Biosimilars in Ophthalmology: Financial Implications and Beyond

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Anti-vascular endothelial growth factors (anti-VEGF) have transformed retinal disease management. However, the benefit of anti-VEGF therapy is still limited by the high cost of treatment, specifically in areas where patients are not well covered with insurance and need to pay out of their pocket. Off-label bevacizumab usage has been associated with the risk of infection due to a lack of compounding pharmacies in such areas. In India, the entry of ranibizumab biosimilars has made a significant change and improved access to anti-VEGF therapy for many patients. Recent ranibizumab biosimilar approvals by the European Medicines Agency and the US Food and Drug Administration have brought this therapy to the forefront and have the potential to save the nation's healthcare spending on these drugs. However, it is yet to be seen how biosimilar anti-VEGF therapy will fit into the crowded space of anti-VEGF therapy globally.

Keywords

Anti-vascular endothelial growth factor, bevacizumab, biosimilar, ophthalmology, pharmacotherapy, ranibizumab, retina

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Biologics have redefined the outcomes of retinal pathologies by targeting the vascular endothelial growth factor (VEGF) pathway. Anti-VEGF therapy has prevented millions of people from going blind due to retinal vascular pathologies.[1] Apart from preventing morbidity, it has a widespread financial benefit for patients, and the benefits seem to be huge compared with the cost of therapy. The worldwide anti-VEGF market in 2021 was $12.36 billion.[2] One economic impact study estimated up to $8.2 billion in patient benefits and $3 billion in societal value in 3 years from retinal anti-VEGF agents in the USA alone. With treatment innovations and adherence to treatment protocols, additional benefits may be up to $15 billion.[3]

This potential loss due to non-adherence arises from the fact that 53–58% of patients from Medicare drop out during the first year of therapy.[4] Although lack of perceived need, fear of injections, repeated visits and long-term maintenance therapy are barriers to adherence, treatment cost is considered one of the most prominent factors for non-adherence.[5] Though biologics overall account for 2% of the total prescribed medications, they amount to 37% of the net spending.[6] Biosimilars – molecules with similar molecular structure, efficacy and safety to the originator or innovator biologic – are one of the potential cost-saving options.

India became the first market to approve a biosimilar to ranibizumab, and this drug provides a robust baseline from which to compare the safety, efficacy and financial implications of biosimilars.[7] Our group has previously published real-world safety data on biosimilars in different approved indications.[8,9] The cost of anti-VEGF agents being used in ophthalmology has not decreased since their launch. Ranibizumab (marketed in India as Accentrix [Novartis AG, Basel, Switzerland] as part of the regulatory approval to keep the price of the injection lower in middle-income countries) is administered for an average of $350–375 per instance, while biosimilars cost on average $200–225 per instance, a 35–50% discount on the innovator molecule. However, the injection visit involves travelling, consultation charges, scans and loss of work hours, which cost the same for both molecules. On average, our patients save 25–35% per visit if they opt for biosimilars over the originator biologic. In some markets, such as the US market, where fractionation of the bevacizumab vial is readily available, Avastin® (Genentech, Oceanside, CA, USA) is a cost-effective

option. However, the arrival of biosimilars in such a market will now be a conundrum for retinal physicians, as bevacizumab is off-label, and on-label biosimilars have slightly higher costs.

Since innovator biologics have come off patent and their exclusive marketing period has ended, biosimilars have taken up an increasing share of the market. To mitigate this, manufacturers are now using innovative strategies to protect their market share, mostly in the form of patient support programmes. Moreover, manufacturers are providing complimentary injections to patients on long-term therapy, provided they meet certain criteria. This strategy reduces the price of the innovator molecule indirectly by 25–33% (unpublished data). Biosimilars thus have the potential to fulfil their destiny of providing biologic therapy at a reduced cost either directly or indirectly by driving the competitors' costs down. With more biosimilar approvals on the way, the cost could reduce rapidly, and the cost–benefit ratio may become more promising.

However, reducing the cost of innovator therapy brings into question the need for biosimilars; why choose the biosimilar when one could potentially have the innovator for only a slightly higher cost? The most obvious benefit of biosimilars, apart from price, is their widespread availability. Biologics are highly regulated products, with the authorization and approval only granted under certain specifications, such as defined cell lines, a certain level of endotoxins and a controlled microenvironment in a sanctioned facility. Any deviation in the production line potentially degrades their efficacy and safety; thus, regular random sampling is done by authorities to ensure consistency. These necessary but stringent guidelines can potentially limit the production and widespread availability of biologic drugs.[10] With increasing life expectancy and rising incidences of lifestyle diseases such as diabetes and hypertension, the number of patients requiring anti-VEGF therapy is projected to grow. Biosimilar manufacturers provide an alternative approved production facility, which can increase the supply, thereby further decreasing prices. Furthermore, this can prevent prices from being driven up by supply shortages.[10]

Biosimilars face multiple nocebo (i.e. negative placebo) effects in the form of their wrongful description as generics.[11] Also, their approval pathway differs from that of innovator drugs, with trials using small sample sizes, causing it to be perceived as an inferior trial design.[12] However, based on the experience from Europe since 2006, the equivalence trial design that is adapted for the approval of biosimilars has been successful, with none of the molecules being suspended or withdrawn due to safety or efficacy issues till now. These nocebo effects have resulted in a slower uptake of biosimilars in other fields of medicine. India was the first authority to approve a biosimilar to ranibizumab in 2015, and thus, retinal physicians from India have the most experience with biosimilars in ophthalmology. Apart from a few initial experiences of intraocular inflammation secondary to higher levels of endotoxins, biosimilars have been proven to be a safe and effective alternative to innovator ranibizumab.[7] Now, the US Food and Drug Administration has further strengthened the endotoxin limits, which has made these molecules safer; no significant inflammation has been reported.[13]

Until recently, biosimilars were not approved for interchangeability. Interchangeability approval required a more elaborate trial design, which, if completed successfully, allowed innovator molecules to be automatically substituted with biosimilars and vice versa at the pharmacist level. With interchangeability, the decision between the innovator therapy or biosimilar is made directly by the paying party, most often the patient in developing countries or the healthcare provider in developed countries.[14] CIMERLI™ (ranibizumab-eqrn) (Coherus BioSciences, Boulder, CO, USA), a biosimilar to ranibizumab, is the first biosimilar in ophthalmology to be marketed as an interchangeable molecule following its landmark approval in July 2022.[15] This opens new avenues, as many healthcare providers might move to biosimilars due to their safety, efficacy and favourable cost–benefit ratio, without the need for a recommendation from retinal physicians, thereby improving biosimilar uptake and use. Biosimilar drugs, though launched as a cheaper alternative to biologics, are now beginning to have an impact much beyond finances, providing wider availability and empowering patients to decide on their therapy. ❑

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