which to approve similar biological products.[11] Five years later, the US Congress established a pathway for the approval of biological products that are 'highly similar' to their bio-originators.[10]

The regulatory pathways for approval of a biosimilar differ slightly between the EMA and the US FDA, but both follow a 'stepwise approach' and require extensive analytical studies followed by clinical studies comparing PK and PD parameters, immunogenicity, efficacy and safety of the proposed biosimilar to its bio-originator to confirm that there are 'no clinical meaningful differences' between the bio-originator and the biosimilar. The US FDA has articulated a 'totality of the evidence' approach to evaluating the accumulated data, in which all of the information is considered in its entirety without giving greater importance to any one aspect.[12] The EMA follows a similar process.[13] Many other countries have conformed to this approach and established comparable pathways to approve biosimilars.[3]

Biosimilarity is established, following a stepwise approach, by a series of comparative studies with high face validity. Analyses must demonstrate that the biosimilar and its bio-originator have the same primary amino acid sequence. Comparing multiple batches of a biosimilar candidate with many batches of its bio-originator, acquired over time, there must be no significant differences in charge isoforms, glycosylation, other post-translational modifications or impurities. There may be minor differences, but these must not affect critical quality attributes of the biologic. For therapeutic monoclonal antibodies, essential functional properties include Fc receptor binding, complement-dependent cytotoxicity and antibody-dependent cellular cytotoxicity, on which their mechanism of action may depend. Subsequent clinical studies must demonstrate PK and PD equivalence and equivalent efficacy in at least one disease for which the bio-originator is approved, as well as comparable safety and no greater immunogenicity of the biosimilar.

Because a biosimilar can rely on data generated for approval of its bio-originator, the clinical data required by regulatory pathways for biosimilar approval in the EU, the USA and most other countries are abbreviated, contrasted to those required for approval of bio-originators. PK typically is studied by comparing single doses of a biosimilar and its bio-originator in healthy subjects[14–20]; multiple dosing is subsequently assessed in patients.[21–24] Most regulatory agencies define PK equivalence of a biosimilar to its bio-originator as when the 90% CIs for the ratio of geometric means for area under the curve and maximal concentration between the biosimilar and its bio-originator fall within the log-transformed range of 80%–125% (±20%).[5 6] In published PK studies of approved biosimilar tumour necrosis factor (TNF) inhibitors, serum concentration time profiles of the biosimilar and its bio-originator have overlapped closely, and variability of the ratio of geometric means for PK parameters has been much less than that allowed by regulatory requirements.[7–12]

Phase III randomised controlled trials (RCTs) comparing the efficacy of a candidate biosimilar with its bio-originator should be conducted in a disease that is sensitive for detecting potential differences in efficacy between the biosimilar and its bio-originator. However, the same condition may not be the most sensitive in which to detect potential differences in safety, including immunogenicity. RCTs comparing a candidate biosimilar with its bio-originator should be of adequate duration to assess durability of response, safety and immunogenicity. These trials should use endpoints that are sensitive to detecting potential differences between a biosimilar and its bio-originator. Assessment of an outcome measure at early time points, during the rapid rise phase of the time–response curve, provides additional information.[25] Assessing response to treatment during the first 3 months allows comparison of the rapidity of onset. These issues must be taken into consideration when designing phase III RCTs comparing biosimilar with their bio-originators.

Since a phase III RCT comparing a biosimilar with its bio-originator is designed to demonstrate equivalence and aims to prove the null hypothesis, the primary analysis should be performed on the per protocol set.[26] Although an intention-to-treat analysis would bias towards the null hypothesis concluding that the two drugs are equivalent, secondary analyses should be performed on each endpoint using the intention-to-treat approach to account for possible differential dropout in the two treatment arms. The equivalence margin for RCTs comparing the efficacy of a biosimilar with its bio-originator is derived from a meta-analysis of the therapeutic effect of the bio-originator in the original placebo-controlled RCTs, calculated as the risk difference in the endpoint of interest between active drug and placebo. To preserve a proportion of the therapeutic effect of the bio-originator, the equivalence margin used in a comparative effectiveness RCT is usually half or less of the mean absolute difference derived in the meta-analysis.[19] Equivalence margins should be standardised for each bio-originator.[27] The EMA defines two-sided therapeutic equivalence in RCTs comparing a biosimilar with its bio-originator as when the 95% CI for the mean absolute difference in the primary endpoint between the biosimilar and its bio-originator falls within the predefined equivalence margin.[13] However, the US FDA prefers use of the narrower 90% CI to demonstrate therapeutic equivalence.[14]

A biosimilar that has satisfied the requirements of a dedicated pathway for regulatory approval will be neither better nor worse in efficacy and not inferior in safety to the various batches of the bio-originator. Since the processes for manufacturing biologics, including highly sensitive methods to assess quality, have matured over the past decades, major changes in the manufacturing process of the bio-originator are not likely and its efficacy and safety are unlikely to drift. Thus, efficacy and safety of a biosimilar can be expected to remain highly comparable to those of its bio-originator over time.

Patients and healthcare providers should be informed about the nature of biosimilars, their approval process, and their safety and efficacy

Given that biosimilars have only recently become available, many patients and healthcare providers are unfamiliar with this concept. Since biosimilars are usually marketed at a price lower than that of their bio-originators, some presume that biosimilars are of lesser quality. This misconception can and must be corrected by informing patients and healthcare providers about the nature of biosimilars, the rigorous approval process to which they are subjected by regulatory agencies, and the equivalent efficacy and comparable safety of approved biosimilars to their bio-originators.

Harmonised methods should be established to obtain reliable pharmacovigilance data, including traceability, about both biosimilars and bio-originators

During the development of a pharmaceutical product, a limited number of patients receive treatment with the investigational drug. Thus, it is important to gather safety and efficacy data after a drug has been approved and is commercially available. Especially since the clinical part of the development process for biosimilars is abbreviated relative to that for bio-originators, it is critical that postmarketing pharmacovigilance be conducted to confirm the efficacy and safety of a biosimilar over time in a much larger number of patients than were studied in RCTs.

