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REVIEW

Ranibizumab Biosimilars in Treating Retinal Disorders: A Cost-Effective Revolution?

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Abstract: Ranibizumab, is a humanized, monoclonal antibody fragment that binds and inactivates vascular endothelial growth factor-A (VEGF-A) and VEGF-B. One of the main indications for an intravitreal treatment with ranibizumab is age-related macular degeneration (AMD), which is a retinal disease with a high worldwide socioeconomic impact. Biosimilars constitute biological products that demonstrate similar pharmacodynamic and pharmacokinetic characteristics with a reference product, as well as comparable clinical efficacy, safety and immunogenicity. Since the approval of the first biosimilar Razumab, there has been a variety of new biosimilars available on the market. They offer the advantage of the same good clinical and safety results at a better price. All Ranibizumab biosimilars that have gained approval were tested in double masked Phase 3 clinical studies. The use of Ranibizumab biosimilars in neovascular AMD is well reported in the bibliography. Nevertheless, over the last few years, there is a tendency of using biosimilars in other retinal diseases like retinopathy of prematurity (ROP), diabetic macular edema (DME) or polypoidal choroidal vasculopathy (PCV). In conclusion, ranibizumab biosimilars offer a promising avenue for the management of retinal diseases, especially in countries with lower socioeconomic status, where there is lack of availability of innovator ranibizumab. However, further research is required to fully explore their efficacy, safety, and long-term outcomes in a plethora of retinal diseases.
Keywords: ranibizumab, biosimilars, age-related macular degeneration, diabetic macular edema, retinal disorders, retinal vein occlusion, cost-effectiveness

Introduction

Age-related macular degeneration (AMD) is the leading cause of blindness on a world basis, especially in countries with higher socioeconomic status and has two forms: dry or non – neovascular and wet or neovascular (nAMD).[1,2] Prevalence of AMD rises after 50 years. One of the main indications for the therapy with Ranibizumab is neovascular AMD (nAMD), which constitutes only 10–15% of all AMD but carries the responsibility for the most AMD-related visual loss cases.[3] Nowadays, the current standard therapeutic approach of AMD includes therapy with intravitreal injections of anti-vascular endothelial growth factor (anti-VEGF), such as ranibizumab, aflibercept, brolucizumab and faricimab. However, the high costs of anti-VEGF therapy carry an important economical burden for the healthcare systems.[4]

Ranibizumab, is a recombinant, humanized, monoclonal antibody fragment that binds and neutralizes all forms of active vascular endothelial growth factor (VEGF) A.[5,6] Ranibizumab has been used for the treatment of nAMD since its approval from the Food and Drug Administration (FDA) in 2006 and the European Medicines Agency (EMA) in 2007.[7]

Biosimilars are biological medical products that are comparable and have no clinical meaningful differences from an already-approved reference medicine.[8] Design and development of a biosimilar is challenging, considering that minor changes in the structure of the drug, can lead to alterations in the efficacy and safety of the end drug.[9] They also undergo an extensive evaluation process, in order to be approved for use in clinical practice. Due to their new appearance in ophthalmology, biosimilars are as of today faced with some hesitancy from the clinicians. Razumab was the first biosimilar of ranibizumab to receive an approval in India and to be used in a clinical setting.[10]

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In this literature review article, we aim to provide a synopsis of the available data regarding the biosimilars of ranibizumab. Topics such as mechanism of action of ranibizumab, the efficacy of its biosimilars in the treatment of various retinal diseases as well as their safety and immunogenicity profile through the outcomes of all major clinical studies, will be elucidated.

