Biosimilars for Retinal Diseases: An Update

ASHISH SHARMA, NILESH KUMAR, NIKULAA PARACHURI, FRANCESCO BANDELLO, BARUCH D. KUPPERMANN, AND ANAT LOEWENSTEIN

• PURPOSE: **To review the biosimilars of anti–vascular endothelial growth factor agents for retinal diseases and provide an update about their development.**
• DESIGN: **Literature review.**
• METHODS: **A comprehensive literature review was performed for scientific articles, clinical trials, and press releases for the development of biosimilars in ophthalmology.**
• RESULTS: **To date, Razumab (Intas Pharmaceuticals Ltd, Ahmedabad, GJ, India) is the only approved biosimilar for ophthalmic use, but the landscape will rapidly change in the future with multiple biosimilar candidates, which are currently in phase 3 trials, showing promising early results.**
• CONCLUSION: **Biosimilars hold the potential to reduce the financial burden of the highly efficacious biologic therapy in retinal pathologies. However, the off-label bevacizumab may differentiate the success of biosimilars in different geographic regions. (Am J Ophthalmol 2021;224:36–42. © 2020 Elsevier Inc. All rights reserved.)**

BIOLOGICS TARGETING VASCULAR ENDOTHELIAL growth factor (anti-VEGF) have revolutionized the treatment of retinal vascular pathologies.[1] However, this treatment has caused a significant financial burden on the healthcare sector.[2] Cost of the therapy and unmet expectations for visual gains are the most common reasons for the discontinuation of treatment, especially in developing countries.[3] Biosimilars are the biologically derived products that are "highly similar to approved biologics, having similar safety, purity, and potency, notwithstanding minor differences in clinically inactive components."[4] The development of biosimilar molecules requires a huge amount of research and development resources, unlike generics.[4] Furthermore, marketing approval requires the fulfillment of a robust framework of guidelines to ensure the safety and efficacy of the biosimilars.[5] Despite the high expenditure mentioned above, the overall cost and time to develop a biosimilar is much less than the innovator biologic. Typically, an innovator biologic takes up to 10-15 years to develop, with an expenditure of about 1,200 to 2,500 million US dollars. However, a biosimilar can be manufactured in 8-10 years with approximately one-tenth of the cost (100-200 million US dollars).[6] The reason for this reduction of cost and time in cases of biosimilars is that huge investment in clinical trials is not needed.[4] Biosimilars are required to have a robust analytical bioequivalence to innovator biologics to prove similarity.[4] Thus the preclinical studies are the most important in biosimilar development, as it is at this stage that the molecule has to demonstrate its similarity to biologics for physical and biochemical attributes while demonstrating comparable pharmacodynamic and toxicology profile.[4] Furthermore, clinical trials with fewer participants and shorter follow-up when compared to innovator biologics are allowed by the regulatory authorities to evaluate safety, efficacy, and immunogenicity of the proposed candidate.[5]

The key patents, which provide the market exclusivity to the United States Food and Drug Administration (US FDA)–approved innovator anti-VEGFs (ranibizumab, Genentech, South San Francisco, California, USA; and aflibercept, Regeneron, Tarrytown, New York, USA) used in retinal diseases are nearing expiry. The innovator ranibizumab patent expires in 2020 (USA) and 2022 (Europe), whereas the patent for innovator aflibercept will expire in 2027 (USA and Europe).[7] Both the innovator drugs aflibercept and ranibizumab come off patent in Japan and the People's Republic of China in 2022.[4] Therefore, several intended biosimilars to these 2 innovator anti-VEGFs are now in advanced phases of clinical trials and are nearer to marketing realization than ever (Tables 1 and 2).

Our group had published about the "ophthalmic biosimilar molecules in the pipeline" and their development status in 2018.[4] Furthermore, we had published the "regulatory guidelines related to ophthalmic biosimilars across the globe" in 2019.[5] This article aims to review and update the development status of biosimilars to the 2 FDA-approved innovator anti-VEGF agents (ranibizumab and aflibercept). This will help ophthalmologists to have an understanding about the options of biosimilar anti-VEGFs that might reduce the healthcare burden in the near future.

