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COMMENT

Retina: a unique subspecialty in the biosimilar landscape

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Retina as a subspecialty has transformed since the introduction of anti-vascular endothelial growth factor (anti-VEGF) therapeutics more than a decade ago. Approved intravitreal anti-VEGF agents such as ranibizumab (2006) and aflibercept (2011) have made a significant impact on the visual outcomes of various retinal vascular and choroidal neovascular diseases along with off-label intravitreal bevacizumab [1, 2]. Newer anti-VEGF molecules such as brolucizumab (2019) have been approved in the recent past; however, their use has been limited due to higher rates of inflammation and associated retinovascular complications [3, 4]. Recently, port delivery system (PDS) with ranibizumab received United States Food and Drug Administration (US-FDA) approval as the first sustained-release, long-acting anti-VEGF therapy platform [5]. Faricimab, an intravitreal bispecific antibody that targets both VEGF and angiopoietin 2, has also received US-FDA approval recently [6].

The patents for ranibizumab expired in 2020 and that of aflibercept by 2023 [7]. The expiry of patents has opened up an era of intravitreal anti-VEGF biosimilars [8]. US-FDA and European Medical Agency (EMA) have approved the first biosimilar of ranibizumab in the recent past [9]. India was the first country to approve a biosimilar of ranibizumab (2015) [10]. At least 20 biosimilar molecules of ranibizumab, aflibercept, and bevacizumab are in the pipeline [7]. Although biosimilars are new to ophthalmology, they have been successfully used in other subspecialties such as rheumatology, dermatology, gastroenterology, oncology, and hematology [11]. This article will highlight how retina is a unique landscape for biosimilars.

INTRAVITREAL ROUTE

The vitreous cavity, where drugs are injected, is a small, relatively self-contained environment. Most biosimilars are systemically distributed and their clinical development programs do pharmacokinetic (PK) testing with serial blood sampling in healthy volunteers at a phase 1 trial level. A drug injected intravitreally has minimal systemic exposure. Therefore, the ideal way to analyze PK for an intravitreally administered drug would be to obtain serial intravitreal fluid samples. However, it is not considered safe enough and, therefore, unethical to obtain vitreous samples for this purpose alone. The regulatory agencies have long recognized this issue and, traditionally, have allowed for efficacy, safety, immunogenicity, and PK evaluation in a single trial. In addition, systemic PK sampling is used in a subset of patients of such trials to evaluate safety rather than to establish bioequivalence [12].

PRESENCE OF BEVACIZUMAB

Anti-VEGF therapy for retinal diseases has become unique due to the widespread use of bevacizumab injected intravitreally in an off-label fashion by retina specialists across the globe. This is different from all other specialties of medicine in which biosimilars are being developed. Bevacizumab provides a safe and effective treatment option at 1/20th of the cost of available on-label anti-VEGF agents. Biosimilars, in general, is cost savings compared to their reference on-label therapeutic. However, the savings associated with a biosimilar does not come anywhere close to that of off-label bevacizumab use. A biosimilar still requires a significant cost to develop with reverse engineering and then test for ultimate approval, which will limit how much cost saving is possible [7].

REGION SPECIFIC

In common to all biosimilars are variable coverage and healthcare policies of a given region or country. However, in the retina space, another factor related to bevacizumab compounding comes into play. Most of the developing countries do not have established compounding pharmacies where bevacizumab can be aliquoted into small doses used for intravitreal injections with high safety standards. This has led to multiple incidences of infectious endophthalmitis associated with off-label intravitreal bevacizumab use [13, 14]. Hence, biosimilars, which are available at a reduced price without the need for fractionation, are likely to more acceptable in such markets. On the contrary, most of the developed countries have compounding pharmacies that meet certain regulatory standards to help ensure the safe supply of the bevacizumab product for intraocular use. This could be the crucial differentiator for the success of biosimilars in developing vs developed countries.