Traceability is an issue for all drugs, not only for biosimilars. To facilitate postmarketing pharmacovigilance, the non-proprietary name of a biosimilar must be readily distinguishable from that of its bio-originator. In 2012, the WHO proposed that a unique four-letter 'biological qualifier' code be appended as a suffix to the core name. This nomenclature system would be applied retrospectively to the bio-originator and prospectively to designate biosimilars.[28] The US FDA has followed these WHO recommendations and, in 2017, issued guidance regarding non-proprietary naming of biological products, in which it specifies that the 'biological qualifier' code suffix consists of four lower-case letters and that it is unique and 'devoid of meaning'.[29] The five biosimilars approved in the USA to treat inflammatory diseases have been designated as adalimumab-adbm, adalimumab-atto, etanercept-szzs, infliximab-abda, and infliximab-dyyb. Similarly, a 'biological qualifier' code suffix will be appended retroactively to the core name of each bio-originator, so that these may be distinguished from biosimilars. This naming convention for biologics should facilitate traceability and allow effective postmarketing surveillance of the safety and efficacy of both biosimilars and their bio-originators. Within the European medicines regulatory network, pharmacovigilance is organised primarily at a national level in the Member States of the EU and the European Economic Area using brand names for postmarketing surveillance of both biosimilars and bio-originators. An advantage of using brand names is that these can be easily recalled and reported by both patients and their healthcare providers. Suspected adverse events are submitted to the EudraVigilance database, which allows monitoring safety of medications across the entire network. However, it is unfortunate that there has not yet been global agreement on nomenclature for all biologics. Regardless of the method used to distinguish among biosimilars and bio-originators, batch numbers are essential for tracing potential problems. However, although recorded by the dispensing pharmacist, batch numbers are infrequently noted by patients or healthcare providers and may be difficult to obtain when an adverse event occurs.

Consensus recommendations

The availability of biosimilars must significantly lower the cost of treating an individual patient and increase access to optimal therapy for all patients with rheumatic diseases

As the prevalence of chronic disease increases in both high-income and lower-income countries, pharmaceutical consumption must shift to lower cost products so as to improve access to all who need these medications.[30] An approved biosimilar should provide patients with an equivalent biologic at a cost lower than that of the bio-originator. Unlike a new medication, a biosimilar

of equivalent efficacy and comparable safety has no attribute other than price to distinguish it from its bio-originator.

The expenses associated with developing a biosimilar are but a fraction of those incurred during the development of a bio-originator. Thus, once patents for bio-originators have expired, the use of less expensive biosimilars should help to offset the necessary expense of using other medications to fulfil unmet therapeutic needs. Regardless, payers must transfer the savings realised from the reduced cost of developing a biosimilar back to the patient by improving access to treatment with lower copayments for medications or by lowering insurance premiums.[31]

A 2014 RAND Corporation study estimated the potential cost savings of biosimilars in the US market to be $44.2 billion over the subsequent decade, of which TNF inhibitors would account for 21% ($9.3 billion).[32] This study assumed that market competition would result in the price of a biosimilar being 35% lower than that of its bio-originator. However, at the time of the launch in September 2015 of filgrastim-sndz (Zarxio), the first biosimilar approved in the USA, its wholesale acquisition cost (WAC) was only 15% lower than that of bio-originator filgrastim.[33] Similarly, at the time of its launch in November 2016, the WAC of infliximab-dyyb (Inflectra) in the USA was only 15% lower than that of bio-originator infliximab.[34] However, discounts and ex-post rebates provided to third-party payers and pharmacy benefit management companies by bio-originator manufacturers might reduce or even eliminate the price differential between a biosimilar and its bio-originator. Small price differentials between biosimilars and bio-originators likely will decrease the market penetration of biosimilars and further reduce direct cost savings. A price discounted only 15% below that of the bio-originator may not be sufficient to motivate use of a biosimilar. Thus, to ensure market uptake of biosimilars, it is important that they be priced considerably lower than bio-originators.

In other countries, the price of biosimilars is lowest where market competition is greatest. In Canada, at the time of its launch in March 2015, the price of Inflectra was 34% lower than that of bio-originator infliximab.[35] The prices of biosimilars in the EU typically have been 20%–40% lower than those of the corresponding bio-originators, but this is much less than the 80% price reduction realised with generic small molecule drugs.[36] However, in Norway, where the national hospital system has a competitive tender process for the exclusive contracts to supply medications that are administered in-hospital, the tender accepted for Remsima in 2014 was 39% lower than that offered for bio-originator infliximab and that accepted in 2015 was 69% lower.[37] As expected, the market share of biosimilar infliximab is much larger in those countries where the price of the biosimilar is much lower than that of bio-originator infliximab.[38] The use of a tender system has important implications for maintaining a competitive environment and is likely to reduce both the price of biologics that no longer are protected by patent and that of biosimilars. However, such a system may also pose a threat to the level of market competition over the long term and might ultimately result in a market in which only one version of a biologics (biosimilar or bio-originator) is available (ie, 'winner-take-all').

In the EU5 (France, Germany, Italy, Spain and the UK), using a conservative budget impact model, the introduction of an etanercept biosimilar priced 10%–25% lower than bio-originator etanercept could yield net savings of €286 to €728 million over the subsequent 5 years.[39] Such savings could fund treatment with the biosimilar for many more patients. Presumably, the proportion of the cost of a biosimilar that is shared by the patient will be lower than that shared for a bio-originator. Thus, with more affordable drugs, patients may be more likely to adhere to their prescribed medication regimens. Moreover, in developing markets in which access to biologics is restricted by cost, the availability of a lower cost biosimilar might allow a patient to receive a treatment that previously was more difficult to obtain or unavailable. Thus, biosimilars should increase global access to effective treatments for inflammatory diseases.

Approved biosimilars can be used to treat appropriate patients in the same way as their bio-originators

Once a biosimilar has demonstrated high structural similarity and clinical equivalence to its bio-originator in a sensitive population and has been granted marketing authorisation, it can be considered to be essentially the same biologic as a new batch of the bio-originator. The finding of biosimilarity justifies use of an approved biosimilar in all the indications for which the bio-originator is authorised.

As no clinically significant differences in immunogenicity between biosimilars and their bio-originators have been detected, antidrug antibodies to biosimilars need not be measured in clinical practice

Antidrug antibodies (ADAs) typically develop in patients who are treated protractedly with biologics. Virtually all monoclonal antibodies induce an immune response with production of ADAs, often to the antigen-combining region (anti-idiotype antibodies).[40] ADAs bound to therapeutic monoclonal antibodies may form immune complexes which, when cleared by the reticuloendothelial system, result in lower trough drug concentrations and potentially decreased efficacy.[41] When the titre and affinity of ADAs for the biologic are high, the therapeutic effect is neutralised. Neutralising ADAs may be detected within 6 months after initial exposure to the biologic.[42]

Assays to detect ADAs have evolved over time to become more sensitive and specific.[41] Early studies of therapeutic monoclonal anti-TNF antibodies, using a bridging ELISA, identified ADAs in a small proportion of patients.[43] Subsequent studies have used assays that are less sensitive to drug interference, such as the homogeneous mobility shift assay method or the pH-shift anti-idiotype antigen-binding test, in which acid dissociation of drug–ADA complexes allows detection both of free ADAs and of those bound to drug.[44 45] In recent clinical trials, ADAs have been detected in a larger proportion of patients using the sensitive electrochemiluminescence bridging immunoassay.[46] However, the clinical relevance of ADAs, especially as to how they might differentiate biosimilars from their reference drugs, remains unclear.

