

Biosimilar to Biosimilar Anti-VEGF Switching for Retinal Diseases

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Introduction

Antivascular endothelial growth factor (anti-VEGF) therapy has revolutionized the management of retinal vascular diseases. However, the cost of this therapy resulting from the long-term, repeated need for intravitreal injections in the majority of cases is seen as a burden on patients and healthcare systems.

After the expiration of exclusivity of innovator ranibizumab (Lucentis, Genentech), a biosimilar, ranibizumab-nuna (Byooviz, Samsung Bioepis), received approval from the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) in September 2021.¹ A second ranibizumab biosimilar, ranibizumab-eqrn (Cimerli, Coherus Biosciences), received FDA approval in August 2022. It was approved by the UK regulatory authority in early 2022 under the name Ongavia (Teva Pharmaceutical Industries Ltd). It subsequently received EMA approval under the name Ranivisio (Teva Pharmaceutical Industries Ltd). Another biosimilar ranibizumab, Ximluci (Stada Arzneimittel and Xbrane Biopharma), was also approved in the UK and Europe.

India was the first country to approve and start using a ranibizumab biosimilar in 2015 (Razumab, Intas Pharmaceuticals). In the past 2 years, India has approved 2 additional ranibizumab biosimilars. In addition, 3 molecules (Razumab, Intas Pharmaceuticals Ltd; Ranieyes, Lupin Ltd; Ranizurel, Reliance Life Sciences) are available in India.¹

Competition between biosimilars led to further price drops in India after the initial price drop of Razumab, making it less expensive than Lucentis. The same might happen in other regions. The possibility that patients will need to switch from one biosimilar to another (cross-switch), for whatever reason, is also anticipated to rise as the market for biosimilars expands and the number of biosimilar drugs for each approved biological reference product increases. Therefore, the question arises about the safety and efficacy of switching from one biosimilar ranibizumab to the other. Here, we discuss evidence for cross-switching between biosimilars from other medical specialties

regarding the safety and efficacy of such switches and how that information could help physicians in retina practice.

Biosimilar Cross-Switching Results From Other Specialties

Allocati et al² performed an extensive evaluation of anti-tissue necrosis factor biosimilar agents. Of the 19 studies of biosimilar switching they analyzed, none directly compared biosimilar with biosimilar of a reference molecule. However, based on the available studies, the authors concluded that patients with chronic inflammatory illnesses can safely and effectively switch from one biosimilar (infliximab, adalimumab, or etanercept) to another biosimilar of the same biologic medication in terms of disease activity, remission rate, loss of response, adverse events, and immunogenicity (when analyzed).

Other studies evaluating several switches, including studies of patients receiving treatment with an originator molecule and then subsequently switching to one biosimilar and then to another, came to a similar conclusion. Trials evaluating immunogenicity found similar antidrug antibodies levels shortly after switching or after extended follow-up and that switching between biosimilars did not change the immune response. At present, the number of studies being performed for switching between biosimilars is minimal, largely because there are no

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regulatory requirements in place that require biosimilars of a single reference product to be evaluated and compared.³

Anti-VEGF Switching for Retinal Diseases

In retinal disease management, various kinds of switching have occurred between the available anti-VEGF molecules. This includes switching from low-cost, off-label bevacizumab to innovator ranibizumab and innovator ranibizumab to aflibercept. Furthermore, a switch from aflibercept to ziv-aflibercept has been tried.⁴ These switches were not only part of the real world but also part of various clinical trials. Despite differences in molecular structure, such as off-label bevacizumab being a full-length monoclonal antibody, innovator ranibizumab being the Fab fragment of an antibody without the Fc portion, and aflibercept having a fusion-trap arm and an Fc portion, no safety concerns about the switches have been reported. Switching to brolucizumab, which contains a fragment of the Fab fragment without the Fc portion, has been associated with some immunogenic reactions. However, the reactions were predominantly caused by the brolucizumab itself rather than switching.⁵

Biosimilar Cross-Switching for Retinal Diseases

As described, switching between anti-VEGF molecules of different structures has been found to be safe; therefore, cross-switching between biosimilar ranibizumab molecules that have a similar, although not identical, structure is unlikely to cause safety concerns. The only study of switching from innovator ranibizumab to biosimilar ranibizumab found no safety or efficacy concerns.⁶ However, it was a short study and thus would have limited value in terms of wide interpretability. In India, retina physicians have generally and anecdotally experienced no or limited concerns after switching between biosimilars. Hopefully, more data will become available from India, the US, and Europe because more than several biosimilars of ranibizumab are now available for clinical use.

Although the manufacturing process of proprietary biosimilars is likely different among manufacturers, the various biosimilar molecules have similar protein and structural mapping. Furthermore, regulatory requirements establish that there can be no clinically meaningful differences between the biosimilar molecule and the innovator molecule. Therefore, it is highly unlikely (although not impossible) that switching from one biosimilar to another would cause safety concerns for the management of retinal diseases.