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From the Lotus Eye Hospital and Institute, Avinashi Road, Coimbatore, Tamil Nadu, India (A.S., N.K., N.P.); University Vita-Salute, Scientific Institute San Raffaele, Milan, Italy (F.B.); Gavin Herbert Eye Institute, University of California, Irvine, Irvine, California, USA (B.D.K.); and Division of Ophthalmology, Tel Aviv Sourasky Medical Center, Tel Aviv University, Tel Aviv, Israel (A.L.).

Inquiries to Ashish Sharma, Lotus Eye Hospital and Institute, Avinashi Road, Civil Aerodrome Post, Peelamedu, Coimbatore, Tamil Nadu, 641014 India; e-mail: drashish79@hotmail.com

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TABLE 1. Biosimilars of Innovator Ranibizumab (Lucentis)

Product Name	Company	Stage of Development
India		
Razumab[8]	Intas Pharmaceuticals Ltd	DCGI (2015) approved
R TPR 024[9]	Reliance Life Sciences Pvt Ltd	Phase 3 completed
Lupin's ranibizumab[10]	Lupin Ltd	Phase 3 active
Europe		
FYB201[11]	Formycon AG//Bioeq, Germany	Resubmission of BLA to US FDA (second half of 2020), phase 3 completed
Xlucane[12]	Xbrane Biopharma, Sweden	Phase 3 active
South Korea		
SB11[13]	Samsung Bioepsis Co Ltd	Phase 3 active
Japan		
SJP-0133[14]	Senju Pharmaceuticals, Japan	Phase 3 active

BLA = biologics license application; DCGI = Drug Controller General of India; US FDA = United States Food and Drug Administration.

METHODS

WE CONDUCTED A COMPREHENSIVE LITERATURE SEARCH of the PubMed and Google Scholar databases and included articles up to July 15, 2020, using the following keywords: Biosimilars in ophthalmology, Biosimilar to anti-VEGF, Biosimilar to ranibizumab, and Biosimilar to aflibercept. During the revision stage of this manuscript, we further added some updated information that we found with the search methodology as described above. Articles cited in the reference lists obtained by this method were reviewed and included if considered appropriate, and were filtered manually to exclude duplicates. Google search engine was used to search for the press releases and investors' reports by the pharmaceutical companies to retrieve information about the timeline of the development of these biosimilars. There was no language restriction, and Google translator was used for translating the native-language articles into English. A total of 53 sources were analyzed for the preparation of the manuscript, including the revision stages. Twenty-one articles from PubMed indexed journals, 18 webpages including investors' reports and press releases, 10 clinical trial registries, 3 conference papers from archives, and 1 video from online archive were included. Twenty-one of these sources pertained to the biosimilars of ranibizumab and 8 to the biosimilars of aflibercept.

RESULTS

• **BIOSIMILARS TO RANIBIZUMAB:** A total of 7 molecules were found in this category. The first molecule is Razumab, which is approved in India. Six other molecules (FYB201, Germany; R TPR 024 and Lupin's ranibizumab, India; Xlucane, Sweden; SB11, and SJP-0133, Japan) are in the advanced stages of clinical trials (Table 1).

Razumab (Intas Pharmaceuticals Ltd, Ahmedabad, GJ, India), is, to date, the only biosimilar to innovator ranibizumab to have gained marketing approval (in 2015) from the drug regulator of India, who is the Drug Controller General of India, for neovascular age-related macular degeneration (nAMD), diabetic macular edema, and retinal vein occlusion (RVO).[7] As physicochemical, pharmacodynamic, and pharmacokinetic properties are to be matched with the innovator molecules, Razumab has been tested head-to-head with innovator ranibizumab by Griaud and associates.[20] The study demonstrated that Razumab was not different from innovator ranibizumab in terms of relative binding and potency, but some differences were observed in the serine and asparagine sequences. Post-marketing, Sharma and associates have published clinical data of nAMD and RVO cases (Re-ENACT and Re-ENACT 2) and reported the drug to be safe and effective.[8,21,22] However, incidences of sterile intraocular inflammation were reported in a few specific batches soon after its market approval.[23] Manufacturers identified the cause as higher endotoxin levels owing to the buffer used in the manufacturing process. After revision of the manufacturing process, the safety of the molecule was re-established and presented at various scientific meetings (Banker A. Paper presented at American Society of Retina Specialists Annual Meeting. August 9-14, 2016; San Francisco, California, unpublished data) and (Shah R. Use of biosimiliar ranibuzumab (razumab) in macular pathology. Paper presented at 18th Euretina Congress. September 20-23, 2018; Vienna, Austria, unpublished data).

