

# How Similar are Biosimilars? Time to Switch a Position

Esther Houri Levi MD<sup>1,2</sup> and Howard Amital MD MHA<sup>1,2</sup>

<sup>1</sup>Department of Medicine B and Center of Autoimmune Diseases, Sheba Medical Center, Tel Hashomer, Israel

<sup>2</sup>Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

**KEY WORDS:** biosimilars, biological therapy, etanercept, efficacy, rheumatoid arthritis  
*IMAJ* 2021; 23: 376–377

Biosimilars are biological agents that share a high degree of similarity to the protein structure and function of originally approved biological medications, of which patent protection has expired. Biosimilars were first introduced at 2005, after implementing an approval procedure based on sharing similar pharmacokinetics characteristics as well as equal efficacy and safety outcomes in a single clinical indication. Obviously, the reason for facilitating their use is to provide efficacious and safe medications to a maximal number of patients at the lowest possible price. These medicines include biologic molecules such as somatotropins and epoetins, and over the last several years, biosimilars of monoclonal antibodies were introduced for the treatment of autoimmune and malignant conditions.

Biosimilars are not a replica of the original drug, but they are expected to have identical amino acid sequences with small changes in terms of glycosylations, forming a microheterogeneity pattern of the molecule. These modifications are unavoidable due to the nature of the production of biological drugs, which are derived from living cells. It should be noted that even during the manufacturing of an original biologic drug there is a certain degree of microheterogeneity between batches, and those changes are monitored and are acceptable [1,2].

The process of development and approval of a biosimilar drug is different from that of a generic product of small

chemistry synthesized drugs, in which demonstration of equivalence to the original medicine is usually sufficient to conclude equality. To develop and license a biosimilar one must show a highly similar molecule to that of an already approved original biologic drug, as well as no clinically significant differences in safety, purity, and potency. However, the goal developing biosimilars is to demonstrate biosimilarity between the new product and the original drug, not to independently establish safety and effectiveness; therefore, the process is much shorter and usually does not involve large and long clinical trials as with new biologic drugs [3]. In general, this process appears to be safe, but adverse events cannot always be anticipated, such as a well-known example of pure red cell aplasia appearing after the use of certain erythropoietin formulation that caused cross-reacting neutralizing antibodies [4]. Therefore, post-marketing monitoring, as well as reports regarding adverse events and real-world data surveillance are essential for the ongoing evaluation of the efficacy and safety of these drugs.

In their article appearing in this issue if the *Israel Medical Association Journal (IMAJ)*, Atzeni et al. [5] reported on their experience with a biosimilar to Etanercept, an anti-tumor necrosis factor (anti-TNF) blocking fusion protein among patients with rheumatoid arthritis (RA). They conducted a retrospective clinical trial involving 81 consecutive RA patients treated for at least 6 months with either the originator (Enbrel®, Pfizer, UK) or the biosimilar to etanercept (Benepali®, Biogen, USA). In total, 51 patients received etanercept and 30 received the biosimilar. Notably, 19 patients of the biosimilar group were

switched to the biosimilar agent following initial therapy with the originator drug. The study demonstrated that the two groups were equal in term of status after 6 months, using different modalities of evaluation that are used in the rheumatology practice. Regarding safety, 9 patients were off treatment after 6 months due to minor adverse events or inefficacy. All of these patients belonged to the biosimilar treated group. This observation corresponds to other publications, which examined the safety and efficacy of biosimilars to etanercept in various clinical settings. All of which demonstrated that biosimilar and originator etanercept are equivalent [6-9].

The biosimilar era encourages competition between pharmaceutical companies. As a result, the expensive expenditure for biological therapy are pushed down. It provides the opportunity to prescribe biological agents to populations worldwide that were, until now, unprivileged due to costs. Thus, many individuals are granted improved medical care.

We believe that this study [5] also provides data underlining that individuals can be switched from an originator medication to a biosimilar without endangering their clinical status. Many medical associations were reluctant to face this fact and to favor switches. Several seminal studies involving various indications clearly indicated that switching from an originator to a biosimilar is safe and carries no risk of disease flares [10-12].

As for now, the biosimilar monoclonal antibodies are here to stay. Physicians should feel comfortable using them as long as all the regulatory guidelines were completed. The competition they add to the medicinal market should be welcomed.

