Clinical Ophthalmology

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ORIGINAL RESEARCH

CompaRative Safety Analysis of Innovator and BioSimilar Ranibizumab in Chorioretinal Vascular Diseases - The CRsIBS Study

Debdulal Chakraborty[1], Tushar Kanti Sinha[1], Sourav Sinha[2], Rupak Kanti Biswas[2], Aniruddha Maiti[3], Subhendu Boral[1], Arnab Das[2], Soumava Mandal[4], Ranabir Bhattacharya[1], Shouvick Dan[1], Dinesh Rungta[1]

[1]Department of Vitreoretinal Services, Disha Eye Hospitals, Kolkata, West Bengal, India; [2]Department of Vitreoretinal Services, Netralayam Superspeciality Eye Care, Kolkata, West Bengal, India; [3]Department of Vitreoretinal Services, Global Eye Hospitals, Kolkata, West Bengal, India; [4]Department of Vitreoretinal Services, Susrut Eye Foundation and Research Centre, Kolkata, West Bengal, India

Correspondence: Debdulal Chakraborty, Department of Vitreo-Retinal Services, Disha Eye Hospitals, Kolkata, West Bengal, India, Tel +91 33 6636 0000, Email devdc@rediffmail.com

Purpose: To compare the safety profiles of biosimilar ranibizumab (Razumab™) and innovator ranibizumab (Accentrix™) in the management of chorioretinal vascular diseases across a large, diverse patient cohort in a multicenter retrospective study.

Methods: This multicenter, retrospective study analyzed data from 39,226 eyes treated with either biosimilar or innovator ranibizumab across 21 centers in India between January 2016 and March 2024. Eligible patients received intravitreal injections for conditions including age-related macular degeneration (AMD), diabetic macular edema (DME), retinal vein occlusion (RVO), and myopic choroidal neovascularization (CNVM). Patients were followed for a minimum of three months, with adverse events documented during follow-up visits. Safety outcomes were assessed based on ocular and systemic adverse events, with statistical analyses comparing frequencies between groups using chi-square and t-tests.

Results: A total of 46,520 injections were administered in the innovator group (20,283 eyes; mean 2.29±1.53 injections per eye) and 45,310 injections in the biosimilar group (18,943 eyes; mean 2.39±1.61 injections per eye). Both groups showed comparable safety profiles. Ocular adverse events were mostly mild, with similar rates of transient blurring, subconjunctival hemorrhage, and ocular pain. Serious ocular events, including endophthalmitis, were rare (2 cases in each group). Systemic adverse events, such as myocardial infarction and cerebrovascular accidents, were also rare, with no statistically significant differences between groups. A higher incidence of anterior chamber inflammation was noted in the biosimilar group (p=0.005), while headache was significantly more common in this group (p=0.0002).

Conclusion: This large-scale real-world study demonstrates that biosimilar ranibizumab offers a comparable safety profile to innovator ranibizumab in the management of chorioretinal vascular diseases. The affordability of biosimilar ranibizumab enhances its potential as a cost-effective alternative, particularly in resource-limited settings, without compromising safety.

Keywords: anti VEGF, ranibizumab, biosimilar ranibizumab, chorio-retinal vascular disease

Introduction

Chorio-retinal vascular diseases, including age-related macular degeneration (AMD), diabetic macular edema (DME), and retinal vein occlusion (RVO), are becoming increasingly significant global public health challenges.[1,2] Data shows that global life expectancy at birth has improved, rising from 46.5 years in 1950 to 71.7 years in 2022, with projections suggesting it will reach 77.3 years by 2050.[2] The aging population is expected to raise the global prevalence of AMD from 170 million in 2014 to 288 million by 2040.[2] Patient with diabetes mellitus are anticipated to rise from 415 million in 2015 to 642 million by 2040, contributing to an increase in diabetic retinopathy.[3,4] This upward trend contributes

Received: 3 January 2025
Accepted: 4 March 2025
Published: 28 March 2025

significantly to vision loss due to maculopathies and chorioretinal vascular disease, profoundly affecting patients' quality of life and general well-being.[4,5] Consequently, the need for effective treatment strategies are becoming more urgent.

