INVITED REVIEW

Biosimilar Anti–Vascular Endothelial Growth Factor Therapy for Retinal Diseases: A Comprehensive Review

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ABSTRACT

Anti–vascular endothelial growth factor (anti-VEGF) therapy has transformed the management of retinal vascular and neovascular diseases, including neovascular age-related macular degeneration (nAMD), diabetic macular edema (DME), retinal vein occlusions (RVO), and myopic choroidal neovascularization (CNV). [1] These conditions are among the leading causes of irreversible visual impairment worldwide. Although originator anti-VEGF biologics have demonstrated robust efficacy and safety, their high cost, need for repeated intravitreal injections, and long-term treatment burden present significant challenges to patients and healthcare systems. These limitations are particularly relevant in the context of aging populations, the global diabetes epidemic, and increasing demand for retinal services. Biosimilar anti-VEGF agents have emerged as cost-effective alternatives developed to be highly similar to reference biologics in terms of structure, function, efficacy, safety, and immunogenicity. [2] This review provides a comprehensive overview of biosimilar anti-VEGF therapy for retinal diseases, including the scientific principles underlying biosimilar development, global regulatory pathways, currently available and emerging biosimilar agents, clinical evidence across major retinal indications, safety and immunogenicity considerations, real-world experience including switching studies, economic implications, and future perspectives.

Keywords: Biosimilar: Anti-VEGF: Ranibizumab: Bevacizumab: Aflibercept 2mg

INTRODUCTION

Vascular endothelial growth factor (VEGF) is a central mediator of angiogenesis and vascular permeability and plays a pivotal role in the pathogenesis of several retinal diseases. In pathological states, VEGF overexpression leads to abnormal neovascularization, breakdown of the blood–retinal barrier, increased vascular permeability, and accumulation of intraretinal or subretinal fluid. These processes result in macular edema, hemorrhage, and progressive vision loss. Retinal diseases driven by VEGF dysregulation—including nAMD, DME, and RVO—are among the most common causes of irreversible visual impairment and blindness globally.

The introduction of intravitreal anti-VEGF therapy marked a paradigm shift in the treatment of these conditions. Landmark randomized clinical trials demonstrated that VEGF inhibition could stabilize vision and, in many cases, produce meaningful visual improvement—outcomes that were rarely achievable with earlier treatment modalities such as laser photocoagulation or surgery alone. As a result, anti-VEGF agents rapidly became the standard of care for a wide range of retinal indications. [1-6]

Despite their success, anti-VEGF therapies present significant challenges. Most retinal diseases treated with anti-VEGF agents are chronic and require long-term, often lifelong, treatment with repeated intravitreal injections.

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This creates a substantial burden for patients, caregivers, and healthcare systems. The cumulative cost of therapy is considerable, particularly with originator biologics, and may limit access and adherence. Even in high-income countries, escalating biologic drug expenditures have raised concerns about long-term sustainability. In low- and middle-income countries, high out-of-pocket costs frequently result in delayed treatment, undertreatment, or complete lack of access. Against this background, biosimilar anti-VEGF agents have emerged as an important strategy to improve affordability and expand access to effective retinal care without compromising clinical outcomes.

Scientific Basis and Development of Biosimilars

Biosimilars are biological medicinal products that are highly similar to an already approved reference biologic, notwithstanding minor differences in clinically inactive components. Unlike generic versions of small-molecule drugs, which can be chemically synthesized and reproduced identically, biologics are large, structurally complex proteins produced in living systems. Consequently, exact replication is not possible, and some degree of variability is inherent even between different batches of the same originator product.

The development of a biosimilar therefore follows a rigorous, stepwise approach centered on demonstrating similarity rather than independently establishing efficacy. The process begins with extensive analytical characterization to establish molecular comparability between the biosimilar and the reference product. This includes assessment of the primary amino acid sequence, higher-order protein structure, folding patterns, aggregation behavior, charge variants, and post-translational modifications such as glycosylation.

Functional assays are a critical component of biosimilar development. These assays evaluate biological activity, including VEGF binding affinity, inhibition of receptor activation, and downstream signaling pathways. Only after analytical and functional similarity has been convincingly demonstrated do developers proceed to preclinical and clinical studies. Importantly, clinical development programs for biosimilars are typically smaller than those conducted for originator biologics and are designed to confirm comparable pharmacokinetics, efficacy, safety, and immunogenicity rather than to re-establish therapeutic benefit. [7]

Regulatory Frameworks for Biosimilar Approval

Regulatory agencies worldwide have established distinct approval pathways for biosimilars that differ from those used for originator biologics. These pathways are designed to balance scientific rigor with development efficiency and affordability.