Regulation

Because regulatory agencies do not appear to be concerned about the mild differences across biosimilars of a reference product, it is doubtful that in the near future they will be compared in

randomized controlled trials.⁷ There is no legal requirement or industry-driven motivation for licensed biosimilars of the same reference product to be assessed for biosimilarity, even if the clinical equivalence of a biosimilar and its reference product is extensively validated and well documented.

Beyond individual patient needs, physicians should regularly take into account the extremely low likelihood that head-to-head clinical trials of biosimilars and the same reference product will be done in the event of a switch from one biosimilar to another. Furthermore, there are an increasing number of biosimilars in the market, making it extremely difficult to run conventional parallel trials comparing all potential sequence combinations. The FDA approval of Cimerli as an interchangeable drug without additional studies is another indicator that biosimilarity approval is sufficient evidence and that extrapolation to biosimilar cross-switching, a natural eventual market consequence of the approval of multiple biosimilars to the same reference originator molecule, can be considered safe.

Pharmacovigilance, which allows for the recognition and classification of adverse drug reactions, is essential for monitoring the use of biosimilars and is mandated by regulatory agencies throughout the world. There are changes in the production of originators, which have been deemed to be of moderate to high risk but have been permitted by the regulatory agencies without additional studies, although with continued and extended strict pharmacovigilance.

Limitations

The real-world evidence regarding switching from biosimilar to biosimilar is from systemic diseases. No study has yet been published for the retina *per se*. However, we are in the process of publishing the data from our clinical experience in India.

Conclusions

Evidence from other specialties has not yielded safety or efficacy concerns regarding cross-switching between biosimilars. Retina specialists have been switching between different anti-VEGF molecules in their practice over the past 15 years and have not reported safety concerns. Therefore, it is highly unlikely that switching between biosimilars would lead to safety concerns. Studies of switching might be unnecessary and could be counterproductive for the biosimilar field given the growing body of evidence suggesting no problems in practice coupled with the stringent regulatory requirements. However, real-world data would help strengthen the hypothesis based on experience from systemic diseases. Furthermore, pharmacovigilance is likely to be the best way to use these molecules and would help in realizing cost savings without compromising patient safety.

Ethical Approval

Ethical approval was not required for this paper.

Statement of Informed Consent

Informed consent was not required for this article.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Dr. Sharma is a consultant to Novartis, Allergan, Bayer, Lupin, and Intas and has received a speaker fee from Biogen. Dr. Loewenstein is a consultant to Allergan, Novartis, Roche, Notal Vision, Fiorsightslabs, Beyeonics, and Bayer Health Care. Dr. Kuppermann performs clinical research for Alcon, Alimera, Allegro, Allergan, Apellis, Clearside, Genentech, GSK, Ionis, jCyte, Novartis, Regeneron, and ThromboGenics and is a consultant to Alimera, Allegro, Allergan, Cell Care, Dose, Eyedaptic, Galimedix, Genentech, Glaukos, Interface Biologics, jCyte, Novartis, Ophthotech, Regeneron, Revana, and Theravance Biopharma. Drs. Parachuri and Kumar declared no conflicts of interest.

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References

1. Sharma A, Kondo M, Iwahashi C, et al. Approved biosimilar ranibizumab-a global update. *Eye (Lond)*. 2023;37(2):200-202. doi:10.1038/s41433-022-02246-5
2. Allocati E, Godman B, Gobbi M, Garattini S, Banzi R. Switching among biosimilars: a review of clinical evidence. *Front Pharmacol*. 2022;13:917814. doi:10.3389/fphar.2022.917814
3. Mysler E, Azevedo VF, Danese S, et al. Biosimilar-to-biosimilar switching: what is the rationale and current experience? *Drugs*. 2021;81(16):1859-1879. doi:10.1007/s40265-021-01610-1
4. Mansour AM, Stewart MW, Farah ME, Mansour HA, Chhablani J. Ziv-aflibercept: a cost-effective, off-label, highly potent antagonist of vascular endothelial growth factor. *Acta Ophthalmol*. 2020; 98(5):e540-e548.
5. Sharma A, Kumar N, Parachuri N, et al. Brolucizumab and immunogenicity. *Eye (Lond)*. 2020;34(10):1726-1728. doi:10.1038/s41433-020-0853-9
6. Sharma A, Kumar N, Parachuri N, Bandello F, Kuppermann BD, Loewenstein A. Ranibizumab biosimilar (Razumab) vs innovator ranibizumab (Lucentis) in neovascular age-related macular degeneration (n-AMD)- efficacy and safety (BIRA study). *Eye (Lond)*. 2022;36(5):1106-1107. doi:10.1038/s41433-021-01616-9
7. Godman B, Allocati E, Moorkens E. Ever-changing landscape of biosimilars in Canada; findings and implications from a global perspective. *GaBI J*. 2019;8(3):93-97.