Definition of Biosimilars

To begin with, the definition of biosimilars and differentiation from biobetters is essential. As mentioned in the introduction, biosimilars are biological products that exhibit high similarity to an approved innovator product, without any differences in efficiency, purity and safety.[11] In contrast, biobetters are novel medical products that are based on already marketed biologics that possess enhanced efficacy with higher selectivity as well as improved safety profile, with lower toxicity or immunogenicity.[12] The first biosimilar to be placed in the market was Omnitrope® (a recombinant human growth hormone) that received an approval from EMA in 2006. Since then, many biosimilars in numerous fields of medicine have been approved.[13]

Pharmacological Properties of Ranibizumab

VEGF-A is a glycoprotein that plays a key role in endothelial cell migrations, vascular leakage and angiogenesis.[14] In case of tissular hypoxia, VEGF-A expression is stimulated.[15] Ranibizumab is a monoclonal antibody fragment that is produced by the gram-negative bacterium, *Escherichia coli,* and has a molecular weight of 48kD. The rationale for developing Ranibizumab as a fragment antigen-binding (Fab) is based on the hypothesis that its small size enables better tissue penetration through all retinal layers.[16]

Each molecule of ranibizumab possesses only one binding site for VEGF, allowing each VEGF dimer to be bound by two ranibizumab molecules.[17] Ranibizumab blocks all isoforms of VEGF-A and through its mechanism of action prevents the interaction of VEGF-A with its receptors leading to reduced vascular permeability, angiogenesis and endothelial cell proliferation.[6,18]

With regard to pharmacokinetics in adults, it has been estimated that ranibizumab has a mean vitreous half-time of 8.6 days and reaches its maximal serum concentration 0.5 days after intravitreal (ITV) administration.[19] Pharmacological studies indicate that a single dose of ranibizumab (0.5 mg) results in a serum concentration of 1.5 ng/mL one day after administration. However, following monthly injections, patients exhibit serum levels ranging from 0.3 ng/mL to 2.36 ng/mL.[20] In addition, a systemic-to-vitreous exposure ratio of 1 to 90,000 has been reported.[19]

In relation to pharmacokinetics of ranibizumab in infants, the Rainbow trial evaluated the pharmacokinetics of ranibizumab in preterm infants with retinopathy of prematurity (ROP). Median half-time of ocular elimination of ranibizumab was found to be 5.6 days, much lower than the reported equivalent data from adults [8.6 days], while the median elimination rate in the serum was estimated 0.3 days, showing a three-times lower rate compared to adults.[21]

Ranibizumab Biosimilars in nAMD

The first biosimilar molecule of ranibizumab to be approved in 2015 was Razumab® (Intas Pharmaceuticals, Ahmedabad, India; BRm; Razumab®) for the treatment of nAMD and macular edema secondary to retinal vein occlusions.[22] The decision for approval was made by the Drug Controller General of India based on the promising results from a large multicenter study on the use of Razumab, the RE-ENACT study.

The RE-ENACT 2 was a multicenter retrospective study with 17 centers across India that included 103 patients with neovascular AMD that were treated with the biosimilar Razumab.[10] The patients received 3 (range 1–5) injections and were divided into classic choroidal neovascularization (CNV) and occult CNV subgroups. The endpoints were controlled at week 4, 8, 12, 16, 20, 24, 30, 36, and 48. More specifically, a significant improvement in Best-Corrected Visual Acuity (BCVA) from baseline to 48 weeks was reported in both classic (baseline, 0.98 ± 0.08; week 48, 0.50 ± 0.1) and occult (baseline, 0.69 ± 0.18; week 48, 0.54 ± 0.24) CNV subgroups. Similarly, a significant decrease in Central Subfield Thickness (CSFT) from baseline to week 48 where reported for classic and occult subgroups (449.67 ± 18.26 vs 306.40 ± 12.46 and 375.08 ± 20.63 vs 275.00 ± 42.45 respectively). The final two endpoints considered by the authors were the analysis of intra- and subretinal fluid (IRF and SRF, respectively). They found a significant ($P < 0.05$) reduction

in the number of patients with IRF or SRF and observed no significant changes in intraocular pressure when compared to the baseline. RE-ENACT 2 manifested no new safety concerns compared to the reference ranibizumab. Moreover, Razumab was evaluated in another retrospective real word study, the Balance Trial, with 164 eyes, which were treated either with the ranibizumab or the biosimilar Razumab.[23] The results showed similar efficacy with significant improvement in BCVA and significant decrease in central macular thickness (CMT) at all time points. The authors noted improvements in SRF and IRF, observing no significant differences in these outcomes between the treatment with ranibizumab and its biosimilar, Razumab. Additionally, no serious adverse effects were reported.

