The Future of Biosimilars and Biobetters in Ophthalmology

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Biosimilars have been spreading widely in the field of ophthalmology since the patent expiry of innovator molecules. The patent of the ranibizumab innovator has already expired, and the aflibercept patent will expire in the next few years. India was the first country to launch the biosimilar of ranibizumab (Razumab, Intas Pharmaceuticals Ltd, Ahmedabad, Gujarat, India) in 2015, whose usage has increased over time. After the US Food and Drug Administration approval of ranibizumab's biosimilar, ranibizumab-nuna (Byooviz™, Biogen, Cambridge, MA, USA), it will be interesting to witness the future of these molecules along with that of biobetters, which are yet to be well defined.

Keywords

Biosimilar, biobetters, retina, ophthalmology, biologics, anti-vascular endothelium-derived growth factors

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A biosimilar is a biologic medical product that is an almost identical copy of an original product manufactured by a different company.[1] Biosimilars are officially approved versions of original "innovator" products and can only be manufactured in a well-equipped research and development facility when the original product's patent expires.[1] A biosimilar must demonstrate no clinically meaningful differences in quality, safety and efficacy to its innovator counterpart to receive regulatory approval.[1] It should not be confused with a generic drug, whose chemical formula is simple to replicate; conversely, biosimilars are not the identical copy of innovators, as they differ from the original product in ways that are not clinically meaningful.[1] Another major difference between generic drugs and biosimilars is that the latter are more prone to heterogenicity due to minor changes in their manufacturing process.[2] Conversely, a "biobetter" is a biologic compound that targets the same protein as the reference biologic (innovator) product but is a step-wise improvement in terms of efficacy, safety, duration of activity or route of administration compared with the original innovator.[2] Dr GV Prasad, CEO of Dr. Reddy's Laboratories, India, first introduced the term "biobetters" in a conference on biologics in Mumbai in 2007. Since then, it has been widely used but is still not a well-defined term.

Ophthalmology, especially retina as a subspecialty, has been transformed since the introduction of anti-vascular endothelium-derived growth factors (anti-VEGF) more than 15 years ago. Approved innovative anti-VEGF molecules, such as ranibizumab (Lucentis®; Genentech, Inc., South San Francisco, CA, USA), aflibercept (Eylea®; Regeneron Pharmaceuticals, Inc; Tarrytown, NY, USA) and off-label bevacizumab (Avastin®; Genentech, Inc., South San Francisco, CA, USA), have made a significant difference in the management of various retinal vascular diseases.[3,4] The expiry of patents has ushered in an era of biosimilars.[5] Ranibizumab's patent expired in 2020, and aflibercept's patent will expire soon (2023).[1] India was the first country to approve a biosimilar of ranibizumab in 2015 (Razumab, Intas Pharmaceuticals Ltd, Ahmedabad, Gujarat, India).[6] This biosimilar was approved for its use only in India. On 18 August 2021, the US Food and Drug Administration (FDA) and the European Medical Agency approved the biosimilar of ranibizumab, ranibizumab-nuna (Byooviz™, Biogen, Cambridge, MA, USA).[7] At least 20 biosimilar molecules of ranibizumab, aflibercept and bevacizumab are in the pipeline.[1] Biosimilars are new to ophthalmology; however, they have been successfully used in other subspecialties, such as rheumatology, dermatology, gastroenterology, oncology and haematology.[8] This article highlights the future of biosimilars and biobetters in ophthalmology.

The future of biosimilars in ophthalmology is difficult to predict at this point because ophthalmology differs from other specialities due to various factors that differentiate developing countries from developed countries.[9] A major differentiating factor is the presence of low-cost, off-label compounded bevacizumab. Developing countries such as India do not have a robust system of compounding pharmacies for producing bevacizumab; therefore, biosimilars have a better future in such countries than in developed countries, where bevacizumab compounding is safe. This situation has prompted efforts to develop an on-label bevacizumab, bevacizumab-vikg (ONS-5010/Lytenava™; Outlook Therapeutics, Inc., Iselin, NJ, USA); although bevacizumab-vikg is considered an innovator drug rather than a biosimilar, it can change the

marketplace dynamics.[10] According to the recent survey conducted by the Vitreo Retina Society of India, the use of ranibizumab biosimilar has constantly been increasing since its launch in India.[11] Many other ranibizumab biosimilars have been launched in India in the recent past, such as RanizuRel™ (Reliance Life Science, Mumbai, India).[12] One more ranibizumab biosimilar will be launched soon by Lupin Limited (Mumbai, India).[1] The consistent production of biosimilars indicates that companies in the field of ophthalmology are seeing the growth potential of such products.[13]