The United States Food and Drug Administration (FDA) employ a “totality of evidence” approach that integrates analytical, nonclinical, and clinical data to establish biosimilarity. Clinical trials are typically designed as equivalence or non-inferiority studies conducted in sensitive patient populations. The FDA also provides a separate designation for interchangeability, which allows pharmacy-level substitution, although this designation has not yet been widely applied in ophthalmology.

The European Medicines Agency (EMA) has extensive experience with biosimilars and similarly emphasizes a stepwise development pathway. The EMA permits extrapolation of indications when scientifically justified, allowing a biosimilar approved for one indication to be used across multiple indications held by the reference product without requiring separate clinical trials. Regulatory frameworks in other regions broadly align with these principles, although requirements may vary. Differences in regulatory pathways underscore the importance of robust post-marketing surveillance and real-world data to ensure ongoing safety and effectiveness across diverse patient populations. [8]

Anti-VEGF Biosimilars in Ophthalmology

The world’s first ranibizumab biosimilar, Razumab (Intas Pharmaceuticals, Ahmedabad), was approved by the Drug Controller General of India (DCGI) in 2015 [9]. SB11 (Byooviz; ranibizumab-nuna, Biogen, USA) subsequently became the first ranibizumab biosimilar to receive approval from the US Food and Drug Administration (FDA) [10]. SB11 was evaluated in global Phase III clinical trials in patients with neovascular age-related macular degeneration (nAMD) [11]. In a pivotal study involving approximately 551 patients, intravitreal SB11 0.5 mg demonstrated efficacy and safety comparable to reference ranibizumab (Lucentis) through 1 year of follow-up [11].

At week 8, least-squares mean gains in best-corrected visual acuity (BCVA) were 6.2 letters with SB11 and 7.0 letters with Lucentis; the 90% confidence interval for the between-group difference (–0.8 letters) was within the prespecified equivalence margin of ±3 letters [11]. At 52 weeks, improvements in BCVA and reductions in retinal thickness remained statistically equivalent between treatment arms. Rates of immunogenicity were low and comparable, with approximately 3% of patients in each group developing anti-drug antibodies [11]. Subsequent analyses confirmed sustained noninferiority at 1 year . These findings supported FDA and European Medicines Agency (EMA) approval of SB11 in 2021 (FDA-designated name: ranibizumab-nuna) for nAMD and diabetic retinal diseases [12,13].

Other ranibizumab biosimilars have demonstrated similar outcomes. FYB201 (Cimerli; ranibizumab-eqrn, Sandoz, USA) met predefined equivalence criteria in the Phase III COLUMBUS-AMD trial (n=477) conducted in South Korea [14]. At week 8, mean BCVA improvement was +5.1 letters with FYB201 compared with +5.6 letters for reference ranibizumab; the adjusted difference of –0.4 letters (90% CI –1.6 to 0.9) fell within the ±3-letter equivalence margin [14]. Safety endpoints were likewise comparable between groups. Several additional ranibizumab biosimilars have since received global approvals, consistently demonstrating comparable efficacy and no unexpected safety signals relative to the reference product [13]. Table 1