FYB201 (Formycon AG and bioeq GmbH, Germany) is another biosimilar that gained approval from FDA and EMA in 2022.[3] The COLUMBUS-AMD was a multi-center Phase III study which was conducted to compare FYB201 with the reference ranibizumab. The study included 477 patients with nAMD [238 patients in the FY201 group and 239 patients in the reference ranibizumab group] who received in total 12 injections. BCVA was taken as primary endpoint and was improved at week 8 in both groups with a mean change of +5.1 ETDRS letters in the FYB201 group and +5.6 ETDRS letters in the reference ranibizumab group. Secondary end points included foveal CSFT, which showed a mean reduction of −182.9 μm (FYB201) and −190.8 μm (reference ranibizumab) and foveal center point, with a mean reduction of −213.3 μm in the FYB201 group and −211.0 μm in the reference ranibizumab group. No significant differences between the two groups were noticed, in terms of pharmacokinetics, adverse effects and immunogenicity.

SB11 is a biosimilar that was advanced from Samsung Bioepis, South Korea, and was approved in 2021 by FDA and EMA. The study that proved the biosimilarity of SB11 to ranibizumab was conducted by Woo et al and was a multicenter randomized, double-masked phase 3 trial.[5] Seven hundred and four individuals after randomization received SB11 (n = 351) or ranibizumab (n = 354), and 671 (95.2%) of those reached week 24 (SB11, 334; ranibizumab, 337). Results showed equivalent efficacy of both products regarding primary and secondary endpoints. The mean change of BCVA at week 8 was +6.2 letters in the SB11 group and +7.0 letters in the reference ranibizumab group. Regarding changes in CSFT from baseline at week 4, the SB11 group (n = 342) showed a mean decrease of −108 μm, while the ranibizumab group exhibited a decrease of −100 μm. A relative short period of follow-up (24 months) was a limitation of this study.

RanizuRel (Reliance Life Sciences, Mumbai, India), a ranibizumab biosimilar from India, was approved by the Drug Controller General of India in 2021, after the positive results from a prospective, multicenter, double blind study with 160 subjects.[24] After randomization, subjects received either the biosimilar RanizuRel or the innovator ranibizumab. The results showed no significant difference between the two groups in terms of visual acuity and reduction of CMT, while no serious complications related to the injections were reported.

CKD-701 (Chong Kun Dang, South Korea) is a ranibizumab biosimilar that was evaluated in a multicenter study in Korea with 291 subjects, in which the subjects after randomization received either CKD-701 or reference Ranibizumab.[25] In comparing the biosimilar with the innovator ranibizumab, the authors identified the primary endpoint as the proportion of patients experiencing a loss of fewer than 15 letters in BCVA at three months. In this measure, 143 patients (97.95%) in the CKD-701 group and 143 patients (98.62%) in the reference group were observed (P = 0.67). In terms of BCVA, a mean improvement of +7.0 (CKD-701) and +6.2 (ranibizumab) letters at 3 months was observed without significant difference between the two groups (P = 0.43). The number of patients without IRF and SRF was not significantly different between CKD-701 and ranibizumab group at 3, 6, and 12 months, whereas the central retinal thickness (CRT) was significantly decreased in both groups. The average number of intravitreal injections during the whole study was 8.36 ±3.13 in the CKD-701 group and 8.26 ±2.92 in the reference group, showing no significant difference between the groups (P = 0.619).