The phase 3 trial for nAMD (COLUMBUS-AMD) with FYB201 (Formycon AG, Munich, Germany, and bioeq GmbH, Holzkirchen, Germany) met its primary endpoint and confirmed a similar efficacy and safety profile to innovator ranibizumab. It was a quadruple-masked, multicenter interventional trial to evaluate and compare functional changes in best-corrected visual acuity (BCVA) after

TABLE 2. Biosimilars of Innovator Aflibercept (Eylea)

Product Name	Company	Stage of Development
USA		
MYL-1701P/M710[15]	Mylan Inc/Momenta Pharmaceuticals, Inc	Phase 3 active
ABP-938[16]	Amgen	Phase 3 active
CHS-2020[17]	Coherus BioSciences	Phase 3 to start in 2021
Europe		
FYB203[18]	Formycon AG/Bioeq, Germany	Phase 3 active
South Korea		
SB15[19]	Samsung Bioepsis Co Ltd	Phase 3 active

2 months (8 weeks) of treatment with either FYB201 or innovator ranibizumab. The confidence interval lay within the predefined equivalence limits without any abnormalities regarding safety and immunogenicity.[24,11] Recently, the 48-week results of the phase 3 trial were presented at the American Academy of Ophthalmology 2020 virtual meeting. It showed that similar efficacy was maintained among FYB201-treated patients at 48 weeks, vs innovator ranibizumab (+7.9 letters vs +8.5 letters).[25] The manufacturers filed a biologics license application with the US FDA in December 2019 but withdrew the same, as it required further manufacturing data regarding the production site. These additional requests were not related to the quality of the drug substance or other product characteristics. The reapplication is expected in 2020.[26]

SB11 (Samsung Bioepis Co Ltd, Incheon, South Korea) is another proposed candidate in phase 3, quadruple-masked, multicenter trial to evaluate its efficacy, safety, pharmacokinetics, and immunogenicity against innovator ranibizumab. The trial recruited 705 patients with nAMD who will continue to receive either SB11 or innovator ranibizumab (randomized 1:1) every 4 weeks until week 48, with the last assessment at 52 weeks. Interim results at 24 weeks showed that its primary endpoints, that is, change from baseline in BCVA at week 8 and central subfield thickness (CST) at week 4, were met successfully. The least-squares mean change in BCVA was 6.2 letters for SB11, compared to 7.0 letters for innovator ranibizumab. The least-squares mean change in CST was −108.4 μm for SB11 vs −100.1 μm for innovator ranibizumab. The confidence intervals of the difference between the 2 treatments in regard to BCVA (±3 letters) and CST (±36 μm) were within the predefined equivalence margins. The treatment-emergent adverse events were 66% for SB11 compared to 66.9% for innovator ranibizumab, while the incidences for anti-drug antibody were 3.0% and 3.1%, respectively.[13] Recently the European Medicines Agency has accepted to review the marketing authorization application for SB11.[27] US FDA filling is expected in 2020.[12]

XPLORE, the phase 3 trial of Xlucane (Xbrane Biopharma, Solna, Sweden) is a multicenter, double-masked trial to assess the change in BCVA at 8 weeks compared to baseline as its primary endpoint. The study involves 580 participants with nAMD, randomized 1:1 to receive either Xlucane or innovator ranibizumab every 4 weeks until 52 weeks, when secondary outcomes will be evaluated.[28] The XPLORE trial had recruited 355 of the 580 (61%) planned patients as of April 21, 2020. The manufacturer has stated that they would like to meet the deadline for marketing approval in the United States and Europe as soon as the patent for innovator ranibizumab expires.[9]

R TPR 024 (Reliance Life Sciences Pvt Ltd, Navi Mumbai, MH, India) completed the phase 3 prospective, multicenter, randomized, double-masked, 2-arm, parallel-group, active-control, comparative trial in November 2019. It recruited 159 patients with nAMD who were randomized and injected with R TPR 024 or innovator ranibizumab every 4 weeks for 24 weeks with a follow-up period of 6 months.[14] The detailed results have not yet been released.