The introduction of anti-vascular endothelial growth factor (anti-VEGF) therapy has revolutionized the management of chorioretinal vascular diseases.[5,6] Currently, several anti-VEGF agents are available, including ranibizumab (Lucentis™/Accentrix™: Novartis Healthcare, Mumbai, India), aflibercept (Eylea™; Bayer, Germany), brolucizumab (Beovue™/Pagenax™, Novartis Healthcare, Basel, Switzerland), faricimab (Vabysmo™; Roche), and off-label bevacizumab. Anti-VEGF therapy has become the cornerstone of treatment, offering not only the possibility of halting disease progression but also, in many cases, restoring vision. However, the chronic nature of these diseases often requires repeated intravitreal injections to maintain therapeutic benefits. Patients with AMD or DME may require monthly injections over long periods, which presents a significant treatment burden in terms of patient compliance and healthcare costs.[1,5,6] The high cost of anti-VEGF biologics, such as ranibizumab, aflibercept etc. is particularly challenging in low and middle-income countries, where financial constraints can impede access to adequate treatment, leading to suboptimal outcomes.[5,6] To address this issue, off-label use of bevacizumab, a more affordable alternative, is commonly practiced in treating chorio-retinal vascular diseases. While effective, bevacizumab's off-label use is not without risks, including concerns about safety due to cluster endophthalmitis linked to compounded batches for intravitreal use.[7]

In this context, biosimilar ranibizumab offers a promising alternative.[8] Biosimilars are designed to match their reference biologics in terms of efficacy, safety, and immunogenicity, but at a lower cost.[8–11] Razumab™ (Intas Pharmaceuticals, Gujarat, India), a biosimilar ranibizumab, has shown comparable safety and efficacy to the innovator product in both clinical trials and smaller real-world studies.[8,9,12] Additionally biosimilars ranibizumab can play a crucial role in easing the financial burden associated with treating chorio-retinal vascular diseases, especially in regions where healthcare costs limit access to treatment. By offering therapeutic equivalence to their reference biologics at a significantly lower cost, biosimilars can enhance patient compliance. Specifically, biosimilar ranibizumab has shown cost savings of 35–50% compared to the original product, without compromising on efficacy or safety.[8,11] Recent cost-effectiveness studies suggest that biosimilar ranibizumab may be the most cost-effective treatment option compared to existing anti-VEGF agents under both treat-and-extend (TnE) and pro-re-nata (PRN) regimens.[12] India is at the forefront of biosimilar development for ophthalmic use, with three approved biosimilar ranibizumab products currently available for clinical use.[12–16]

While efficacy is important, safety is paramount when it comes to use of biosimilars specially as intravitreal agents. Despite the potential of biosimilars, large-scale real-world data on their safety compared to innovator biologics is still lacking. Our study seeks to address this gap by analyzing the safety of biosimilar ranibizumab (Razumab™) compared to the innovator ranibizumab across a large cohort of Indian patients treated within four major hospital networks.

Materials and Methods

Study Design

This multicenter, collaborative, retrospective, chart review included patients from 21 eye care centers in India belonging to 4 eye hospital networks. The study was conducted to evaluate and compare the safety profiles of innovator ranibizumab (Accentrix™: Novartis Healthcare, Mumbai, India) and biosimilar ranibizumab (Razumab™: Intas pharmaceuticals, Gujarat, India) in patients with various chorio-retinal vascular diseases. The treatment regimen followed was three monthly doses followed by PRN / three monthly doses followed by treat-and-extend (TnE) from baseline /pro re nata (PRN) from baseline, depending on the underlying diagnosis, based on the retinal physician's discretion, and the patient compliance factors. All injections were performed in an operating theatre under sterile technique using topical anaesthetic drops. Povidone iodine 5% was applied to eyes both immediately before and after each injection. Topical moxifloxacin 0.5% was administered post injection for 1 week. The study protocol was approved by the Central Ethics committee at Disha Eye Hospital (ECR/846/Inst/WB/2016/RR-24.) and was conducted in accordance with the Declaration of Helsinki, good clinical practices and relevant regulatory guidelines. Data was extracted from electronic medical records of eligible patients. All patient data were anonymized to ensure confidentiality.

The study included all patients treated with either the innovator or biosimilar ranibizumab between 1st Jan 2016 and 31st March 2024. Key inclusion and exclusion criteria were as follows: Patients were selected if they had received at least one intravitreal injection of either innovator ranibizumab or biosimilar ranibizumab during the study period. Patients aged 18 years or older, diagnosed with chorioretinal vascular disease such as: wet AMD, DME, branch retinal vein occlusion (BRVO), central retinal vein occlusion (CRVO), myopic choroidal neovascularization (CNVM), patients requiring, anti VEGF as pre-operative adjunct and also some miscellaneous conditions were considered eligible. Additionally, complete follow-up data for a minimum of 3 months post-treatment was necessary to be included for analysis.