The last biosimilar to receive an approval from FDA and EMA is XSB-001 (Ximluci from STADA Arzneimittel AG). XSB-001 in Phase III study demonstrated biosimilarity to the reference ranibizumab.[26] This double-masked study involved 528 patients (292 in the XSB-001 group and 290 in the reference product group) with mean age of 74.1 years. At week 52, least square (LS) mean (SE) change in BCVA was 6.4 (0.8) in the XSB-001 group and 7.8 (0.8) letters in the reference ranibizumab group. No clinically significant differences between the two groups in terms of safety or immunogenicity were noticed. In addition, pharmacokinetic analysis provided similar plasma levels of ranibizumab between the XSB-001 group and the reference ranibizumab group on day 1 (2230 pg/mL and 2190 pg/mL respectively)

as well as at week 20 (2450 pg/m and 2150 pg/m respectively). The authors reported a similar rate of treatment-emergent adverse events between the two groups (67.5% for the XSB-001-group and 70.6% for the reference ranibizumab).

Lupin's biosimilar ranibizumab showed promising results in a prospective phase 3 study in India with 202 patients in a relatively short follow-up time of 3 months.[27] The results showed comparable visual outcomes and safety profile between the Lupin's biosimilar and the innovator ranibizumab. However, as of today, to the best of our knowledge, this agent has not yet gained approval.

A summary of the studies on the use of ranibizumab biosimilars in nAMD is depicted in Table 1.

Table 1 Overview of Studies on the Use of Ranibizumab Biosimilars in nAMD

Author Year	Biosimilar	Number of Eyes	Key Findings
Sharma et al 2020[10]	Razumab® Intas Pharmaceuticals, India	103	• The average BCVA and subfield thickness was significantly improved at all time endpoints. • IOP changed minimally and not significantly. • Decrease in proportions of patients having IRF or SRF.
Holz et al 2021[3]	FYB201 (bioeq GmbH, Holzkirchen, Germany)	477	• BCVA improved +5.1 (in the FYB201 group) and +5.6 ETDRS letters in the reference ranibizumab group at week 8. • Primary endpoint was met as the 90% CI was within the predefined equivalence margin. • Adverse events were comparable between treatment groups.
Woo et al 2023[5]	SB11 (Samsung Bioepis)	705	• Mean BCVA changed from baseline at week 8 6.2 (0.5) letters in the SB11 group and 7.0 (0.5) letters in the ranibizumab group. • Changes of SE in CST from baseline at week 4 were −108 (5) μm in the SB11 group and −100 (5) μm in the ranibizumab group. • Similar occurrence of adverse effects in the SB11 and ranibizumab groups. • Low immunogenicity.
Apsangikar et al 2021[24]	RanizuRel (Reliance Life Sciences, Mumbai, India)	160	• 105 patients in the test arm (RanizuRel) lost fewer than 15 letters in BCVA from baseline, compared to 53 patients in the reference arm (ranibizumab). • The mean number of letters ETDRS that were gained at 6 months was 15.66 in the group of ranibizumab and 12.11 ETDRS letters in the group of RanizuRel, with a non-significant difference between the two groups (p=0.07534). • The mean change in CMT at 6 months was −64.42 μm in the ranibizumab group and −89.93 μm in the biosimilar group without significant difference between the two groups.
Yoon et al 2022[25]	CKD-701 (Chong Kun Dang, South Korea)	143	• The BCVA improved with a mean improvement of +7.0 (CKD-701) and +6.2 (ranibizumab) letters at 3 months (P = 0.43). • The percentage of patients with subretinal or intraretinal fluid at 3, 6, and 12 months did not differ significantly between the groups of the study. • The number (SE) of injections was 8.36 (3.13) in the CKD-701 group and 8.26 (2.92) in the reference ranibizumab group (P = 0.62). • The incidence of adverse events and immunogenicity were not statistically different in the study arms.
Singh et al 2022[27]	Lupin's Ranibizumab	174	• On the 90th day, the calculated treatment contrast between Lupin's ranibizumab and the innovator ranibizumab group fell within the pre-established equivalence margin of 8.5% concerning the percentage of patients who exhibited a reduction of fewer than 15 letters. • Consistent improvement of mean BCVA was reported at days 31, 61, and 90 as compared to the baseline, in both therapeutic groups.