Table 1. *Manufacturers and brands of biosimilar ranibizumab*

Molecule	Manufacturer	Brand names (Marketing Company / Country)	Approval Authority (Date)
SB11	Samsung Bioepis Co. Ltd., South Korea	Byooviz / ranibizumab-nuna (Biogen, USA & Europe) Amelivu (Samsung Bioepis, South Korea)	US-FDA (17 Sep 2021) EMA (18 Aug 2021) Health Canada (Mar 2022) MFDS Korea (May 2022)
FYB201	Formycon AG / Bioeq AG, Germany	Cimerli / ranibizumab-eqrn (Coherus, USA) Ongavia (Teva, UK) Ranivisio (Bioeq/Teva, EU) Ranopto (Teva, Canada) Ravegza (MS Pharma, MENA) Epruvy (Germany) BioUcenta (Sub-Saharan Africa)	US-FDA (25 Aug 2022) EMA/EC (25 Aug 2022) UK MHRA (17 May 2022)
XSB-001	STADA Arzneimittel AG, Germany (with Xbrane Biopharma)	Ximluci (STADA, EU & UK)	EMA/EC (09 Nov 2022) UK MHRA (Early 2023) US-FDA (Applied; not approved)
QL1205	Qilu Pharmaceutical Co., Ltd., China	Rimmyrah (Qilu Pharma, EU/ Spain)	EMA CHMP positive opinion (09 Nov 2023) EC Marketing Authorisation (05 Jan 2024)
SJP-0133	Senju Pharmaceuticals Co. Ltd., Japan	Ranibizumab-BS (Senju, Japan)	PMDA Japan (21 Sep 2021)
Razumab	Intas Pharmaceuticals Ltd., India	Razumab (Intas, India)	DCGI India (20 Feb 2015)
R-TPR-024	Reliance Life Sciences, India	Ranizurel (Reliance, India) Visumab (Cipla, India)	DCGI India (26 Mar 2020)
LUBT010	Lupin Limited, India	Ranieyes (Lupin, India)	DCGI India (29 Oct 2021) EMA (Under review / application submitted)
Sun Ranibizumab	Sun Pharmaceutical Industries Ltd., India	Oceva (Sun Pharma, India)	DCGI India (24 Mar 2023)

Footnotes:
1. Dates indicate first marketing authorization unless otherwise specified.
2. EMA dates refer to European Commission (EC) marketing authorization; CHMP dates indicate positive scientific opinion.
3. Products listed as ‘applied’ or ‘under review’ have not yet received final marketing authorization.
4. Brand names may vary by marketing partner and country, while the biosimilar molecule remains identical.
5. This table includes ranibizumab biosimilars approved by major regulatory authorities or nationally authorized products as of 2025.

Multiple bevacizumab biosimilars (including Mvasi, Zirabev, Onbevzi, Alymsys, and Bevatas) have been approved for oncologic indications [15]. These agents are occasionally used by retina specialists following compounding for off-label treatment of neovascular AMD. Their extensive safety experience in systemic use, together with longstanding clinical familiarity with repackaged reference bevacizumab (Avastin), has reinforced confidence in therapeutic VEGF inhibition equivalence [16]. An ophthalmic, on-label formulation of bevacizumab (bevacizumab-gamma; LYTENAVA, Outlook Therapeutics, USA) has recently received approval from the UK Medicines and Healthcare products Regulatory Agency (MHRA) [17]. Table 2

Biosimilars of aflibercept 2 mg are also approaching widespread clinical adoption, despite ongoing proprietary and legal disputes between Regeneron and several biosimilar manufacturers [18]. Iran became the first country to approve an aflibercept 2 mg biosimilar, and real-world outcomes have been reported by our group, the International Retina Biosimilar Study Group [19]. SB15 (aflibercept-yszy; Opuviz, Samsung Bioepis, South Korea) and MYL-1701P (aflibercept-jbvf; Yesafili, Biocon, India) were the first two aflibercept biosimilars approved by the FDA [18].

SB15 was evaluated in a Phase III trial enrolling 449 patients with nAMD. At week 56, mean BCVA gains were +7.4 letters in the SB15 group and +7.0 letters in the Eylea group; the between-group difference of 0.4 letters (95% CI –2.5 to 3.2) was well within the predefined ±3-letter equivalence margin [20]. Reductions in central retinal thickness and rates of adverse events were nearly identical between treatment arms [20]. MYL-1701P was assessed in a Phase III trial involving 355 patients with diabetic macular edema (DME). Yesafili demonstrated clinical equivalence to Eylea, with an adjusted mean BCVA difference of 0.04 letters at week 8. The incidence of treatment-emergent ocular adverse events was comparable between Yesafili (30.9%) and Eylea (29.5%), with no new safety concerns identified. Rates of treatment-induced or treatment-boosted anti-drug antibodies were 2.8% in the Yesafili group and 5.7% in the Eylea group. Several additional aflibercept 2 mg biosimilars have since been approved globally, all demonstrating efficacy and safety comparable to reference aflibercept [21]. Table 3

In summary, accumulating evidence for ranibizumab and aflibercept biosimilars consistently demonstrates noninferiority across primary efficacy endpoints, most commonly change in BCVA, with predefined 90–95% confidence intervals well within established equivalence margins. These margins are typically ±3 letters for visual

Table 3. *Bevacizumab biosimilars and ophthalmic formulation relevant to retinal use*