The immunogenicity of a candidate biosimilar is best compared with that of its bio-originator in a clinical trial conducted in treatment-naïve patients.[12 47] These trials often have included a single crossover from the bio-originator to the candidate biosimilar. Thus far, such switches have not induced ADA formation. The proportion of subjects that develop ADAs to a biosimilar and to its bio-originator should be similar. Since neutralising ADAs are more clinically relevant, proportion of subjects developing these should also be reported.[48] If immunogenicity findings are to be extrapolated from a clinical trial in one disease to other indications, the patient population chosen for study should be that which is most likely to develop an immune response to the biologic.[12] Accordingly, patients not receiving concomitant immunosuppressive medications are preferred. However, in the clinical trials comparing the infliximab biosimilar CT-P13 with bio-originator infliximab, the prevalence of ADAs was higher in patients with rheumatoid arthritis receiving infliximab 3 mg/kg intravenously with concomitant methotrexate than in patients

with ankylosing spondylitis receiving infliximab 5 mg/kg as monotherapy.[21 46] Thus, genetic factors, the underlying disease process and the dose of the biologic administered may be more important than concomitant immunosuppressive medications in determining the predisposition to develop ADAs.

Although not typically measured in clinical practice by rheumatologists, trough drug concentrations provide a more relevant, indirect comparative assessment of immunogenicity between a biosimilar and its bio-originator than does detection of ADAs. As no clinically significant differences in immunogenicity between biosimilars and their bio-originators have been detected, ADAs to biosimilars need not be measured in clinical practice.[49 50] However, the assessment of immunogenicity should not be dismissed completely, as it is a useful measure for active pharmacovigilance. Evaluating comparative immunogenicity data, acquired in both clinical and postmarketing studies of biosimilars, should help to increase confidence in using biosimilars among healthcare providers.[51]

Relevant preclinical and phase I data on a biosimilar should be available when phase III data are published

As substantial emphasis has been placed on analytical and PK comparisons in the development of biosimilars, preclinical analytical data and phase 1 PK data should be available in peer-reviewed journals when data from phase III RCTs are published. Data from relevant physicochemical, in vitro functional and PK studies of a biosimilar should be published before or simultaneously with those from the phase III comparative effectiveness RCT. Physicochemical and in vitro functional data comparing the biosimilar with its bio-originator have been published in peer-reviewed journals for the infliximab biosimilar SB2, the etanercept biosimilars SB4 and GP 2015, and the adalimumab biosimilar ABP 501.[52–56] For the infliximab biosimilar CT-P13, selected physicochemical and in vitro functional data were published as supplementary data in appendices to the primary publications reporting the results of the phase I and phase III studies that compared CT-P13 with bio-originator infliximab.[21 46]

Phase I PK data comparing biosimilars with their bio-originators have usually been published in a peer-reviewed journal before or simultaneously with publication of the results of the phase III study in manuscript form. Results of the phase I PK study comparing ABP 501 with bio-originator adalimumab were published before publication of a manuscript reporting the phase III data.[18 57] Similarly, results of the phase I PK study comparing SB2 with bio-originator infliximab were published before the phase III study was published,[17 58] and results of the phase I PK study comparing SB4 with bio-originator etanercept were published before the phase III study was published.[19 59] The phase I and phase III studies comparing CT-P13 with bio-originator infliximab,[21 46] and those comparing GP2015 with bio-originator etanercept both were published simultaneously.[20 60] The availability of this information, when the phase III RCT data are published, facilitates assessment of biosimilarity based on a 'totality-of-the-evidence' approach.[61]

Since the biosimilar is equivalent to the bio-originator in its physicochemical, functional and pharmacokinetic properties, confirmation of efficacy and safety in a single indication is sufficient for extrapolation to other diseases for which the bio-originator has been approved

Based on the extensive historical clinical experience with the bio-originator in each of its licensed indications, regulatory agencies allow efficacy and safety data for a biosimilar to be extrapolated from one approved indication to others in which the biosimilar has not been studied, if the mechanism of action of the bio-originator is considered to be the same in each disease.[62 63] The comprehensive preclinical comparison of the biosimilar to its bio-originator, in which their similarity is confirmed by many different analytical and functional assays, forms the basis for this 'extrapolation of indications.' Thus, after having demonstrated efficacy and safety equivalent to its bio-originator in at least one RCT conducted in patients with a disease for which the bio-originator is authorised, a biosimilar may apply for approval in any or all indications for which its bio-originator already has been authorised without an RCT in each indication.

By this process, biosimilars have usually been granted marketing authorisation in all indications for which the bio-originator has been approved but in which the biosimilar has not been studied. In this context, experts from national and international organisations have argued that convincing data from RCTs are needed for each individual indication.[64–72] However, biosimilars have always demonstrated efficacy equivalent to that of their bio-originators when studied in more than one indication.[21 46 73 74] Also, the biosimilar infliximab, CT-P13, has exhibited efficacy and safety comparable to bio-originator infliximab in several small, prospective case series of patients with indications for which approval had been based on extrapolation of data from the RCTs.[75–78] Although Health Canada initially denied the biosimilar infliximab CT-P13 extrapolation of data from clinical trials conducted in patients with rheumatoid arthritis and ankylosing spondylitis to inflammatory bowel diseases, this decision was ultimately reversed by the same regulatory authority.[79] Nonetheless, biosimilars have demonstrated efficacy and safety when used in clinical practice to treat approved indications in which they had not been studied in comparison to their bio-originators.[78]

Currently available evidence indicates that a single switch from a bio-originator to one of its biosimilars is safe and effective; there is no scientific rationale to expect that switching among biosimilars of the same bio-originator would result in a different clinical outcome but patient perspectives must be considered

Switching patients from bio-originators to their biosimilars and from one biosimilar to another should be evidence-based. Current data suggest that treating a patient with an approved biosimilar should yield results comparable to those achieved when the patient is treated with the bio-originator. However, no study to date has evaluated the efficacy or safety of switching between different biosimilars of the same bio-originator.

Ideally, the consequences of switching from a bio-originator to a biosimilar should be compared with that of continued treatment with the bio-originator in an RCT, conducted in patients who are receiving stable treatment with the bio-originator. Extensions to phase III RCTs of several biosimilars, in which subjects treated initially with the bio-originator were switched to the biosimilar, have been published.[80–84] Observing no loss of efficacy and no increase in the rate of adverse events following this single switch supports making this switch in clinical practice, only if the biosimilar costs less than the bio-originator. However, if a patient has failed to respond to a specific biologic, a biosimilar of that product should not subsequently be prescribed.