(*Continued*)

Table 1 (Continued).

Author Year	Biosimilar	Number of Eyes	Key Findings
Loewenstein et al 2023[26]	XSB-001 (Ximluci; STADA Arzneimittel AG)	582	• At week 8, the LS mean (standard error [SE]) change in BCVA from baseline was 4.6 (0.5) ETDRS letters in the XSB-001 group and 6.4 (0.5) letters in the reference ranibizumab group. • The 90% CI and 95% CI for LS mean difference in change from baseline were within the predefined equivalence margin. • LS mean (SE) change in BCVA was 6.4 (0.8) and 7.8 (0.8) letters, respectively, at week 52. • No meaningful differences between treatment groups in anatomical, safety, or immunogenicity end points through week 52.
Chakraborty et al 2023[23]	Razumab® (Intas Pharmaceuticals, India)	164	• BCVA was significantly improved from 0.57±0.27 logMAR to 0.41±0.23 at 12 months in the ranibizumab group and from 0.61±0.25 to 0.24±0.16 in the razumab group. • CMT was significantly decreased in the razumab group from 407.82±53.07μm at the baseline to 283.09±19.66 μm at week 12. • Similar improvement of SRF and IRF without significance. • No major adverse effects were noticed.

Abbreviations: BCVA, Best Corrected Visual Acuity; CI, Confidence Interval; CST, Central Subfield Thickness; CMT, Central Macular Thickness; LS, Least Squares, IOP, Intraocular Pressure: SRF, Subretinal Fluid; IRF, Intraretinal Fluid.

Ranibizumab Biosimilars in Other Retinal Conditions

In this section, we provide a comprehensive summary of the most important studies that demonstrated the efficacy of Ranibizumab biosimilars in the treatment of retinal conditions other than nAMD.

The RE-ENACT study was a retrospective, multicenter study, which in a pooled analysis evaluated the effect of Razumab in patients who had received ≥3 injections in a sample of 160 patients with retinal vein occlusion (RVO).[22] From week 8, the improvement in BCVA gained statistical significance (0.55 ± 0.02; $p < 0.0001$), which remained till week 12 (0.47 ± 0.02; $p < 0.0001$). CMT, IRF and SRF were the other end points of the RE-ENACT study. More particularly, a significant reduction in CMT was observed at both week 8 [339.28 ± 8.12 μm] and week 12 [298.23 ± 6.68], while the reduction in the proportion of patients having IRF or SRF was significant at all screening points (weeks 4, 8, and 12). An analysis in subgroups of branch and central RVO revealed similar results, with Razumab showing no safety concerns.

In a large study from India on ROP, 118 eyes of 59 neonates received Razumab.[28] The authors reported complete resolution of ROP in 22 eyes (19%) at an average of 55 days post-treatment. The study found a 35% recurrence rate of neovascularization, affecting 42 eyes. The remaining 54 eyes (46%) showed no recurrence of ROP but also did not achieve complete vascularization of the retina. Notably, neonates who presented with ROP recurrence after Razumab treatment had negative prognostic factors, such as significantly lower gestational age and birth weight, and longer stays in the neonatal intensive care unit (NICU).

Regarding diabetic macular edema, the biosimilar Razumab (from Razumab-Intas, India) was compared with the reference Ranibizumab in a study involving 333 eyes from 303 patients.[29] Treatment with Razumab showed an improvement in the mean BCVA at 6 months from 0.64 ± 0.39 logMAR to 0.47 ± 0.31 logMAR, similar to the reference group with 0.50 ± 0.29 logMAR from 0.71 ± 0.42 logMAR. As for CMT, an overall reduction by 117 ± 196 μm at the last follow-up was reported, with no statistically significant differences between Razumab and the reference ranibizumab. The authors mentioned no difference in the mean number of injections taken between the two groups.