**Correspondence**

**Dr. H. Amital**

Head, Dept. of Medicine B, Sheba Medical Center, Tel Hashomer 52621, Israel  
**Phone:** (972-3) 530-2652  
**Fax:** (972-3) 535-4796  
**email:** howard.amital@sheba.health.gov.il

**References**

1. European Medicines Agency, Committee for Medicinal Products for Human Use. Similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues. Guideline on similar biological medicinal products containing biotechnology - derived proteins as active substance: quality issues. [Available from <https://www.ema.europa.eu/en/similar-biological-medicinal-products-containing-biotechnology-derived-proteins-active-substance>]. [Accessed 20 October 2012].
2. European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP) Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues. [Available from [https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-similar-biological-medicinal-products-containing-mono-clonal-antibodies-non-clinical\\_en.pdf](https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-similar-biological-medicinal-products-containing-mono-clonal-antibodies-non-clinical_en.pdf)]. [Accessed 30 May 2012].
3. U.S. Food and Drug Administration. Draft guidance on biosimilar product Development. [Available from <https://www.fda.gov/vaccines-blood-biologics/general-biologics-guidances/biosimilars-guidances>]. [Accessed 20 October 2012].
4. Seidl A, Hainzl O, Richter M, et al. Tungsten-induced denaturation and aggregation of epoetin alfa during primary packaging as a cause of immunogenicity. *Pharm Res* 2012; 29 (6): 1454-67.
5. Atzeni F, Gerratana E, Bongiovanni S, Talotta R, Miceli G, Salaffi F, Sarzi-Puttini P. Efficacy and safety of biosimilar and originator etanercept in rheumatoid arthritis patients: real-life data. *IMAJ* 2021; 23 (6): 344-49.
6. 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 (1): 51-7.
7. Lee YJ, Shin D, Kim Y, et al. A randomized phase I pharmacokinetic study comparing SB4 and etanercept reference product (Enbrel®) in healthy subjects. *Br J Clin Pharmacol* 2016; 82: 64-73.
8. Emery P, Vencovský J, Sylwestrzak A, et al. 52-week results of the phase 3 randomized study comparing SB4 with reference etanercept in patients with active rheumatoid arthritis. *Rheumatology (Oxford)* 2017; 56 (12): 2093-101.
9. Bae SC, Kim J, Choe JY, et al. HERA Study Investigators. A phase III, multicentre, randomised, double-blind, active-controlled, parallel-group trial comparing safety and efficacy of HD203, with innovator etanercept, in combination with methotrexate, in patients with rheumatoid arthritis: the HERA study. *Ann Rheum Dis* 2017; 76 (1): 65-71.
10. Glintborg B, Loft AG, Omerovic E, et al. To switch or not to switch: results of a nationwide guideline of mandatory switching from originator to biosimilar etanercept. One-year treatment outcomes in 2061 patients with inflammatory arthritis from the DANBIO registry. *Ann Rheum Dis* 2019; 78 (2): 192-200.
11. Jørgensen KK, Olsen IC, Goll GL, et al; NOR-SWITCH study group. 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 (10086): 2304-16.
12. 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; 76 (12): 1986-91.

**Capsule**

**Unexpected benefits of microbiota**

Cachexia is a condition of muscle wasting seen in cancer that contributes to mortality. On the basis of previously reported connections between gut microbiota and cachexia, **de Clercq** and colleagues transplanted fecal microbiota from healthy obese donors to patients with cancer cachexia and compared their outcomes with those of patients receiving autologous microbiota. Unexpectedly, the allogeneic transplantations had no effect on cachexia

but they did improve patient responses to chemotherapy and overall survival. The findings are intriguing but also raise numerous questions about the specific effects of the microbiota: There were no non-obese donor controls, so it is possible that any allogeneic microbiota transplantation might be beneficial.

*Clin Cancer Res* 2021; 10.1158/1078-0432.CCR-20-4918  
 Eitan Israeli

**Capsule**

**Phagocytosis promotes plaque**

Many of the human genes associated with increased risk for Alzheimer's disease (AD) are exclusively expressed in the brain by microglia. Microglia express the tumor-associated macrophage (TAM) receptor tyrosine kinases Axl and Mer, which have been linked to AD. **Huang** et al. performed molecular, genetic, cell biological, and in vivo two-photon imaging analyses of AD mouse models crossed into Axl- and Merk-knockout mouse mutants. Induced expression of Axl and Mer in plaque-associated microglia led to the recruitment of the TAM ligand

Gas6 and to the formation of dense accumulations of phagocytosed amyloid within the microglia. An AD mouse model lacking Axl and Mer did not phagocytose amyloid as normal. Despite this, the mice developed fewer plaques than AD mice with normal microglia. Thus, TAM receptor signaling is required for microglial recognition of amyloid plaques, and, counterintuitively, TAM-driven microglial phagocytosis promotes plaque deposition and growth.

*Nat Immunol* 2021; 22: 586  
 Eitan Israeli