An Update on Biosimilars in Rheumatic and Musculoskeletal Disorders

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DOI: https://doi.org/10.17925/RMD.2023.2.1.46

Biosimilars contain a version of the active substance of an approved biologic medicine. They were introduced several years ago; the first biosimilar was approved by the European Medicine Agency in 2006. They are now commonly used to treat several immune-mediated conditions, and large evidence-based national and international guidelines support their use. Biosimilars are licensed for use after going through a comprehensive approval process to demonstrate clinical equivalence to the reference biologic in at least one randomized controlled trial. Once biosimilarity is demonstrated in one indication, this can be used to approve the drug for other indications if the mechanism of action is the same across different indications. Biosimilars do not have any clinically meaningful differences from the originator medicine in terms of quality, safety and efficacy but have a cost-saving benefit. NHS England supports the use of biosimilars, stating that clinicians should use the best-value biological product, including biosimilars. In 2021, the National Institute for Health and Care Excellence lowered the biologic eligibility criteria for rheumatoid arthritis by recommending the use of anti-tumour necrosis factor medications with licensed biosimilars for treating moderate rheumatoid arthritis after conventional disease-modifying anti-rheumatic drugs have failed. This recommendation has enabled more patients to access advanced therapy at an earlier stage of the disease, thus potentially increasing the likelihood of inducing remission and limiting disease progression.

Keywords

Biologics, biosimilars, cost effectiveness, efficacy, guidelines, rheumatic diseases, rheumatoid arthritis, safety

Disclosures: Christopher Holroyd has received honoraria and/or been a member of the advisory boards for: Abbvie, BMS, Celltrion, Chugai, Galapagos/Gilead, Janssen, Lilly, Napp, Novartis, Pfizer and UCB. Mariam Malik has no financial or non-financial relationships or activities to declare in relation to this article.

Review process: Double-blind peer review.

Data availability: Data sharing is not applicable to this article as no datasets were generated or analysed during the writing of this article.

Compliance with ethics: This article involves a review of the literature and did not involve any studies with human or animal subjects performed by any of the authors.

Authorship: The named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship of this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval for the version to be published.

Received: 5 April 2023

Accepted: 1 June 2023

Published online: 7 July 2023

Citation: *touchREVIEWS in RMD.* 2023;2(1):46–49

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Support: No funding was received in the publication of this article.

Biologics are medications derived from biological sources used to treat several immune-mediated inflammatory diseases. These medications interfere with autoimmune processes by inhibiting specific molecular or cellular targets. They are highly effective medications, mostly used in cases of moderate-to-severe disease activity. As such, biologics have revolutionized the treatment of and transformed outcomes for patients with rheumatological conditions, including rheumatoid arthritis,[1] psoriatic arthritis,[2] spondyloarthritis[3] and systemic lupus erythematosus.[4]

Biosimilar medicines contain a version of the active substance of an approved biological medicinal product, known as the reference product.[5] They are made by or derived from a biological source. Biosimilars include monoclonal antibodies, soluble receptors, growth factors and hormones. They do not meaningfully differ from the reference product in terms of quality, safety and efficacy, and they are more cost effective.[6,7] Biosimilars can be up to 70% less expensive than the originator biological medicine.[8]

The history of biosimilars

The first biosimilar medicine was a human recombinant growth hormone named somatropin (Omnitrope®; Sandoz Inc., Princeton, NJ, USA), which was approved in Europe by the European Medicines Agency (EMA) in 2006.[9] The first biosimilar medicines used in rheumatology, Remsima® (Celltrion Healthcare, Oncheon, Korea) in Europe and Inflectra™ (Pfizer, New York, NY, USA) in the USA (prior to marketing the biosimilar was called CT-P13), are biosimilars to infliximab used to treat rheumatoid arthritis.[10] These medications were introduced to the UK in 2015.[10] Since then, several biosimilar medicines have been introduced and successfully used to treat many conditions. Currently, 76 biosimilars are approved for use in Europe by the EMA.[11]

The approval process for biosimilars

Biosimilars are thoroughly evaluated before approval; they are tested to demonstrate clinical equivalence/biosimilarity to the reference biologic in at least one randomized controlled trial.[12,13] The approval process is comprehensive, and the EMA's scientific committees evaluate the authorization for biosimilar medicines before they can be approved.[14–16] Biosimilars are evaluated according to the same standards of quality, safety and efficacy that apply to all biologic medicines. They can only be authorized once the period of data exclusivity on the reference biologic medicine has expired, meaning that the particular biologic must have been authorized for at least 8 years before another company can apply for approval of a biosimilar medicine.[7] When biosimilarity is demonstrated in one indication, this can be used to approve the biosimilar for other indications, provided that the mechanism of action is the same across different indications; this scientific principle is called extrapolation.[17]

Table 1: Rheumatology biosimilars currently approved by the European Medicines Agency