In a retrospective study from Soman et al,[30] Razumab® (Intas Pharmaceuticals, Ahmedabad, India; BRm; Razumab®) was evaluated in 41 eyes from 41 patients with polypoidal choroidal vasculopathy (PCV) (22 eyes were treated with ranibizumab, while 19 eyes with Razumab). Results between the two groups were comparable in terms of BCVA gains

(P=0.19). Surprisingly, the mean number of intravitreal injections were significantly more in the Ranibizumab reference group than in the Razumab group (Innovator ranibizumab: 5.41 ± 0.94; Biosimilar ranibizumab: 4 ± 1.45; $P = 0.0004$). At week 52, the group of innovator ranibizumab exhibited a significant reduction in the SRF but not in the subfoveal choroidal thickness (SFCT) and the group of Razumab showed significant reduction in the SFCT but not in the SRF.[30]

Finally, in a retrospective case series from India, the efficacy of the biosimilar Razumab was evaluated in comparison to innovator ranibizumab and to bevacizumab in patients with dry AMD, as well as in patients with macular edema due to diabetes and retinal vein occlusion.[31] This study included 202 patients, who were divided into the active nAMD group (n=115) and the macular edema (secondary to diabetes or RVO) group (n=87). The primary outcome was a statistically significant improvement in the BCVA in both groups at 3 months. Regarding CMT, the reduction was significant in the nAMD group at both 3 and 6 months and in the macular edema group at 3 months, but at 6 months the reduction was significant only in the reference ranibizumab group. The mean numbers of intravitreal injections were 6.68 in the reference ranibizumab group, 6.4 in the bevacizumab group and 4.7 in the biosimilar Razumab group.

A summary of the studies on the use of ranibizumab biosimilars in retinal conditions other than nAMD is depicted in Table 2.

Safety Profile and Immunogenicity

Safety is a factor of paramount importance when it comes to the use of biosimilars. After the evaluation of a possible biosimilarity, pre-clinical and clinical evaluations follow and in order to be approved, a controlled clinical trial that compares the clinical efficacy and safety of the biosimilar to the reference product has to be carried out.[32]

Table 2 Overview of Studies on the Use of Ranibizumab Biosimilars in Other Retinal Conditions

Author Year	Biosimilar Tested	Number of Eyes	Disease	Key Findings
Sharma et al 2019[22]	Razumab® Intas Pharmaceuticals, India	160	RVO	• Significant BCVA improvement from week 8 (0.55 ± 0.02; $p < 0.0001$) and week 12 (0.47 ± 0.02; $p < 0.0001$). • Significant decrease in CMT at week 4, 8 and 12. • The proportion of patients with IRF and SRF significantly decreased from baseline to weeks 4, 8, and 12.
Prajapati et al 2023[28]	Razumab® Intas Pharmaceuticals, India	118	ROP	• Complete resolution of ROP along with complete vascularization was seen in 22 eyes (19%) at a median of 55 days, 42 eyes (35%) showed a recurrent neovascularization at a median of 51 days post injection. • The cumulative incidence of recurrence of neovascularization was significantly superior in eyes with APROP (43%, 95% CI = 27%–63%) compared to eyes without APROP (13.4%, 95% CI, 8%-22%) ($P < 0.001$).
Chakraborty et al 2022[29]	Razumab® Intas Pharmaceuticals, India	333	DME	• Mean BCVA improved from 0.71 ± 0.42 logMAR to 0.50 ± 0.29 logMAR in the bRBZ group ($p < 0.001$) at 6 months. There were no differences in BCVA compared to innovator ranibizumab ($p > 0.05$ for all time points). • The CMT reduction was comparable between the two groups. • The mean number of injections did not differ significantly between the two groups (3.81 ± 1.2 in iRBZ vs 3.55 ± 1.2 in bRBZ) ($p > 0.05$).
Soman et al 2022[30]	Razumab® Intas Pharmaceuticals, India	22	PCV	• Comparable visual outcomes to the innovator ranibizumab, good safety profile.
Retra et al 2022[31]	Razumab® Intas Pharmaceuticals, India	202	AMD RVO DME	• Comparable results to innovator ranibizumab and bevacizumab. • Significant improvement of BCVA at 3 months in the group of AMD and in the group of macular edema due to RVO or DME. • CMT was significantly decreased at 3 months in both groups of patients that received the biosimilar razumab. • No major complications were reported.