Molecule	Brand name	Company / Country	Regulatory approval status
Bevacizumab biosimilar	Mvasi	Amgen / Allergan, USA	Approved for oncologic indications (US-FDA, EMA)
Bevacizumab biosimilar	Zirabev	Pfizer, USA	Approved for oncologic indications (US-FDA, EMA)
Bevacizumab biosimilar	Onbevzi	Samsung Bioepis, Republic of Korea	Approved for oncologic indications (EMA)
Bevacizumab biosimilar	Alymsys	Samsung Bioepis, Republic of Korea	Approved for oncologic indications (EMA, UK MHRA)
Bevacizumab biosimilar	Bevatas	Intas Pharmaceuticals, India	Approved for oncologic indications (EMA)
Bevacizumab-gamma	LYTENAVA®	Outlook Therapeutics, USA	UK MHRA approved for ophthalmic, on-label use

Footnotes:
1. Bevacizumab biosimilars listed above are approved for systemic oncologic indications and are not labeled for ophthalmic use.
2. In retinal practice, these agents may be used off-label following compounding for intravitreal administration.
3. Longstanding clinical experience with reference bevacizumab (Avastin®) has supported confidence in VEGF inhibition equivalence.
4. Bevacizumab-gamma (LYTENAVA®) is an ophthalmic, on-label formulation approved by the UK Medicines and Healthcare products Regulatory Agency (MHRA).
5. Regulatory status reflects information available at the time of publication.

Table 2. *Manufacturers and brands of biosimilar aflibercept 2 mg*

Molecule	Commercial / Brand Name (Country)	Company	Approval Authority (Status / Date)
MYL-1701P (aflibercept-jbvf)	Yesafili (US, EU)	Biocon Biologics (India) / Momenta & Viatris (USA)	US-FDA (2024) EMA (2024)
SB15 (aflibercept-yszy)	Opuviz (US, EU) Afilivu (Korea)	Samsung Bioepis, Republic of Korea	US-FDA (2024) EMA (2024) MFDS Korea (2023)
FYB203 (aflibercept-mrbb)	Ahzantive (US)	Formycon AG, Germany	US-FDA (2024) EMA (2024)
SOK583A19 (aflibercept-abzv)	Enzeevu (US) Afqlir (EU)	Sandoz, Switzerland	US-FDA (2024) EMA (2024)
ABP-938 (aflibercept-ayyh)	Pavblu (US)	Amgen, USA	US-FDA (2024) EMA (2024)
CT-P42	Eydenzelt (Korea)	Celltrion, Republic of Korea	MFDS Korea (2023) US-FDA (2024) EMA (2024)
ALT-L9	Eyluxv (EU)	Alteogen, Republic of Korea	EMA (2024) MFDS Korea (Applied)
SCD411	Avzylt (Canada)	Sam Chun Dang, Republic of Korea	Health Canada (2023) EMA (2024) MFDS Korea / PMDA Japan (Approved) US-FDA (Applied)
AVT06	Mynzepli	Alvotech, Switzerland	EMA (2024) PMDA Japan (2024) US-FDA (Applied)
OT-702	Boyoujing® (China)	Ocumension Therapeutics / Shandong Boan Biologics, China	NMPA China (2025)
P041	Tyalia (Iran)	CinnaGen, Iran	Iranian National Regulatory Approval
QL1207	—	Qilu Pharmaceutical Co., China	NMPA China (2023)

Footnotes:

1. All products listed are biosimilar aflibercept formulations at the 2 mg intravitreal dose.
2. Dates indicate first marketing authorization unless otherwise specified.
3. EMA approval refers to European Commission marketing authorization following CHMP positive opinion.
4. Products listed as 'applied' have not yet received final regulatory approval.
5. Brand names may vary by country and marketing partner while the biosimilar molecule remains identical.
6. This table reflects regulatory status as of 2025.

acuity and ±50 µm for central retinal thickness, paralleling those used in the pivotal innovator trials.