Biologic medication	Mode of action	Approved biosimilar
Infliximab	Anti-TNFα	Flixabi™ (Biogen Inc., Cambridge, MA, USA), Inflectra™ (Pfeizer, New York, NY, USA)/Remsima® (Celltrion, Inc., Incheon, South Korea), Zessly® (Novartis, Basel, Switzerland)
Adalimumab	Anti-TNFα	AMJEVITA™ (Amgen, Thousand Oaks), Amsparity, Hefiya, Hukyndra, Hulio, Hyrimoz, Idacio, Imraldi, Libmyris, Yuflyma
Etanercept	Anti-TNFα	Benepali, Erelzi, Nepexto
Rituximab	Anti-CD20	Blitzima, Rixathon, Riximyo, Ruxience, Truxima
Teriparatide	Recombinant formulation of endogenous PTH	Movymia, Mvasi, Sondelbay, Terrosa
Tocilizumab	Anti-IL-6R	EMA has recently accepted the Marketing Authorization Application for BIIB800 (tocilizumab biosimilar)[32]

EMA = European Medicines Agency; IL-6R = interleukin 6 receptor; PTH = parathyroid hormone; TNF = tumour necrosis factor.

History of biosimilar use in rheumatology

In 2013, the first biosimilar was approved for use in rheumatology by EMA: Remsima/Inflectra, a biosimilar of infliximab.[18,19] Two initial studies were undertaken to gain approval: the PLANETRA (ClinicalTrials.gov identifier: NCT01217086) and PLANETAS (ClinicalTrials.gov identifier: NCT01220518) studies.[20,21] PLANETRA, a randomized, double-blind study investigating the efficacy and safety of the biosimilar compared with the innovator infliximab in patients with active rheumatoid arthritis, found that the biosimilar demonstrated equivalent efficacy and safety to the originator infliximab when given with methotrexate.[20] The biosimilar was well tolerated and was equally effective at week 30 compared with reference infliximab, with a similar safety profile to the originator.[20] The PLANETAS study compared the pharmacokinetics, safety and efficacy of Remsima/Inflectra and originator infliximab in patients with ankylosing spondylitis, showing similar safety and efficacy for the two drugs up to week 30.[21]

Biosimilar preparations of infliximab were subsequently followed by biosimilars for etanercept (2016),[22] rituximab (2017),[23] teriparatide (2017)[24] and adalimumab (2017).[25] It is important to note that the latter has the largest market share of any biologic worldwide,[26] and no fewer than 10 biosimilar preparations of adalimumab have currently been approved worldwide.[25]

Following biosimilar approval, several large real-world studies have added to the evidence regarding the switch from originator to the biosimilar. In Denmark, etanercept was switched from its originator to a biosimilar in 2,061 patients with rheumatoid arthritis, psoriatic arthritis or axial spondyloarthritis in 2016.[27] Treatment outcomes were reviewed at 1 year. Most patients (79%) switched to the biosimilar, and interestingly, the treatment retention rate was slightly higher in patients who switched than in patients who did not switch.[27] In Norway, the 52-week, randomized, double-blind trial NOR-SWITCH (ClinicalTrials.gov identifier: NCT02148640) was conducted between 2014 and 2015 to investigate the effects of switching from the originator infliximab to its biosimilar.[28] Infliximab was switched from its originator to a biosimilar in patients with Crohn's disease, ulcerative colitis, spondyloarthritis, rheumatoid arthritis, psoriatic arthritis or chronic plaque psoriasis. This trial showed that switching from the infliximab originator to a biosimilar was not inferior to continuing treatment with the originator.

The European Medicines Agency statement on biosimilars

In September 2022, the EMA issued a statement on the scientific rationale of the interchangeability of biosimilars.[29] It states, "Biosimilars approved in the EU are interchangeable", meaning that, once approved, a biosimilar can be used instead of its reference product (or *vice versa*), or one biosimilar can be replaced with another biosimilar of the same reference product.[29]

Recommendations on biosimilars

There are consensus-based recommendations regarding the use of biosimilars to treat rheumatological conditions.[30] These were developed by a group of rheumatology, dermatology, and gastroenterology specialists, pharmacologists, patients and a regulator from 10 countries. Five overarching principles and eight consensus recommendations regarding trials, immunogenicity, extrapolation, switching and cost were made. The eight recommendations are the following:[30]

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.
2. Approved biosimilars can be used to treat appropriate patients in the same way as their bio-originators.
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.
4. Relevant preclinical and phase I data on a biosimilar should be available when phase III data are published.
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.
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.
7. Multiple switching between biosimilars and their bio-originators or other biosimilars should be assessed in registries.
8. No switch to or among biosimilars should be initiated without the prior awareness of the patient and the treating healthcare provider.[30]

