

# Introduction of biosimilar monoclonal antibodies: the changing face of rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis treatment

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The introduction of biological medicines has revolutionized the treatment of chronic inflammatory diseases such as rheumatoid arthritis (RA), ankylosing spondylitis (AS) and psoriatic arthritis (PsA) enabling and maintaining clinical remission and improving quality of life in many patients [1,2]. As many of these biologics approach patent expiration, biosimilars are now starting to become available, potentially allowing clinicians to broaden access for patients in need of effective treatment as well as providing overall cost benefits to healthcare systems.

Biosimilars are biological medicines which are highly similar but not identical to the reference original biologic product [3,4], and are only made available after the patents and Supplementary Protection Certificates have expired. (In European Union member countries, a supplementary protection certificate is a unique intellectual property right that extends the duration of the exclusive right which enters into force after expiry of a patent upon which it is based).

Due to the complex nature and variability of biological medicines (they are proteins produced by living organisms) no two batches are ever exactly the same [4]. Thus, being nonidentical is a normal feature of biotechnologic processes [5], and both passive and active drifting is expected to occur over time, hence the strict regulations to control the

manufacturing and monitoring of biosimilars. Even with biologic drugs that have been on the market for over 10 years, manufacturing changes occur frequently, and, provided manufacturers demonstrate that the process change does not alter the safety or efficacy of the biologic [5], no label change is required. In general, the difference between a biosimilar and its reference biologic is similar to the difference between a biologic before and after an approved manufacturing process change.

Biosimilar monoclonal antibodies (mAbs) are a new generation of biologic medications expected to challenge the pharmaceutical market with products that are comparable in terms of efficacy, safety and quality, while potentially providing substantial cost savings. The time for that seems ideal since cash-strapped healthcare providers are under increasing pressure to curb costs. The European economic situation is characterized by an aging population, driving increases in public expenditure in both health and long-term care [6]. Biosimilar mAbs offer healthcare providers and payers treatments that are expected to cost in the range of 10–30% less than the originators, potentially saving billions of Euros, which could possibly be used to treat more patients with these drugs, for example, to initiate treatment earlier in the course of the disease in order to avoid structural damage [7].



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The key to uptake of biosimilar mAbs sits with rheumatologists or experts in other fields and their understanding of the evidence base and of the benefits they provide to patients and the medical community as a whole. It is critical that physicians familiarize themselves with the rigorous regulatory procedure biosimilar manufacturers must follow in order to demonstrate that the drug is comparable to the originator biologic in terms of efficacy, safety and quality. This is critical to have confidence to make decisions about when to prescribe a biosimilar to patients.

This paper focuses on Remsima® (infliximab) as the first biosimilar mAb to enter the market for rheumatic diseases, but there are a number of others expected to launch over the next few years, including adalimumab and rituximab [8].

### Regulating biosimilars

The EMA process for evaluating a biosimilar is different to the process for an originator biologic. The 'normal' regulatory pathway requires a biologic to show clinical efficacy and safety to determine the mode of action. The approach for biosimilars concentrates more on the quality and analytical characteristics and less on the clinical studies [9], which play more of a confirmatory role. The goal is for the biosimilar to have the same, and in some cases better, quality as the reference biologic [10].

Regulators place significant emphasis on *in vitro* studies as the first step to the biosimilar comparability exercise as they can detect differences between the biosimilar and the reference product, such as factors impacting on pharmacokinetics. From this it is determined what additional tests may be required.

Whilst biosimilars are subject to greater scrutiny and there is pressure for manufacturers to introduce sophisticated systems to monitor for safety, European Union pharmacovigilance legislation in 2011 did not single them out. The legislation stated that all new medicines launched after this date are subject to closer monitoring and should be identified by a black triangle, including, but not limited to, biosimilars [11].

### First biosimilar mAb for rheumatoid arthritis, ankylosing spondylitis & psoriatic arthritis

Recently, EMA approved CT-P 13 (Remsima®), a biosimilar of infliximab (Remicade®), for all disease areas in which the reference biologic is approved: RA, AS, Crohn's disease (adults and children), ulcerative colitis (adults and children), PsA and psoriasis [12]. EMA evaluated Remsima on the totality of the evidence, including two randomized, double-blind, multicenter studies, conducted to confirm EMA's preclinical evalu-

ation. Both studies were of 54 weeks' duration with an open-label extension to 102 weeks. The PLANETAS study was a pharmacokinetic study of 250 patients with AS. The PLANETRA study was a Phase III study of 606 patients with RA. Together, these studies confirmed that CT-P 13 is equivalent to the reference product in terms of efficacy and comparable in terms of safety [13,14].