INTERCHANGEABILITY

Interchangeable biologics are biosimilars that are approved by the FDA to be substituted by a third party for the reference biologic. In a simple way, they can be substituted similar to how generic drugs are substituted at the pharmacy level. Patients can rely on the safety of these products just as they would on the reference medicine.

Anti-VEGF drugs are administered exclusively by physicians (or nurses in some countries) and not dispensed by pharmacists or paramedical personnel, and thus drug choice options are discussed between the patient and the treating physician. Thus, interchangeability will be a less common phenomenon in ophthalmology, which

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requires a more robust data set for approval. Until now, the US-FDA has approved only two interchangeable biosimilars (Semglee and Cyltezo) for non-ophthalmic diseases.

AWARENESS

The long-term availability of biosimilars in many medical specialties outside of ophthalmology has made clinicians generally well aware of these therapeutics. With biosimilars being new to the retina specialty, there may be slow adoption due to theoretical safety concerns of these biologics that are more difficult to manufacture than small molecules. The first biosimilar of ranibizumab was launched in India in 2015 and has just started to be frequently used by ophthalmologists [15]. However, the rest of the world is still waiting for the availability of the first biosimilar of ranibizumab that has been recently approved by the US-FDA and EMA [9]. Recently, Cardinal Health conducted research via a series of survey questions with community-based retina specialists ($N = 37$) from across the US. This was to understand the awareness and perspectives of ophthalmologists toward biosimilars. When ophthalmologists were asked about their familiarity with biosimilars, 31% of respondents said they are not familiar. Furthermore, more than 50% said they have read about research related to biosimilars, but were not very clear about its various aspects of manufacturing, approval, and clinical trial design [16].

To summarize, retina as a subspeciality is a unique space for biosimilar development, approval, and awareness. This space is likely to be relatively replete with anti-VEGF options with many biosimilars of ranibizumab and aflibercept molecules in the pipeline along with the approved newer therapies such as brolucizumab, PDS with ranibizumab, and faricimab. Education should be at the forefront about biosimilars in retina as the world prepares for the market availability of the first US-FDA–approved biosimilar in this field [17]. Biosimilars are poised to bring significant cost savings to help mitigate the financial burden associated with the management of neovascular age-related macular degeneration, diabetic retinopathy and other retinal vascular diseases. The success of ophthalmic biosimilars in the developed world would primarily depend on the pricing and awareness of these molecules along with the confidence in the clinical data generated from the clinical trials. Biosimilar companies will need to educate providers around the world on biosimilars in the retina space and draw upon the relatively longstanding use of biosimilars in India where it has been widely adopted without significant safety issues. Retina as a subspecialty provides unique opportunities along with the specific challenges in the field of biosimilars. It is yet to be seen how biosimilars will find the right fit in this interesting but soon-to-be crowded anti-VEGF treatment space.

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AUTHOR CONTRIBUTIONS

AS: conception, analysis, drafting, integrity check, final approval. NP, NK, CDR, FB, BDK: drafting, revision, analysis, integrity check.

COMPETING INTERESTS

AS: consultant for Novartis, Allergan, Bayer and Intas. CDR: consultant for Allergan, Chengdu Kanghong, Genentech/Roche, Novartis, Kodiak, Notal, Merck, Shire-Takeda, Adverum, Graybug, and Eyepoint and receives research support from Allergan, Chengdu Kanghong, Genentech/Roche, Novartis, Kodiak, Iveric, and Adverum. FB: consultant for Allergan, Bayer, Boehringer-Ingelheim, FidiaSooft, Hofmann La Roche, Novartis, NTC Pharma, Sifi, Thrombogenics, Zeiss. BDK: clinical research: Alcon, Alimera, Allegro, Allergan, Apellis, Clearside, Genentech, GSK, Ionis, jCyte, Novartis, Regeneron, ThromboGenics; consultant for Alimera, Allegro, Allergan, Cell Care, Dose, Eyedaptic, Galimedix, Genentech, Glaukos, Interface Biologics, jCyte, Novartis, Ophthotech, Regeneron, Revana, Theravance Biopharma. NK and NP: None.

ADDITIONAL INFORMATION

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