Safety of Biosimilar Anti-VEGF Therapy

The safety profiles of anti-VEGF biosimilars in clinical trials have closely paralleled those of their respective reference biologics. In Phase III studies evaluating ranibizumab biosimilars, both ocular and systemic adverse events (AEs) occurred at comparable frequencies between biosimilars and originator products. For instance, the SB11 trial did not identify any new safety concerns, with rates of endophthalmitis, intraocular inflammation, retinal detachment, and other ocular adverse events showing no statistically significant differences between SB11 and Lucentis [22,23]. Importantly, immunogenicity has remained minimal. In the pivotal SB11 study, anti-drug antibodies were detected in approximately 3.0% of patients receiving SB11 and 3.1% of those treated with Lucentis at 24 weeks, and no neutralizing antibodies were observed in either group [23]. Similarly, Phase III trials of FYB201

and SB15 reported rates of anti-drug antibody formation and serious adverse events that were comparable to those seen with their respective reference products [14,20]. These observations align with the concept that, when manufacturing processes are rigorously controlled, minor structural variations inherent to biosimilars do not translate into unforeseen toxicities.

Despite these reassuring trial data, ongoing clinical vigilance remains essential. Post-marketing experience has largely corroborated the favorable safety profiles observed in controlled studies. A large multicenter registry evaluating Razumab, encompassing more than 9,400 injections across 6,400 eyes, reported an infectious endophthalmitis incidence of just 0.01%, comparable to rates reported in registries for bevacizumab and Lucentis [24]. Immune-mediated inflammatory events were rare; however, isolated clusters of sterile intraocular inflammation were observed with early production batches of Razumab, leading the manufacturer to enhance purification processes. Following these modifications (implemented after January 2019), no additional cases of sterile endophthalmitis were reported [24]. This experience highlights the critical role of pharmacovigilance and demonstrates that safety signals can be promptly addressed without long-term adverse consequences.

Data from professional surveys and clinical registries further support favorable real-world performance. Surveys of vitreoretinal specialists in India have shown increasing adoption of ranibizumab biosimilars, accompanied by high levels of physician-reported confidence in their safety [25,26]. No widespread or unexpected complications were identified. Likewise, smaller observational reports from other centers using ranibizumab or aflibercept biosimilars have documented anticipated ocular safety outcomes, with incidences of intraocular inflammation and endophthalmitis remaining within historical ranges established for the reference biologics.

Long-term safety monitoring continues through established pharmacovigilance systems, including VAERS in the United States and EudraVigilance in Europe, as well as through disease-specific registries such as the Fight Retinal Blindness! registry [27,28]. These platforms facilitate detection of rare adverse events across large populations and extended exposure. To date, no novel class-specific safety concerns have been identified for anti-VEGF biosimilars. While clinicians are encouraged to report any unexpected events, the cumulative evidence remains reassuring. Overall, when administered using standard injection techniques and appropriate monitoring, anti-VEGF biosimilars appear to be as safe as their reference counterparts. As clinical experience continues to expand, confidence in their long-term safety is expected to increase further, consistent with patterns observed following the introduction of other biologic therapies [29].

Real-World Evidence

Real-world evidence complements data from randomized clinical trials by reflecting routine clinical practice and has been the major requirement of retina pohysicin as per the survey conducted in various geographic reigions. We have initialed a group called International Retina Biosimilar Study Group (Inter BIOS Group) and has piubliched real word data efficacy and safety from various countries about ranibizumab and aflibercept biosimilars. So fat all the real world studies found biosimilrs to be safet and effective without any concern. [19, 30-33]

Economic Impact and Access to Care

The economic implications of biosimilar anti-VEGF therapy are substantial. Reduced drug acquisition costs can translate into significant savings for healthcare systems and patients. In many regions, biosimilars have enabled expanded access to anti-VEGF therapy, increased treatment frequency, and improved adherence. These benefits are particularly important in low- and middle-income countries, where cost remains a major barrier to care.

Challenges and Future Directions

Despite their promise, biosimilar anti-VEGF agents face several challenges. Physician and patient acceptance, regulatory heterogeneity, and the need for robust post-marketing surveillance remain important considerations. Ongoing education and transparent communication regarding biosimilar development, regulation, and clinical evidence are essential to support wider adoption. Future developments may include interchangeability designations, broader availability of aflibercept biosimilars, and further reductions in treatment costs.

CONCLUSION

Biosimilar anti-VEGF agents represent a major advancement in the management of retinal diseases. By offering clinically comparable, safe, and more affordable alternatives to originator biologics, biosimilars have the potential to improve access to care, enhance adherence, and reduce the global burden of visual impairment. As evidence and clinical experience continue to accumulate, biosimilar anti-VEGF therapy is likely to become an integral component of contemporary retinal practice worldwide.

DISCLOSURES

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