SJP-0133 (Senju Pharmaceutical, Osaka, Japan) has completed recruiting for phase 3 trials and aims to complete the study by 2022. It is a randomized, single-masked, active-control trial with a sample size of 338. Three intravitreal injections of SJP-0133 or innovator ranibizumab will be given once every 4 weeks from the start of treatment to week 8 followed by pro re nata injections from week 12 to week 48. The main outcome criterion for assessment is BCVA.[10] To the best of our knowledge it is the only biosimilar to ranibizumab to date that has a comparative trial with a pro re nata regime instead of a fixed dosing interval.

The biosimilar candidate by Lupin Ltd, Mumbai, MH, India entered a phase 3 parallel-group, double-masked, multicenter, prospective trial in March 2019 and recruited 200 patients (India specific) to be injected every month for 3 months and analysis of primary outcome (change in BCVA from baseline) to be done at the end of 3 months.[29] Recruitment is going on for the phase 3 global trial. The company intends to recruit 656 patients for the global trial. Global trial patients will be given an injection every 4 weeks over a treatment period of 48 weeks. The primary outcome (change in BCVA from baseline) will be assessed at 8 weeks[15] (Table 1).

• **BIOSIMILARS TO AFLIBERCEPT:** A total of 5 molecules (MYL-1710P, ABP-938, and CHS-2020, USA; FYB203, Germany; SB15, South Korea) are in advanced stages of clinical trials (Table 2).

MYL-1701P (formerly known as M710; Mylan, Inc, Canonsburg, PA, USA/Momenta Pharmaceuticals, Inc, Cambridge, MA, USA) is being evaluated in a double-masked, multicenter phase 3 trial in 324 diabetic patients with central diabetic macular edema, randomized 1:1 to receive MYL-1701P or innovator aflibercept every 8 weeks until 48 weeks.[30] Patients will be followed up every 4 weeks until 52 weeks. The primary outcome measure is change in BCVA at 8 weeks from the baseline. Mylan expects to target US FDA submission in 2021 with anticipated marketing in the United States by 2023 if approved.[16]

ABP-938 (Amgen, Thousand Oaks, CA, USA) is another candidate in phase 3 trials. It aims to recruit 566 patients with nAMD in its multicenter trial. Subjects will be randomized 1:1 in 2 groups receiving either ABP-938 or innovator aflibercept every 8 weeks. The patients receiving innovator aflibercept will be rerandomized 1:1 at 16 weeks, with half the patients being switched to ABP-938. The patients will receive drugs until 48 weeks and will be followed up until 52 weeks. The primary outcome measures change in BCVA at 8 weeks from the baseline The study is proposed to be completed by July 2023.[18]

FYB203 (Formycon AG, Munich, Germany, and Bioeq GmbH, Holzkirchen, Germany) has initiated the phase 3 clinical trial (MAGELLAN-AMD), which started recruiting in March 2020. It is a randomized, double-masked, multicenter study to compare the efficacy and safety of FYB203 in comparison to innovator aflibercept in patients with nAMD. The company plans to recruit 400 subjects, with a primary outcome (change in BCVA from baseline) assessment at 8 weeks.[31] Formycon and Bioeq announced intention to submit a Marketing Authorisation Application (MAA) in the United States, European Union, and Japan for nAMD.[19]

SB15 (Samsung Bioepis Co, Ltd) has initiated phase 3 randomized, double-masked, parallel-group, multicenter study trials. The company has a plan to recruit 446 patients. Subjects will be randomized 1:1 in 2 groups receiving either SB15 or innovator aflibercept every 4 weeks for the first 3 months, followed by every 8 weeks until week 48. At week 32, subjects in the innovator aflibercept group will rerandomize into SB15 or the innovator aflibercept group. After rerandomization, subjects transited to the SB15 group will receive SB15 once every 8 weeks until week 48, and subjects remaining in the innovator aflibercept group will continue to receive the innovator aflibercept once every 8 weeks until week 48. Primary outcome assessment (change in BCVA from baseline) will be done at 8 weeks.[17]

CHS-2020 (Coherus BioSciences, Redwood City, CA, USA) has advanced in its preclinical trials with an expected initiation of phase 3 trials by 2021 and a biologics license application filing with the US FDA by 2025[32] (Table 2).