An RCT was conducted in Norway to assess the effect of switching from bio-originator infliximab (Remicade) to the biosimilar infliximab CT-P13 on efficacy and safety in the various indications for which both had been approved. NOR-SWITCH was a 52-week, double blind, non-inferiority, phase IV RCT that

enrolled 482 patients with a variety of diseases: Crohn's disease (n=155), ulcerative colitis (n=93), spondyloarthritis (n=91), rheumatoid arthritis (n=78), psoriasis (n=35) and psoriatic arthritis (n=30), each of whom had been on stable treatment with bio-originator infliximab for at least 6 months.[78] The primary endpoint was worsening in disease-specific composite measures and/or agreement between the investigator and the patient that increased disease activity required a change in treatment by week 52. This study demonstrated non-inferiority of switching from the bio-originator to the biosimilar, using a non-inferiority margin of 15%, as compared with continuation of treatment with the bio-originator for the aggregate of subjects with the various diseases enrolled. However, NOR-SWITCH was not powered to compare these two treatment strategies in subjects with any individual disease. Similar proportions of patients in each group developed treatment-emergent adverse events (TEAEs), serious adverse events and TEAEs resulting in study drug discontinuation, and the prevalence and incidence of ADAs, as well as trough drugs levels, were similar between the two groups. Thus, NOR-SWITCH supports the practice of switching patients with stable disease activity from bio-originator infliximab to the biosimilar CT-P13. However, these results cannot be generalised to other biologics and their biosimilars or to frequent switching back-and-forth between bio-originator and biosimilar. For each new biosimilar and application device, an RCT should be conducted to evaluate safety and continued efficacy after switching from the bio-originator or to another biosimilar. However, once sufficient experience has been gained, additional switching studies may no longer be necessary.

Even if data from RCTs support the practice of switching from a bio-originator to its biosimilar or between biosimilars, patients must feel comfortable receiving the treatment that they have been prescribed. To achieve this, rheumatologists should inform patients about the rigorous development process during which biosimilars have been assessed and shown to be highly similar to their bio-originators. Patient perspectives must be taken into account. Patients should understand that an approved biosimilar may be like another batch of its bio-originator and should provide similar therapeutic benefit with comparable safety. They also should be informed about the economic implications of switching, which should allow more patients to benefit from treatment with biologics. However, if some patients remain uneasy about switching from the bio-originator to a biosimilar, even with this information, their preferences must be considered when making a therapeutic decision.

Multiple switching between biosimilars and their bio-originators or other biosimilars should be assessed in registries

Substitution, in which a biosimilar is prescribed in place of its bio-originator, must be distinguished from interchangeability, wherein someone other than the prescribing healthcare provider initiates the switch from bio-originator to biosimilar or between two biosimilars. Of note, in the EU, the term 'substitution' implies what is considered in the USA to be 'interchange'. Thus, terminology must be harmonised worldwide. In the EU, the EMA does not have the authority to designate a biosimilar as being interchangeable; rather, this judgement must be made by regulatory agencies in each Member State.[85]

To support the designation of interchangeability, an RCT that incorporates multiple switches between the two biologics must be conducted. The US FDA has issued draft guidance on demonstrating interchangeability of a biosimilar with its bio-originator, in which it suggests that postmarketing pharmacovigilance data should be combined with data from at least one prospective RCT that compares repeated switching between the bio-originator and the biosimilar to continuous treatment with the bio-originator.[86] Subjects in the 'switching arm' of such a study switch at least three times between the bio-originator and the biosimilar, whereas subjects in the 'non-switching arm' continue treatment with only the bio-originator. After the last switch from the bio-originator to the biosimilar, subjects in the 'switching arm' should remain on the biosimilar. The primary endpoints for such a study should be PK parameters; secondary endpoints should evaluate efficacy, safety and immunogenicity. However, to date, no biosimilar has been evaluated according to this study design.

Systematic postmarketing pharmacovigilance should be carried out using biologics registries and by conducting long-term, observational cohort studies to which data are reported regularly by prescribing healthcare providers and patients who are treated with specific products. Biologics registries in many countries have provided insight into the short-term and long-term safety of biologics.[87–93] Data collected about the use of biosimilars should be integrated into these existing biologics registries. Pertinent standardised data must be collected to address any remaining uncertainty regarding the safety of biosimilars. Although not designed primarily to assess efficacy, the durability or potential loss of efficacy after switching from a bio-originator to its biosimilar might become evident in such a registry.

No switch to or among biosimilars should be initiated without the prior awareness of the patient and the treating healthcare provider

Patients with rheumatological diseases may be reluctant to switch medications, even when their disease remains active, because of fear of disease worsening or of developing an adverse effect on a new medication.[94] However, the concern that therapeutic efficacy might be lost after switching from a bio-originator to its biosimilar has not been supported by currently available data.

In the EU, the introduction of infliximab and etanercept biosimilars has generated market competition, which has resulted in price reductions for their reference products and for the other bio-originator TNF inhibitors.[38] Patients and their healthcare providers share the responsibility to consider equity when choosing a course of treatment and must consider cost in the decision-making process. However, in some countries, the choice of biologic is often imposed by payers rather than being made by either the patient or his or her treating healthcare provider.

Transparency is of utmost importance in the therapeutic relationship between a patient and his or her healthcare provider. Therapeutic decisions must be made jointly by the patient in consultation with the healthcare provider. As with all changes in treatment, the patient and the healthcare provider should be fully aware of any change and should agree with its implementation.

CONCLUSION

The differing opinions about biosimilars that have been published by various national and international medical subspecialty organisations illustrate the lack of confidence shared by many clinicians regarding the appropriate use of biosimilars.[64–72 95–98] However, a rapidly growing body of evidence has begun to reduce residual uncertainty about their use. This consensus statement aims to raise awareness about biosimilars and to discuss the key issues that healthcare providers must consider when using biosimilars to treat their patients. The assembled group of experts and patients achieved a high level of agreement about the evaluation of biosimilars and their use to treat rheumatological diseases.

The participants were confident that biosimilars approved by authorities in a highly regulated area are unlikely to differ from their bio-originators in clinically meaningful ways. Nevertheless, given the complex nature of all biopharmaceuticals, the treating clinician must be the only one to decide whether to prescribe a biosimilar in place of a bio-originator on a case-by-case basis with full awareness of the patient. The group believed that adequate evidence exists to support the decision to switch from a biologic, which no longer is protected by patent, to its biosimilar. In addition, the group concluded that there is sufficient evidence about safety and efficacy of biosimilars to allow for extrapolation of indications. However, there remained concern about switching between two biosimilars or between a bio-originator and its biosimilar on multiple occasions because adequate studies have not yet been conducted to assess these circumstances. To facilitate making informed decisions about therapeutic substitution with biosimilars, healthcare providers are encouraged to gather pharmacovigilance data in registries about the outcome of such switches made in the context of clinical practice. Data available as of December 2016 support the use of biosimilars by rheumatologists to encourage a fair and competitive market for biologics. Biosimilars now provide an opportunity to expand access to effective but expensive medications, increasing the number of available treatment choices and helping to control rapidly increasing drug expenditures.