The British Society of Rheumatology has also made some recommendations regarding the use of biosimilars.[31] It advises that all biologics and biosimilars should be prescribed using their brand name to avoid substituting the desired biosimilar medication. According to these recommendations, the most cost-effective medications should be included as an option when starting a new therapy. When switching,

patients must be given enough information to make an informed decision, with the involvement of a multidisciplinary rheumatology team. If the desired medication is not available, then the dispensing pharmacy must contact the clinician to seek advice, and the patient must be informed about the discussion concerning their medication. To ensure safety, all manufacturing companies should participate in existing pharmacological studies. Multiple factors need to be considered when prescribing biologic medications, including the acceptability of the device to the patient, patient education, home care provision and patient support. The biosimilars used in rheumatology that are currently approved by the EMA are outlined in *Table 1*.[11,32]

The advantages of biosimilars

Biosimilar medications have similar efficacy to the originator drugs, with the added benefit of being cost saving and, hence, more accessible for patients.[33] NHS England supports the use of biosimilar medicines and advises that trusts should aim to use the best-value biological products, including biosimilars, to save of up to £300 million per year by using cost-effective biological medications.[33] Their aim is that "at least 90% of new patients will be prescribed the best value biological medicine within 3 months of launch of a biosimilar medicine, and at least 80% of existing patients within 12 months, or sooner if possible".[34]

In July 2021, the National Institute of Health and Care Excellence, which had previously reserved biologics only for severe disease, lowered the eligibility threshold for prescribing biologics in rheumatoid arthritis due to the significantly lower cost of biosimilars.[35] The National Institute of Health and Care Excellence now recommends adalimumab, etanercept, infliximab and abatacept for treating moderate rheumatoid arthritis (disease activity score 28 of 3.2–5.1) after conventional disease-modifying anti-rheumatic drugs have failed. These changes have allowed more patients to access treatment, which should improve outcomes in terms of remission rates, quality of life and disease progression.

The disadvantages of biosimilars

There may be some concerns surrounding the use of biosimilars; for example, patients may be concerned about the efficacy and side effects of biosimilars compared with originator drugs. In some cases, switching from the reference biologic to a biosimilar may lead to a nocebo effect (where a negative outcome occurs due to a belief that the intervention may cause harm), presenting as a subjective increase in disease activity and pain.[36] This can affect compliance with treatment and negatively affect management outcomes. Hence, it is important that clinicians emphasize the effectiveness of good clinical communication with their patients. Moreover, several useful documents have been produced by various societies to help patients understand what biosimilars are and the rationale for their use.[37] Similarly, some physicians may have reservations about switching from the reference biologic to biosimilars, particularly because switching may affect or alter disease control in stable patients. Physician confidence in prescribing biosimilars can be enhanced by improving their understanding of these medications based on the evidence from randomized control trials showing the safety and efficacy of biosimilars.[38,39]

Another consideration is the administrative burden of switching medications (e.g. the need for trained staff to facilitate switching), particularly if this is being done on a large scale across multiple indications. As mentioned above, prescribers must also ensure that biosimilars are prescribed using their brand name to avoid prescription errors. Clinical pharmacists can play an important role in the safe and effective use of biosimilars, particularly in educating the biosimilar medicine key stakeholders, rheumatology clinical nurse practitioners and patients. It is important to maintain a good pharmacist–physician–patient relationship to achieve trust and confidence in prescribing biosimilars.[40]

Switching between biosimilars

With the increasing number of biosimilars now available, switching between biosimilars is not uncommon. A study performed a systematic search (MEDLINE, Embase and Cochrane Library) reviewing 19 clinical studies on anti-tumour necrosis factor agents, assessing clinical efficacy and safety of biosimilar-to-biosimilar switch in chronic inflammatory diseases.[41] There were no significant concerns about switching between biosimilars, whether for the first or second time, particularly if patients were in remission at the time of switching.[41]

A second systematic review of studies about switching from one biosimilar to another suggested that it is a safe and effective clinical practice.[42] There has not been any reduction in effectiveness or increase in adverse events in biosimilar-to-biosimilar switching studies conducted to date.

Multiple switches may raise the concern of possible immunogenicity. However, clinical studies comparing switching between biosimilars have been reassuring so far.[41] Nevertheless, it is important to acknowledge that multiple switches may lead to some challenges, including patient concerns.[43] There is a need to increase physicians' and patients' confidence in biosimilars, including switching.

Conclusion

In summary, biosimilar medications have been in widespread use for several years now. They offer equivalent efficacy and safety profiles to the originator biologic drugs but have the added benefit of being cost effective, which has resulted in increased access to these medications. Several biosimilar medications have been approved for use across various fields of medicine to treat many conditions, and more biosimilars are in development. The future seems bright for this new class of medicines, and hopefully, they will result in earlier and better access to advanced therapies and improve disease control and quality of life for patients. ❑

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