Ranibizumab-nuna is expected to be available for clinical use in June 2022 in the USA.[7] Recently, we conducted a survey, entitled "Bio-USER Survey" (unpublished data), to investigate the awareness of biosimilars in ophthalmology amongst retina specialists practising in the US and Europe. The survey showed that practitioners from the USA are more comfortable using off-label compounded bevacizumab than European practitioners. The survey also showed that retina specialists from both the USA and Europe need more information before they start using it in their clinical practice. These findings are similar to those recorded by a survey conducted by Cardinal Health.[14] The Bio-USER survey also revealed that most physicians would like to see real-world data before adopting biosimilars.

Biobetters could be a game changer; as of now, however, there are no clear regulatory policies for the approval of biobetters.[15] Currently, they are considered new drugs and have to undergo the full-length process of a clinical trial. This could be why companies prefer to launch these products as new molecules. Based on the current understanding of biobetters, ranibizumab is thought to be a biobetter of bevacizumab. Similarly, the recently approved port delivery system with ranibizumab is probably a biobetter of ranibizumab. In the Republic of Korea, Ildong Pharmaceuticals (Seocho-gu, Seoul, Republic of Korea) is developing a biobetter for patients receiving ranibizumab that is hoped will improve its efficacy and lessen resistance to the drug.[16] Theoretically, a biobetter of brolucizumab could be developed to make it safer in terms of inflammation as an adverse event. At present, the advantages of biobetter molecules are that these drugs can be patented and their research and development costs can lower because their targets are known.

Historically, the adoption of most biosimilars has been slow for most systemic diseases, with a few exceptions.[17] However, biosimilars have helped the affordability and accessibility of these molecules to a larger population. Europe is the most mature region in terms of biosimilar approval and usage. Over the last 10 years, the EU monitoring system for safety concerns has not identified any relevant difference in the nature, severity or frequency of adverse effects between biosimilars and their reference medicines.[18] This shows the strength of the existing regulations.[18] Biosimilars go through a different approval pathway to their originators; for example, they only require one phase III clinical trial compared with the original product, which requires two trials to be approved. Furthermore, unlike the originator, biosimilars' approval in one indication can be extrapolated.[19] However, the future of biosimilars in ophthalmology cannot be generalized globally due to the regional differences stated above. How ranibizumab-nuna is priced could play an important role in its adoption. Usually, the development of biosimilars involves a much higher capital investment than that of generic drugs. Therefore, biosimilar products cannot be priced too low. In general, biosimilar products provide a price advantage of 20–30% over an innovator.[20] However, as the competition increases, the pricing of biosimilars decreases further. For example, the first ranibizumab biosimilar in India costs 40% less than its originator, and two more ranibizumab biosimilars that received approval in India in the recent past are even lower in cost. Lower pricing is the only advantage that biosimilars provide compared with innovator molecules. As the cost of producing biosimilars is actually not much lower than the original biologic product (~20–30%), biosimilars remain a costly option compared with the off-label bevacizumab. Given that bevacizumab can be compounded off label, and given that compounded bevacizumab will be unavailable for use in the USA if an on-label bevacizumab is approved for use by the FDA, the cost of anti-VEGF therapy in the USA is likely to increase substantially.

To summarize, the field of ophthalmology is uniquely placed in the development of biosimilars due to the various factors described above. As biologic pharmacotherapy has advanced at a rapid pace, retina, a subspecialty of ophthalmology, is crowded with existing therapies, such as ranibizumab, off-label bevacizumab, aflibercept and brolucizumab, and newer innovative therapies, such as the port delivery system with ranibizumab (Susvimo™; Genentech, Inc., South San Francisco, CA, USA), faricimab-svoa (Vabsymo™; Genentech, Inc., South San Francisco, CA, USA) and the biosimilar ranibizumab-nuna. In such a crowded space, the future of biosimilar molecules depends on their pricing and on the companies' efforts to educate and mitigate concerns regarding the safety and efficacy of these molecules. Furthermore, biobetters need more clarity from regulators about their approval process. As of now, they are considered new molecules, and originator companies are using them to have an edge on biosimilars by reducing some of the research and development costs because the target is known. ❑

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