Abbreviations: AMD, Age-related Macular Degeneration; BCVA, Best Corrected Visual Acuity; bRBZ, Biosimilar Ranibizumab; CI, Confidence Interval; CMT, Central Macular Thickness; DME, Diabetic Macular Edema; IOP, Intraocular Pressure; iRBZ, innovator ranibizumab; SRF, Subretinal Fluid; IRF, Intraretinal Fluid; PCV, Polypoidal Choroidal Vasculopathy; ROP, Retinopathy of Prematurity; RVO, Retinal Vein Occlusion.

A large meta-analysis from Hatamnejad et al included four randomized controlled trials with overall 1544 eyes that were treated with ranibizumab biosimilars (FYB201, SB11, RanizuRel and Lupin's ranibizumab) for nAMD and showed no significant differences between the ranibizumab biosimilars and the innovational agent.[33]

Moreover, immunogenicity plays an important role, as biosimilars are proteins with post-translational changes and antigenic variations. This could trigger a more intense immune response, through a possible antibody neutralization or activation of T-cells.[27] The factors that have an impact on immunogenicity can be categorized into patient- or disease-related factors; for instance, age, pre-existing antibodies, genetics, concomitant treatment or product-related factors, such as protein structure and post-translational modifications, impurities and aggregation.[34] In addition, immunogenicity can have negative consequences on both pharmacokinetic and pharmacodynamic profile of the therapeutic protein.[35] For example, an interaction of anti-drug antibodies with the therapeutic protein can lead to inhibition of binding to the targeted receptors. Another possible negative aspect is an increase or a decrease of the clearance of the therapeutic protein through the action of anti-drug antibodies that affect the exposure of the therapeutic protein. Hence, those pathophysiological suggestions underscore the importance of immunogenicity, as a paramount factor that has to be substantially evaluated before the approval of a biosimilar.

In this context, Singh et al, in a double masked study, compared among others the immunogenicity between Lupin's ranibizumab with reference ranibizumab, in a sample of 174 patients (87 in each group).[27] Samples of the patients were collected at day 1, day 30, and day 60. Results revealed lower anti-drug antibodies in blood of the patients that had received Lupin's ranibizumab (5 out of 101, 4.95%) compared to those that were treated with ranibizumab (13 out of 101, 12.87%). It is important to note that the authors accounted for the influence of anti-drug antibodies from previous therapies by adjusting the results accordingly.

Similarly, Woo et al tested the immunogenicity of biosimilar SB11 compared with the reference ranibizumab in a larger study group (n=705).[5] This group tested immunogenicity at shorter intervals of time (at weeks 0, 1, 4, 8, 16, 24, 36, and 52) and found encouraging results with low antidrug antibodies up to week 24 of 3.0% (10 of 330) in the SB11 group and 3.1% (10 of 327) in the ranibizumab group.

Cost Effectiveness

Anti-VEGF molecules are offered at a high cost, leading to a significant financial burden. This is particularly challenging in countries where healthcare systems do not provide reimbursement. As a consequence, the high cost can result in the discontinuation of anti-VEGF therapy, leading to poor visual outcomes.[36] In contrast, lower-cost anti-VEGF molecules can lead to improved therapy adherence among patients. This, in turn, results in better accessibility and enhanced visual outcomes.[37]

Reported data from the European Union (EU) showed that in 2022 the approval of 71 biosimilars led to savings of $11.8 billion between 2016 and 2022.[36] Moreover, it is important to report some interesting results of the Bio-USER survey, which assessed the awareness of retinal specialist in EU and US on anti-VEGF molecules and found out that 34.8% of the clinicians were willing to make a switch from ranibizumab to a biosimilar.[38] Only 11.6% were not willing to switch despite the lower cost. Results of this survey also showed that 56.25% of the physicians had concerns about the quality of biosimilars and especially about their safety and immunogenicity, as well as about their efficacy in less common retinal disorders, underlying the importance of safety and immunogenicity profile that has to be analyzed as a major factor before the approval of a biosimilar.