Author affiliations
[1]Division of Rheumatology, Department of Medicine, UMass Memorial Medical Center and University of Massachusetts Medical School, Worcester, Massachusetts, USA
[2]Department of Internal Medicine, Centre for Rheumatic Diseases, Hietzing Hospital, Vienna, Austria
[3]Department of Medicine/Rheumatology and Clinical Immunology, Charité Universitätsmedizin and Deutsches Rheumaforschungszentrum (DRFZ), Berlin, Germany
[4]Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Chapel Allerton Hospital, Leeds, UK
[5]Department of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway
[6]Division of Rheumatology, Department of Medicine 3, Medical University of Vienna, Vienna, Austria
[7]Department of Rheumatology, Leiden University Medical Center, Leiden, The Netherlands

Correction notice This article has been corrected since it published Online First. The collaborators statement has been added.

Collaborators Members of the Task Force on the Use of Biosimilars to Treat Rheumatologic Diseases: Johannes W J Bijlsma, Jürgen Braun, Vivian P Bykerk, Silvio Danese, Maarten P T de Wit, João Goncalves, Tom W J Huizinga, John D Isaacs, Arthur F Kavanaugh, Pekka Kurki, Thomas A Luger, Ulf Müller-Ladner, Karel Pavelkam, Huub Schellekens, Anja Strangfeld, Tsutomu Takeuchi, Marieke Voshaar and Michael H Weisman.

Contributors MMS performed the systematic literature review. JK drafted the manuscript with advice from FCB, TD, PE, TKK and JSS. FCB, TD, PE, JK, TKK and JSS were involved in conceiving the study. All authors were involved in analysing and interpreting data and in producing the recommendations, and all have reviewed and approved the final manuscript.

Funding This study was funded by an unrestricted educational grant from Amgen.

Competing interests JK has received research grants paid to his institution from AbbVie, Eli Lilly and Company, Genentech, Pfizer and UCB, and has provided expert advice to AbbVie, Amgen, Boehringer Ingelheim, Bristol-Myers Squibb Company, Crescendo Bioscience, Eli Lilly and Company, Epirus Biopharmaceuticals, Merck Sharp & Dohme, Pfizer, Samsung Bioepis, Sandoz, Roche Laboratories and UCB. TD has received research grants or iDMC honoraria paid to his institution from AbbVie, Ablynx, AstraZeneca, Bristol-Myers Squibb Company, Celgene, GlaxoSmithKline, Samsung Bioepis, Roche Laboratories, Sanofi and UCB, and has provided expert advice to and/or had speaking engagements for AbbVie, Ablynx, Amgen, AstraZeneca, Biogen, Bristol-Myers Squibb Company, Celgene, Epirus Biopharmaceuticals, GlaxoSmithKline, Merck Sharp & Dohme, Pfizer/Hospira, Samsung Bioepis, Roche Laboratories, Sanofi and UCB. PE has received research grants paid to his institution from and has provided expert advice to AbbVie, Bristol-Myers Squibb Company, Eli Lilly and Company, Merck Sharp & Dohme, Novartis, Pfizer, Samsung Bioepis, Sandoz, Roche Laboratories and UCB. TKK has received research grants paid to his institution from AbbVie, Bristol-Myers Squibb Company, Merck Sharp & Dohme, Pfizer/Wyeth, Roche Laboratories and UCB, and has provided expert advice to and/or had speaking engagements for AbbVie, Amgen, Biogen, Bristol-Myers Squibb Company, Celltrion Healthcare, Epirus Biopharmaceuticals, Merck Serono SA, Merck Sharp & Dohme, Mundipharma, Orion, Pfizer/Hospira, Pfizer/Wyeth, Samsung Bioepis, Sandoz, Roche Laboratories and UCB. JSS has received research grants paid to his institution from AbbVie, Eli Lilly and Company, Janssen Biotech, Merck Sharp & Dohme, Pfizer and Roche Laboratories, and has provided expert advice to and/or had speaking engagements for AbbVie, Amgen, AstraZeneca, Astro; Bristol-Myers Squibb Company, Celgene, Celltrion Healthcare, Chugai, Eli Lilly and Company, Gilead, GlaxoSmithKline, ILTOO, Janssen Biotech, Medimmune, MSD, Novartis-Sandoz, Pfizer, Roche Laboratories, Samsung Bioepis, Sanofi and UCB. FCB has provided expert advice to and/or had speaking engagements for AbbVie, Amgen, Epirus Biopharmaceuticals, Merck Sharp & Dohme and Pfizer.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Kay J. Biosimilars: a regulatory perspective from America. *Arthritis Res Ther* 2011;13:112.
2 Kay J, Feagan BG, Guirguis MS, *et al*. Health Canada/BIOTECanada Summit on regulatory and clinical topics related to subsequent entry biologics (biosimilars), Ottawa, Canada, 14 May 2012. *Biologicals* 2012;40:517–27.
3 Scheinberg MA, Kay J. The advent of biosimilar therapies in rheumatology--"O brave new world". *Nat Rev Rheumatol* 2012;8:430–6.
4 Dörner T, Strand V, Castañeda-Hernández G, *et al*. The role of biosimilars in the treatment of rheumatic diseases. *Ann Rheum Dis* 2013;72:322–8.
5 Dörner T, Kay J. Biosimilars in rheumatology: current perspectives and lessons learnt. *Nat Rev Rheumatol* 2015;11:713–24.
6 Dörner T, Strand V, Cornes P, *et al*. The changing landscape of biosimilars in rheumatology. *Ann Rheum Dis* 2016;75:974–82.
7 OCEBM Levels of Evidence Working Group. Oxford Centre for Evidence-based Medicine – Levels of Evidence (March 2009). 2009 http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/ (accessed 18 Jul 2017).
8 The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. ICH official website. 2017 http://www.ich.org/ (accessed 28 Jan 2017).
9 Committee for Medicinal Products for Human Use. Guideline on similar biological medicinal products. 2014 http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/10/WC500176768.pdf (accessed 20 Nov 2016).
10 Biologics Price Competition and Innovation Act of 2009. *United States Code. 111th Congress*. 2nd Session edn. United States, 2010:804–21.
11 Committee for Medicinal Products for Human Use. Guideline on similar biological medicinal products. 2005 http://www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003517.pdf (accessed 20 Nov 2016).
12 US Food & Drug Administration. Guidance for industry. Scientific considerations in demonstrating biosimilarity to a reference product. 2015 http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf (accessed 22 Jun 2016).
13 Committee for Medicinal Products for Human Use. Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues. 2014 http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/01/WC500180219.pdf (accessed 10 Nov 2016).
14 Gu N, Yi S, Kim TE, *et al*. Comparative pharmacokinetics and tolerability of branded etanercept (25 mg) and its biosimilar (25 mg): a randomized, open-label, single-dose, two-sequence, crossover study in healthy Korean male volunteers. *Clin Ther* 2011;33:2029–37.
15 Yi S, Kim SE, Park MK, *et al*. Comparative pharmacokinetics of HD203, a biosimilar of etanercept, with marketed etanercept (Enbrel®): a double-blind, single-dose, crossover study in healthy volunteers. *BioDrugs* 2012;26:177–84.
16 Park W, Lee SJ, Yun J, *et al*. Comparison of the pharmacokinetics and safety of three formulations of infliximab (CT-P13, EU-approved reference infliximab and the US-licensed reference infliximab) in healthy subjects: a randomized, double-blind, three-arm, parallel-group, single-dose, Phase I study. *Expert Rev Clin Immunol* 2015;11(Suppl 1):25–31.
17 Shin D, Kim Y, Kim YS, *et al*. A randomized, Phase I pharmacokinetic study comparing SB2 and Infliximab reference product (Remicade(®)) in healthy subjects. *BioDrugs* 2015;29:381–8.
18 Kaur P, Chow V, Zhang N, *et al*. A randomised, single-blind, single-dose, three-arm, parallel-group study in healthy subjects to demonstrate pharmacokinetic equivalence of ABP 501 and adalimumab. *Ann Rheum Dis* 2017;76:526–33.

