

Commentary: Use of biosimilars for retinal diseases in India: Challenges and concerns

Anti-vascular endothelial growth factor (anti-VEGF) agents including Bevacizumab, Ranibizumab, Aflibercept, and the latest molecule Brolocizumab have caused a paradigm shift in the management of various retinal diseases such as diabetic macular edema, neovascular age-related macular degeneration (AMD), and retinal vein occlusions. These together constitute majority of the retinal causes of vision impairment. Nonetheless, patients usually need multiple and frequent dosing of these agents that cause increased financial burden and other unique challenges to the patients, especially during COVID-19 times.^[1]

Biosimilars are basically a class of products that are biologically made and have similar efficacy, safety, and potency as that of an approved biologic drug. The time and cost required to make a biosimilar is significantly less than that of developing a new biologic drug. The molecule has to be as close to the already known biologic in its function in the pre-clinical stage studies and must show similar pharmacodynamic properties.

Razumab (Intas Pharmaceuticals, India) is the only biosimilar that is approved in India. It is a biosimilar to the popularly used innovator Ranibizumab and is approved by the DCGI since 2015 for neovascular AMD, myopic choroidal neovascularisation, diabetic macular edema, and retinal vein occlusions. Various experimental studies have been conducted comparing Razumab with ranibizumab which have tried to show similar pharmacodynamic and pharmacokinetic properties of the two molecules.^[2,3] Sharma *et al.* have also reported the drug to be safe and effective (Re-ENACT and Re-ENACT 2 Study).^[4,5] However, there are a limited number of studies involving use of biosimilar with small sample sizes. In contrast, innovator molecules have been subjected to rigorous scrutiny with a large number of multicentric randomized control trials and real-world studies to establish their safety and efficacy.

The stability of biosimilars poses a big concern as they are not derived from fixed chemical formulations (unlike the generic drugs). They involve living cells in the manufacturing process different from the original one which brings variability in the molecular structure. These can also introduce impurities such as viruses, protein, and DNA/RNA contaminants.^[3] It is difficult to replicate the exact structure of complex molecules. These result in difficulty to get the required approvals, with long waiting time. The FDA also follows a two-step approach in reviewing the biosimilars. Firstly, it takes review of the analytical data that show how similar are the biosimilar compounds to the already approved drugs. In the second stage, animal studies and clinical data are needed for final approval.

Immunogenicity is a big challenge, which is difficult to tackle.^[3] It occurs reportedly due to the larger size of biosimilar agents owing to its manufacturing process. The quality of manufacturing process alters the efficacy and immunogenicity of these molecules. It involves use of different living cell lines and processes by different developers for its formulation via reverse engineering. There have been reports of intraocular inflammation (up to 10% of cases) with almost all the biosimilar

molecules. This may be due to the immunogenicity caused due to the antibodies against the molecules or due to the raised endotoxin levels. Cases of sterile endophthalmitis have been reported with some batches of Razumab in 2015, 2017, and 2019 which led VRSI to issue advisory to halt its use for a certain period of time.^[6] This cluster occurrence shows that strict pharmacovigilance is required and immunogenicity has to be tested before its introduction into clinical use. There are also concerns regarding interchangeability/substitution with innovator molecule and its reimbursement due to paucity of legislative regulations addressing the use of biosimilars in India.^[7]

Although cost of the biosimilars is on an average 10%–20% cheaper than their innovator counterparts, Ranibizumab and Aflibercept, it is still costlier than a single aliquot of Bevacizumab (off-label use). However, these biosimilars have the potential to act as an alternative to bevacizumab which is often sidelined due its off-label use and compounding issues.

Currently, concerns regarding safety, inadequate regulatory body approvals and medicolegal aspects have discouraged the widespread use of biosimilars by ophthalmologists practicing in India. The current VIBE survey brings out these concerns, hesitancy, and other salient issues regarding adoption of biosimilar agents over the past few years.^[6] These should be taken into account and adequately addressed (with strict pharmacovigilance, postmarketing surveillance and larger multicentric randomized control trials) to pave way for better assimilation in clinical practice. There is a need to apprise the general public and young trainee ophthalmologists about the advantages and disadvantages of these newer agents by incorporating it in their residency training curriculum.^[8-10]

As more and more patents of innovator biological agents are expiring gradually, the production of biosimilars is bound to increase in the future. However, its safety, efficacy, and development process will continue to be a matter of discussion/scrutiny in the near future.

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References

1. Agarwal D, Kumar A. Managing intravitreal injections in adults in COVID-19 and post-COVID-19 era- Initial experiences. *Indian J Ophthalmol* 2020;68:1216-8.
2. Griaud F, Winter A, Denefeld B, Lang M, Hensinger H, Straube F, *et al.* Identification of multiple serine to asparagine sequence variation sites in an intended copy product of LUCENTIS® by mass spectrometry. *mAbs* 2017;9:1337-48.
3. Sharma A, Kumar N, Parachuri N, Bandello F, Kuppermann BD, Loewenstein A. Biosimilars for retinal diseases: An update. *Am J Ophthalmol* 2020; S0002-9394(20)30651-6. doi: 10.1016/j.ajo.2020.11.017.
4. Sharma S, Khan MA, Chaturvedi A, RE-ENACT Study Investigators Group. Real-life clinical effectiveness of

- Razumab® (the World's First Biosimilar of Ranibizumab) in retinal vein occlusion: A subgroup analysis of the pooled retrospective RE-ENACT Study. *Ophthalmol J Int Ophthalmol Int J Ophthalmol Z Augenheilkd* 2019;241:24-31.
5. Sharma S, RE-ENACT 2 Study Investigators Group, Khan M, Chaturvedi A. A multicenter, retrospective study (RE-ENACT 2) on Razumab™ (World's First Biosimilar Ranibizumab) in retinal vein occlusion. *Ophthalmol Ther* 2020;9:625-39.
 6. Sheth JU, Stewart MW, Khatri M, Gupta SR, Chawla S, Rajendran A, *et al*. Changing trends in the use of anti-vascular endothelial growth factor (anti-VEGF) biosimilars: Insights from the Vitreoretinal Society of India Biosimilars of Anti-VEGF Survey. *Indian J Ophthalmol* 2021;69:352-6.
 7. Lyman GH, Zon R, Harvey RD, Schilsky RL. Rationale, opportunities, and reality of biosimilar medications. *N Engl J Med* 2018;378:2036-44.
 8. Kumar A, Agarwal D, Nayak S. Commentary: Improving training in retina in Indian residency programmes. *Indian J Ophthalmol* 2019;67:1819-20.
 9. Kumar A, Agarwal D. Commentary: Restructuring residency training in ophthalmology during COVID-19 era: Challenges and opportunities. *Indian J Ophthalmol* 2020;68:1005-6.
 10. Kumar A, Agarwal D. Resident-to-resident bedside teaching: An innovative concept. *Indian J Ophthalmol* 2019;67:1901-2.

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