In a study evaluating anti-VEGF therapies for nAMD, the focus was on the cost-effectiveness of the ranibizumab biosimilar from a Japanese societal perspective.[39] Using a Markov model, the study compared ranibizumab biosimilar with branded ranibizumab, aflibercept, and their combinations in treat-and-extend (TAE) and pro re nata (PRN) regimens, as well as against best supportive care (BSC).

The findings indicated that ranibizumab biosimilar was more cost-effective in both TAE and PRN regimens. Specifically, ranibizumab biosimilar was dominant (higher quality-adjusted life years and lower total cost) compared to aflibercept TAE, aflibercept to ranibizumab biosimilar TAE, and ranibizumab TAE. In PRN regimens, ranibizumab biosimilar also showed cost-saving advantages over ranibizumab PRN and was dominant over BSC. These results highlight the potential of ranibizumab biosimilar as a more economically viable treatment option for nAMD.

Future Directions

The future of ranibizumab biosimilars and biosimilars in general for retinal disorders is poised for significant advancements, driven by a combination of technological innovation, evolving regulatory landscapes, and a deeper understanding of patient- specific needs. In the coming years, we can expect to see more sophisticated production techniques that not only enhance the efficiency and cost-effectiveness of biosimilars but also improve their safety and efficacy profiles. Regulatory bodies are likely to streamline approval processes, placing greater emphasis on real-world evidence to ensure these biosimilars meet stringent safety and effectiveness standards. The expanding research in this field will likely include comprehensive clinical trials, focusing on direct comparisons between different biosimilars and their reference products, which will be crucial in establishing their roles in clinical practice. Moreover, the increased competition in the biosimilar market is anticipated to make these treatments more accessible, particularly in regions where high costs limit the availability of original biologics. Personalized medicine will also play a key role, with biomarkers and genetic profiling potentially guiding the selection of biosimilars for individual patients, thereby optimizing treatment outcomes. Additionally, exploring new therapeutic combinations and indications for biosimilars could open up novel treatment avenues, addressing unmet needs in retinal disorders. Overall, the future landscape of biosimilars in retinal therapy is set to be dynamic and patient-centric, offering enhanced treatment options and improving the quality of life for patients with retinal disorders.

Conclusion

Reported data from phase III clinical trials and real-world studies show comparable outcomes for a series of ranibizumab biosimilars, in all parameters, such as BCVA, SRF, IRF, CMT and SFCT. In terms of safety and immunogenicity, all phase III published studies indicate that ranibizumab biosimilars exhibit similar safety and immunogenicity to the reference product, without any significant differences.

Most studies published until today focus on patients with nAMD and only a few ones on other retinal diseases, such as ROP, PCV, RVO and DME, tested solely with the biosimilar agent Razumab. However, the use of ranibizumab biosimilars in less common retinal conditions such as myopic CNV has not been documented, and we anticipate new studies to shed light in the future on use of ranibizumab biosimilars in these interesting areas.

Biosimilars hold the important potential of offering similar favorable clinical outcomes to the reference products, at a lower cost. This can lead to a consequential cost reduction of treatment for retinal disease, due to market competition, having an essential impact on the healthcare systems. It is of paramount importance to raise the awareness of clinicians on the strict evaluating process that anti-VEGF biosimilars undergo before receiving the approval as well as on their clinical efficacy and safety, through the results of the existing phase III clinical studies.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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