19 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.
20 von Richter O, Skerjanec A, Afonso M, *et al*. GP2015, a proposed etanercept biosimilar: Pharmacokinetic similarity to its reference product and comparison of its autoinjector device with prefilled syringes. *Br J Clin Pharmacol* 2017;83:732–41.
21 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.
22 Takeuchi T, Yamanaka H, Tanaka Y, *et al*. Evaluation of the pharmacokinetic equivalence and 54-week efficacy and safety of CT-P13 and innovator infliximab in Japanese patients with rheumatoid arthritis. *Mod Rheumatol* 2015;25:817–24.
23 Cohen S, Emery P, Greenwald M, *et al*. A phase I pharmacokinetics trial comparing PF-05280586 (a potential biosimilar) and rituximab in patients with active rheumatoid arthritis. *Br J Clin Pharmacol* 2016;82:129–38.
24 Yoo DH, Suh CH, Shim SC, *et al*. A multicentre randomised controlled trial to compare the pharmacokinetics, efficacy and safety of CT-P10 and innovator rituximab in patients with rheumatoid arthritis. *Ann Rheum Dis* 2017;76:566–70.
25 Kay J, Smolen JS. Biosimilars to treat inflammatory arthritis: the challenge of proving identity. *Ann Rheum Dis* 2013;72:1589–93.
26 Rutherford AI, Galloway JB. Biosimilars in rheumatology: out of the laboratory and into practice. *Expert Rev Clin Immunol* 2016;12:697–9.
27 Kay J, Isaacs JD. Clinical trials of biosimilars should become more similar. *Ann Rheum Dis* 2017;76:4–6.
28 World Health Organization Programme on International Nonproprietary Names (INN). Biological qualifier: An INN proposal. 2014 http://www.who.int/medicines/services/inn/bq_innproposal201407.pdf (accessed 18 Nov 2016).
29 US Food & Drug Administration. Guidance for industry: Nonproprietary naming of biological products. 2017 http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM459987.pdf (accessed 27 Jan 2017).
30 Hoebert J, Laing R, Stephens P. *The world medicines situation 2011: pharmaceutical consumption*. Geneva, Switzerland: World Health Organization, 2011:1–17.
31 MacDougall D, Crowell K, Prager S, *et al*. IMS health white paper: biosimilars: who saves? 2016 https://structurecms-staging-psyclone.netdna-ssl.com/client_assets/dwonk/media/attachments/57dc/387d/6970/2d6c/ad6f/0000/57dc387d69702d6cad6f0000.pdf?1474050173 (accessed 25 Feb 2017).
32 Mulcahy AW, Predmore Z, Mattke S. The cost savings potential of biosimilar drugs in the United States. Perspectives. 2014 http://www.rand.org/pubs/perspectives/PE127.html (accessed 18 Nov 2016).
33 Raedler LA, Zarxio RLA. Zarxio (Filgrastim-sndz): First Biosimilar Approved in the United States. *Am Health Drug Benefits* 2016;9:150–4.
34 Pfizer IncPfizer announces the U.S. availability of biosimilar INFLECTRA® (infliximab-dyyb). Company to begin shipping to wholesalers in late November, 2016Pfizer Inc, 2016 New York, NY. http://www.pfizer.com/news/press-release/press-release-detail/pfizer_announces_the_u_s_availability_of_biosimilar_inflectra_infliximab_dyyb (accessed 7 Jan 2017).
35 Canadian Drug Expert Committee. CDEC final recommendation: Infliximab (Inflectra - Hospia Healthcare Corporation). Common Drug Review. 2014 https://www.cadth.ca/media/cdr/complete/cdr_complete_SE0384_Inflectra_Dec-23-14.pdf (accessed 7 Jan 2017).
36 Haustein R, *et al*. Saving money in the European healthcare systems with biosimilars. *GaBI J* 2012;1:120–6.
37 Mack A. Norway, biosimilars in different funding systems. What works? *GaBI J* 2015;4:90–2.
38 IMS Health. *The impact of biosimilar competition*. London, UK: IMS Health Inc., 2016:1–30.
39 Ruff L, Rezk MF, Uhlig T, *et al*. Budget impact analysis of an etanercept biosimilar for the treatment of all licensed etanercept indications for adults in Europe. *Value Health* 2015;18:A639.
40 van Schouwenburg PA, van de Stadt LA, de Jong RN, *et al*. Adalimumab elicits a restricted anti-idiotypic antibody response in autoimmune patients resulting in functional neutralisation. *Ann Rheum Dis* 2013;72:104–9.
41 van Schouwenburg PA, Rispens T, Wolbink GJ. Immunogenicity of anti-TNF biologic therapies for rheumatoid arthritis. *Nat Rev Rheumatol* 2013;9:164–72.
42 Bartelds GM, Krieckaert CL, Nurmohamed MT, *et al*. Development of antidrug antibodies against adalimumab and association with disease activity and treatment failure during long-term follow-up. *JAMA* 2011;305:1460–8.
43 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.
44 van Schouwenburg PA, Krieckaert CL, Rispens T, *et al*. Long-term measurement of anti-adalimumab using pH-shift-anti-idiotype antigen binding test shows predictive value and transient antibody formation. *Ann Rheum Dis* 2013;72:1680–6.
45 Wang S-L, Hauenstein S, Ohrmund L, *et al*. Monitoring of adalimumab and antibodies-to-adalimumab levels in patient serum by the homogeneous mobility shift assay. *J Pharm Biomed Anal* 2013;78-79:39–44.
46 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.
47 Committee for Medicinal Products for Human Use. Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues. 2012 https://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500128686.pdf (accessed 20 Nov 2016).
48 Shankar G, Devanarayan V, Amaravadi L, *et al*. Recommendations for the validation of immunoassays used for detection of host antibodies against biotechnology products. *J Pharm Biomed Anal* 2008;48:1267–81.
49 Ben-Horin S, Yavzori M, Benhar I, *et al*. Cross-immunogenicity: antibodies to infliximab in Remicade-treated patients with IBD similarly recognise the biosimilar Remsima. *Gut* 2016;65:1132–8.
50 Ruiz-Argüello MB, Maguregui A, Ruiz Del Agua A, *et al*. Antibodies to infliximab in Remicade-treated rheumatic patients show identical reactivity towards biosimilars. *Ann Rheum Dis* 2016;75:1693–6.