Whilst immunogenicity has historically been a challenge for biologics as they are immunogenic by nature, there are a number of factors that can trigger an immune response other than a reaction to the drug. These can include the patient's disease, particularly diseases such as RA known to be associated with immunogenicity, and how the drug is administered [15]. The emergence of biosimilars has led to more robust immunogenicity studies [10]; these were used in the evaluation of CT-P 13, which was found to have a comparable immunogenicity profile to the reference product, raising no safety concerns [14].

### Data extrapolation: is it reasonable?

Data extrapolation is a scientifically established method that has been used for many years [16], including in the approval dossier for filgrastim and epoetin a few years ago. However, some concern by members of the medical community about the legitimacy of this approach has been expressed. This may have contributed to the lower than expected uptake for biosimilars in Europe to date [17] – even though the EMA, alongside other regulatory bodies such as the FDA, advocates extrapolation and states that 'if clinical similarity can be shown in a key indication, extrapolation of efficacy and safety data to other indications of the reference product may be possible' [18]. EMA has started to develop strategies to better educate clinicians about biosimilars, which include data extrapolation [17].

With CT-P 13, the drug was tested for safety and efficacy in the most sensitive populations (RA and AS) – the diseases where any differences between the biosimilar and the reference product are most likely to manifest – and then extrapolated to Crohn's disease, ulcerative colitis, PsA and psoriasis [12].

### Interchangeability: is there a case for switching?

As biosimilar mAbs enter the market, it is expected that they will be prescribed initially to new patients until rheumatologists gain confidence in their use – and if more data on switching from one compound to the other have become available.

Switching patients from the reference product to CT-P 13 may not be on the agenda in the short term, because the data suggesting no significant differences

between the maintenance and switch group in terms of efficacy or safety are derived from open-label studies [13,14]. However, rheumatologists may be encouraged to consider the case for switching based on emerging 'real-world' evidence and interchangeability data such as the Norwegian Nor-Switch study [19]. Investigators anticipate that the Nor-Switch study, which is designed to demonstrate the safety and efficacy of the infliximab biosimilar in that setting, will support switching patients currently receiving the originator. However, this study is still ongoing and data are not yet available.

### The cost benefits of biosimilar mAbs

Since mAbs are very profitable and can generate significant revenues for manufacturers, it is not surprising that this is now the next generation of biosimilars to watch. Around 40% of all requests for scientific advice to EMA between 2003 and 2011 were related to biosimilar mAbs [20]. The experienced expert H. Schellekens expects that biosimilar mAbs will penetrate the market faster than the first generation of biosimilars [21].

With biosimilar mAbs expected to cost 10–30% less than their biologic counterparts, it may be predicted that they will save European healthcare systems up to 20 billion Euros by 2020 [22]. Substantial cost savings such as these can potentially be used in a number of ways, including providing better access to biologics, particularly in countries with lower gross domestic products.