• **SAFETY OF BIOSIMILARS:** Immunogenicity has been the major point of assessment of anti-VEGFs in the recent past. Incidences of intraocular inflammation have been reported with all the innovator molecules, including the recently approved brolucizumab.[33–35] The immunogenicity to biologic (innovator or biosimilar) agents may arise from the antibodies to the molecules, termed the anti-drug antibodies, or owing to other factors such as endotoxin levels.[23,36,37] We have emphasized the need for immunogenicity testing for the biosimilars to be released in the future.[37] Our group has analyzed the immunogenicity data when physicians switched from innovator ranibizumab to biosimilar ranibizumab (Razumab). We have found no alarming immunogenicity signals during such a switch.[38] According to the trials underway, most of the biosimilar drugs have done well in terms of efficacy and safety. However, it remains to be seen if the clinical trial results will be reproduced once these molecules are used in the real world.

• **CHANGES IN PATENT LAWS:** The European Medicines Agency is considered to be the most experienced body in the field of biosimilars. With a recent change in the European patent law effective from July 1, 2019, European manufacturers can manufacture biosimilars and export to countries where protection of the innovator molecule does not exist. They can also initiate manufacturing for local supply (Europe) 6 months before the extended expiry of the patent by innovator companies.[39]

DISCUSSION

THE DEVELOPMENT OF BIOSIMILARS OF ANTI-VEGF MOLECULES to be used in ophthalmology is more often than not driven by economics.[6] The development of 2 agents (PF582 and CHS-3351) that we had mentioned in our previous paper has been discontinued.[4,40,41] The development of PF582 (Pfnex Inc, San Diego, CA, USA) has been on hold since 2018. The drug had progressed through phase 1/2 studies but has not advanced.[40] Development of CHS-3351 ceased when Coherus Inc entered into a marketing agreement with Formycon/Bioeq IP for their biosimilar candidate to ranibizumab FYB201, and allocated the resources to develop CHS-2020, a biosimilar candidate to aflibercept.[41] Failure of progression of these 2 molecules shows that the development process of biosimilars for a manufacturer is not as easy as it seems, though there is an advantage of a less rigorous clinical trial phase. Biosimilars have the potential to make the therapy cheaper for patients owing to their lower investment cost.[6] The presence of bevacizumab, however, might be an important factor to

watch, as it is a very low-cost and effective therapy for similar indications. Comparisons of the Age-Related Macular Degeneration Treatments Trials (CATT) and Inhibit VEGF in Age-related choroidal Neovascularisation (IVAN) trials have proved that bevacizumab and ranibizumab had equivalent effects on visual acuity when given using the same dosing regimen.[42,43] In the United States, bevacizumab is the most common anti-VEGF being used. Similarly, bevacizumab is being used as a first-line drug in many other countries.[44–46] Apart from this, innovator companies can extend the patent claims as Regeneron has extended the patent of Eylea up to 2027. This may derail the plan to launch biosimilar drugs earlier in the United States and Europe.[7] According to a recent virtual symposium, experts from the United States and India have opined that entry of biosimilars might have a different impact in the developing and the developed world. In developing countries, biosimilars can be a potentially cost-effective alternative to bevacizumab without the risk of contamination owing to deficiency of robust compounding pharmacies.[47] However, biosimilars may not have the same impact in the developed world, where bevacizumab is cheap and available without substantial risk.[47] Development of other innovator anti-VEGF therapies, such as a sustained drug delivery device for ranibizumab, and faricimab, might further change the dynamics of how biosimilars would fit in the armamentarium.[48,49]

The highly efficacious biologic therapy has revolutionized outcomes of many retinal vascular pathologies but has added a huge financial burden on the healthcare system.[2]

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