51 Gonçalves J, Araújo F, Cutolo M, *et al*. Biosimilar monoclonal antibodies: preclinical and clinical development aspects. *Clin Exp Rheumatol* 2016;34:698–705.
52 Hong J, Lee Y, Lee C, *et al*. Physicochemical and biological characterization of SB2, a biosimilar of Remicade® (infliximab). *MAbs* 2017;9:365–83.
53 Cho IH, Lee N, Song D, *et al*. Evaluation of the structural, physicochemical, and biological characteristics of SB4, a biosimilar of etanercept. *MAbs* 2016;8:1136–55.
54 Hofmann HP, Kronthaler U, Fritsch C, *et al*. Characterization and non-clinical assessment of the proposed etanercept biosimilar GP2015 with originator etanercept (Enbrel(®)). *Expert Opin Biol Ther* 2016;16:1185–95.
55 Liu J, Eris T, Li C, *et al*. Assessing analytical similarity of proposed Amgen biosimilar ABP 501 to adalimumab. *BioDrugs* 2016;30:321–38.
56 Velayudhan J, Chen YF, Rohrbach A, *et al*. Demonstration of functional similarity of proposed biosimilar ABP 501 to adalimumab. *BioDrugs* 2016;30:339–51.
57 Cohen S, Genovese MC, Choy E, *et al*. Efficacy and safety of the biosimilar ABP 501 compared with adalimumab in patients with moderate to severe rheumatoid arthritis: a randomised, double-blind, phase III equivalence study. *Ann Rheum Dis* 2017:annrheumdis-2016-210459.
58 Choe JY, Prodanovic N, Niebrzydowski J, *et al*. A randomised, double-blind, phase III study comparing SB2, an infliximab biosimilar, to the infliximab reference product Remicade in patients with moderate to severe rheumatoid arthritis despite methotrexate therapy. *Ann Rheum Dis* 2017;76:58–64.
59 Emery P, Vencovský J, Sylwestrzak A, *et al*. A phase III randomised, double-blind, parallel-group study comparing SB4 with etanercept reference product in patients with active rheumatoid arthritis despite methotrexate therapy. *Ann Rheum Dis* 2017;76:51–7.
60 Griffiths CEM, Thaçi D, Gerdes S, *et al*. The EGALITYch study: a confirmatory, randomized, double-blind study comparing the efficacy, safety and immunogenicity of GP2015, a proposed etanercept biosimilar, vs. the originator product in patients with moderate-to-severe chronic plaque-type psoriasis. *Br J Dermatol* 2017;176:928–38.
61 Kozlowski S, Woodcock J, Midthun K, *et al*. Developing the nation's biosimilars program. *N Engl J Med* 2011;365:385–8.
62 US Food & Drug Administration. Guidance for industry. Biosimilars: questions and answers regarding implementation of the Biologics Price Competition and Innovation Act of 2009. 2015 http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm444661.pdf (accessed 31 Oct 2016).
63 Committee for Medicinal Products for Human Use. Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues. 2006 http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003920.pdf (accessed 20 Nov 2016).
64 Argüelles-Arias F, Barreiro-de-Acosta M, Carballo F, *et al*. Joint position statement by "Sociedad Española de Patología Digestiva" (Spanish Society of Gastroenterology) and "Sociedad Española de Farmacología" (Spanish Society of Pharmacology) on biosimilar therapy for inflammatory bowel disease. *Rev Esp Enferm Dig* 2013;105:37–43.
65 Danese S, Gomollon F. Governing Board and Operational Board of ECCO. ECCO position statement: the use of biosimilar medicines in the treatment of inflammatory bowel disease (IBD). *J Crohns Colitis* 2013;7:586–9.
66 Gecse KB, Khanna R, van den Brink GR, *et al*. Biosimilars in IBD: hope or expectation? *Gut* 2013;62:803–7.
67 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.
68 Fiorino G, Danese S. The biosimilar road in inflammatory bowel disease: the right way? *Best Pract Res Clin Gastroenterol* 2014;28:465–71.
69 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.
70 Hlavaty T, Letkovsky J. Biosimilars in the therapy of inflammatory bowel diseases. *Eur J Gastroenterol Hepatol* 2014;26:1–587.
71 Schreiber S, Luger T, Mittendorf T, *et al*. [Evolution of biologicals in inflammation medicine--biosimilars in gastroenterology, rheumatology and dermatology]. *Dtsch Med Wochenschr* 2014;139:2399–404.
72 Committee on Rheumatologic Care. American College of Rheumatology position statement: Biosimilars. 2016 http://www.rheumatology.org/Portals/0/Files/Biosimilars-Position-Statement.pdf (accessed 20 Nov 2016).
73 Cohen SB, Genovese MC, Choy EH, *et al*. Randomized, double-blind, Phase 3 study of efficacy and safety of ABP 501 compared with adalimumab in subjects with moderate to severe rheumatoid arthritis [abstract]. *Arthritis Rheumatol* 2015;67(suppl 10() http://acrabstracts.org/abstract/randomized-double-blind-phase-3-study-of-efficacy-and-safety-of-abp-501-compared-with-adalimumab-in-subjects-with-moderate-to-severe-rheumatoid-arthritis/.
74 Papp K, Bachelez H, Costanzo A, *et al*. Clinical similarity of biosimilar ABP 501 to adalimumab in the treatment of patients with moderate to severe plaque psoriasis: A randomized, double-blind, multicenter, phase III study. *J Am Acad Dermatol* 2017;76:1093–102.
75 Nikiphorou E, Kautiainen H, Hannonen P, *et al*. Clinical effectiveness of CT-P13 (Infliximab biosimilar) used as a switch from Remicade (infliximab) in patients with established rheumatic disease. Report of clinical experience based on prospective observational data. *Expert Opin Biol Ther* 2015;15:1677–83.
76 Benucci M, Gobbi FL, Bandinelli F, *et al*. Safety, efficacy and immunogenicity of switching from innovator to biosimilar infliximab in patients with spondyloarthritis: a 6-month real-life observational study. *Immunol Res* 2017;65:419-422.