### References

- Keyser FD. Choice of biologic therapy for patients with rheumatoid arthritis: the infection perspective. *Curr. Rheumatol. Rev.* 7(1), 77–87 (2011).
- Noaiseh G, Moreland L. Current and future biosimilars: potential practical applications in rheumatology. *Biosimilars* 3, 27–33 (2013).
- Biological and biosimilar medicines: an information and advocacy toolkit for Patients' Organizations, Fact Sheet 2, IAPO. <https://iapo.org.uk/biosimilars-toolkit>
- Weise M, Bielsky M-C, De Smet K *et al.* Biosimilars: what clinicians should know. *Blood* 120(26), 5111–5117 (2012).
- Schneider CK. Biosimilars in rheumatology: the wind of change. *Ann. Rheum. Dis.* 72, 315–318 (2013).
- Ageing report: Europe needs to prepare for growing older. European Commission 2012. [http://ec.europa.eu/economy\\_finance/articles/structural\\_reforms/2012-05-15\\_ageing\\_report\\_en.htm](http://ec.europa.eu/economy_finance/articles/structural_reforms/2012-05-15_ageing_report_en.htm)
- Factors supporting a sustainable European biosimilar medicines market. European Biosimilars Group September 2014. [www.egagenerics.com/images/Website/GfK\\_Final\\_Report\\_Factors\\_Supporting\\_a\\_Sustainable\\_European\\_Biosimilar\\_Medicines\\_Market.pdf](http://www.egagenerics.com/images/Website/GfK_Final_Report_Factors_Supporting_a_Sustainable_European_Biosimilar_Medicines_Market.pdf)
- US\$54 billion worth of biosimilar patents expiring before 2020. [www.gabionline.net/Biosimilars/Research/US-54-billion-worth-of-biosimilar-patents-expiring-before-2020](http://www.gabionline.net/Biosimilars/Research/US-54-billion-worth-of-biosimilar-patents-expiring-before-2020)
- Döner T, Strand V, Casaneda-Hernandez G *et al.* The role of biosimilars in the treatment of rheumatic diseases. *Ann. Rheum. Dis.* 72, 322–328 (2013)
- Brinks V, Hawe A, Basmeh AH *et al.* Quality of original and biosimilar epoetin products. *Pharm. Res.* 28(2), 386–393 (2011)
- ABPI position on biosimilar medicine. [www.abpi.org.uk/our-work/library/industry/Documents/ABPI%20biosimilars%20position%20paper.pdf](http://www.abpi.org.uk/our-work/library/industry/Documents/ABPI%20biosimilars%20position%20paper.pdf)
- Remsima assessment report. [www.ema.europa.eu/docs/en\\_GB/document\\_library/EPAR\\_-\\_Public\\_assessment\\_report/human/002576/WC500151486.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002576/WC500151486.pdf)
- Park W, Miranda P, Brzosko M *et al.* Efficacy and safety of CT-P13 (infliximab biosimilar) over two years in patients with ankylosing spondylitis: comparison between continuing

### Concluding remarks

Biosimilar mAbs are an important milestone for modern medical therapy strategies to treat chronic inflammatory diseases. Especially patients who have been unable to access biologics in the past and the economic burden of healthcare systems could have substantial benefit from this development. However, all physicians and especially rheumatologists need to familiarize themselves with the data that support these products, both preclinical and clinical, to gain confidence to use biosimilars for their patients in all different indications. Evaluating the array of evidence used for EMA approval, the growing body of real world data and their own experience in using these drugs should help to establish this new way to treat patients with a high burden of disease.

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- with CT-P13 and switching from infliximab to CT-P13. Presented at: *ACR/ARHP Annual Meeting 2013*. San Diego, USA, 25–30 October 2013.
- 14 Yoo DH, Prodanovic N, Jaworski J *et al*. Efficacy and safety of CT-P13 (infliximab biosimilar) over two years in patients with rheumatoid arthritis: comparison between continued CT-P13 and switching from infliximab to CT-P13. Presented at: *ACR/ARHP Annual Meeting 2013*. San Diego, USA, 25–30 October 2013.
- 15 Carrascosa JM. Immunogenicity in biologic therapy: implications for dermatology. *Actas Dermosifiliogr*. 104(6), 471–479 (2013).
- 16 Weise M, Kurki P, Wolff-Holz E, Bielsky MC, Schneider CK. Biosimilars: the science of extrapolation. *Blood* 124(22) 3191–3196 (2014).
- 17 Extrapolation for biosimilars.  
<http://gabionline.net/Biosimilars/Research/Extrapolation-for-biosimilars>
- 18 Efficacy, extrapolation and interchangeability of biosimilars.  
[www.gabionline.net/Biosimilars/Research/Efficacy-extrapolation-and-interchangeability-of-biosimilars](http://www.gabionline.net/Biosimilars/Research/Efficacy-extrapolation-and-interchangeability-of-biosimilars)
- 19 The NOR-SWITCH Study.  
<https://clinicaltrials.gov/ct2/show/NCT02148640>
- 20 Biosimilar monoclonal antibodies on the horizon in Europe.  
[www.gabionline.net/Biosimilars/Research/Biosimilar-monoclonal-antibodies-on-the-horizon-in-Europe](http://www.gabionline.net/Biosimilars/Research/Biosimilar-monoclonal-antibodies-on-the-horizon-in-Europe)
- 21 Schellekens H. Who needs biosimilars? Presented at: *European Bioanalysis Forum 5th Open Meeting Old Battles, New Horizons*. Barcelona, Spain, 14–16 November 2012.
- 22 Hausteil R, de Millas C, Hoer A, Haussler B. Saving money in the European healthcare systems with biosimilar. *GaBi* 1(3–4), 120–126 (2012).