77 Gentileschi S, Barreca C, Bellisai F, *et al*. Switch from infliximab to infliximab biosimilar: efficacy and safety in a cohort of patients with different rheumatic diseasesResponse to: Nikiphorou E, Kautiainen H, Hannonen P, et al. Clinical effectiveness of CT-P13 (Infliximab biosimilar) used as a switch from Remicade (infliximab) in patients with established rheumatic disease. Report of clinical experience based on prospective observational data. Expert Opin Biol Ther. 2015;15:1677-1683. *Expert Opin Biol Ther* 2016;16:1311–2.
78 Jørgensen KK, Olsen IC, Goll GL, *et al*. Switching from originator infliximab to biosimilar CT-P13 compared with maintained treatment with originator infliximab (NOR-SWITCH): a 52-week, randomised, double-blind, non-inferiority trial. *Lancet* 2017;389:2304–16.
79 Health Canada. Regulatory decision summary INFLECTRA. 2016 http://www.hc-sc.gc.ca/dhp-mps/prodpharma/rds-sdr/drug-med/rds-sdr-infectra-184564-eng.php (accessed 29 Sep 2016).
80 Kay J, Wyand M, Chandrashekara S, *et al*. BOW015, a biosimilar infliximab, in patients with active rheumatoid arthritis on stable methotrexate doses: 54-week results of a randomized, double-blind, active comparator study [abstract]. *Arthritis Rheumatol* 2014;66:3538.
81 Weinblatt ME, Baranauskaite A, Niebrzydowski J, *et al*. Sustained efficacy and comparable safety and immunogenicity after transition to SB5 (an adalimumab biosimilar) vs. continuation of SB5 or reference adalimumab (Humira®) in patients with rheumatoid arthritis: Results of phase III study [abstract]. 2016 http://acrabstracts.org/abstract/sustained-efficacy-and-comparable-safety-and-immunogenicity-after-transition-to-sb5-an-adalimumab-biosimilar-vs-continuation-of-sb5-or-reference-adalimumab-humira-in-patients-with-rheumatoi/ (accessed 7 Jan 2017).
82 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.
83 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.
84 Emery P, Vencovský J, Sylwestrzak A, *et al*. Long-term efficacy and safety in patients with rheumatoid arthritis continuing on SB4 or switching from reference etanercept to SB4. *Ann Rheum Dis* 2017:annrheumdis-2017-211591.
85 Thimmaraju PK, Rakshambikai R, Farista R, *et al*. Legislations on biosimilar interchangeability in the US and EU – developments far from visibility. GaBI Online - Generics and Biosimilars Initiative 2015. 2015 http://www.gabionline.net/Sponsored-Articles/Legislations-on-biosimilar-interchangeability-in-the-US-and-EU-developments-far-from-visibility (accessed 20 Nov 2016).
86 Food US, Administration D. Guidance for industry: Considerations in demonstrating interchangeability with a reference product, draft guidance. 2017 http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM537135.pdf?source=govdelivery&utm_medium=email&utm_source=govdelivery (accessed 17 Jan 2017).
87 Gómez-Reino JJ, Carmona L, Angel Descalzo M, *et al*. Risk of tuberculosis in patients treated with tumor necrosis factor antagonists due to incomplete prevention of reactivation of latent infection. *Arthritis Rheum* 2007;57:756–61.
88 Askling J, van Vollenhoven RF, Granath F, *et al*. Cancer risk in patients with rheumatoid arthritis treated with anti-tumor necrosis factor alpha therapies: does the risk change with the time since start of treatment? *Arthritis Rheum* 2009;60:3180–9.
89 Greenberg JD, Reed G, Kremer JM, *et al*. Association of methotrexate and tumour necrosis factor antagonists with risk of infectious outcomes including opportunistic infections in the CORRONA registry. *Ann Rheum Dis* 2010;69:380–6.
90 Salmon-Ceron D, Tubach F, Lortholary O, *et al*. Drug-specific risk of non-tuberculosis opportunistic infections in patients receiving anti-TNF therapy reported to the 3-year prospective French RATIO registry. *Ann Rheum Dis* 2011;70:616–23.
91 Sakai R, Komano Y, Tanaka M, *et al*. Time-dependent increased risk for serious infection from continuous use of tumor necrosis factor antagonists over three years in patients with rheumatoid arthritis. *Arthritis Care Res* 2012;64:1125–34.
92 Zink A, Manger B, Kaufmann J, *et al*. Evaluation of the RABBIT Risk Score for serious infections. *Ann Rheum Dis* 2014;73:1673–6.
93 Mercer LK, Galloway JB, Lunt M, *et al*. BSRBR Control Centre Consortium. Risk of lymphoma in patients exposed to antitumour necrosis factor therapy: results from the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis. *Ann Rheum Dis* 2017;76:497–503.
94 Wolfe F, Michaud K. Resistance of rheumatoid arthritis patients to changing therapy: discordance between disease activity and patients' treatment choices. *Arthritis Rheum* 2007;56:2135–42.
95 Fonseca JE, Gonçalves J, Araújo F, *et al*. The Portuguese Society of Rheumatology position paper on the use of biosimilars. *Acta Reumatol Port* 2014;39:60–71.
96 Abad Hernández MÁ, Andreu JL, Caracuel Ruiz MÁ, *et al*. Position paper from the Spanish Society of Rheumatology on biosimilar drugs. *Reumatol Clin* 2015;11:269–78.
97 Azevedo VF, Meirelles ES, Kochen JA, *et al*. Recommendations on the use of biosimilars by the Brazilian Society of Rheumatology, Brazilian Society of Dermatology, Brazilian Federation of Gastroenterology and Brazilian Study Group on Inflammatory Bowel Disease--Focus on clinical evaluation of monoclonal antibodies and fusion proteins used in the treatment of autoimmune diseases. *Autoimmun Rev* 2015;14:769–73.
98 British Society for Rheumatology. Position statement on biosimilar medicines (Revised January 2017). 2017 http://www.rheumatology.org.uk/includes/documents/cm_docs/2017/r/revised_bsr_biosimilars_position_statement_jan_2017.pdf (accessed 14 Mar 2017).

Consensus-based recommendations for the use of biosimilars to treat rheumatological diseases

Jonathan Kay, Monika M Schoels, Thomas Dörner, Paul Emery, Tore K Kvien, Josef S Smolen and Ferdinand C Breedveld

Ann Rheum Dis published online September 2, 2017