Exclusion Criteria

Patients with insufficient follow-up data or those lost to follow-up within three months of injection were excluded from the study. Additionally, patients with co-existing retinal pathologies other than those specified in the inclusion criteria were not included. Individuals with a previous history of anti-VEGF therapy (other than the drugs being compared) within 6 months prior to the first injection were also excluded. Furthermore, patients who received both innovator and biosimilar ranibizumab, interchangeably during the study period were also not considered for inclusion.

Details that were noted for each patient included: demographic information (including age and gender), systemic treatment details, ocular adverse events, including but not limited to ocular pain, watering, intraocular pressure (IOP) rise, subconjunctival hemorrhage, findings suggestive of anterior chamber inflammation, vitritis, retinal pigment epithelial tears, endophthalmitis, and any other treatment-related ocular complications. Systemic adverse events were also recorded, including cardiovascular events (eg, myocardial infarction, cerebrovascular accident, syncope, fever, etc). After each injection, the patients were followed up within a week at 1 week, at 1 month and thereafter as per treatment protocol. Additionally, the patients were advised to follow up immediately in case of occurrence of any ocular or systemic adverse event. At all visits, history was taken by the treating physician regarding the occurrence of any ocular and systemic adverse event as per hospital protocol. Additionally, a thorough clinical examination including best-corrected visual acuity (BCVA) assessment using the Snellen's visual acuity chart, IOP measurement, anterior segment evaluation using slit-lamp biomicroscopy and fundus examination with both slit-lamp biomicroscopy (90 D lens) and indirect ophthalmoscopy (20 D lens) was undertaken by the retina specialist. *S*pectral-domain optical coherence tomography (SD-OCT) was performed at baseline, 1-month and every visit thereafter.

Outcome Measures

The primary outcome was the incidence of ocular and systemic adverse events in patients treated with either innovator or biosimilar ranibizumab. Secondary outcomes included the characterization of these adverse events, specifically the frequency of ocular complications such as endophthalmitis and retinal detachment, as well as systemic events like myocardial infarction and cerebrovascular accidents.

Statistical Analysis

Descriptive statistics were used to summarize the baseline characteristics of patients in both treatment groups. Continuous variables were presented as means with standard deviations (SD), while categorical variables were expressed as frequencies and percentages. The incidence of adverse events was compared between the two groups using the chi-square test or Fisher's exact test for categorical variables and *t*-test or Mann–Whitney *U*-test for continuous variables, as appropriate. A p-value of <0.05 was considered statistically significant. All data was maintained on Microsoft excel and statistical analyses were performed using SPSS 23.0 version.

Results

A total of 39,226 eyes treated with either innovator ranibizumab or biosimilar ranibizumab were included in the analysis. In the Innovator group, a total of 20,283 eyes were treated with 46,520 injections, resulting in an average of 2.29 ±1.53 injections per eye. In the Biosimilar group, 18,943 eyes were treated with 45,310 injections, with an average of 2.39 ±1.61 injections per eye.

In patients with wet AMD, those receiving biosimilar ranibizumab received slightly fewer injections compared to the innovator group (3.68 vs 3.95). For other conditions, the injection frequencies were similar between the groups. A detailed comparison of the number of injections per diagnosis, the average number of injections per eye, and standard deviations for each group are shown in Tables 1 and 2.

In the Innovator Ranibizumab group, the overall average age across all conditions was 60.2 ±12.12 years. In the Biosimilar Ranibizumab group, the overall average age was 58.6 ±12.66 years. The comparison of intraocular pressure (IOP) changes between the Innovator Ranibizumab and Biosimilar Ranibizumab groups revealed a slight difference in the mean IOP increase over time. The Innovator Ranibizumab group had a baseline mean IOP of 17.16 ± 2.56 mmHg, which increased to 17.95 ± 2.63 mmHg at the final follow-up. In contrast, the Biosimilar Ranibizumab group showed a baseline mean IOP of 17.04 ± 2.93 mmHg, rising to 18.61 ± 3.24 mmHg at the final follow-up. *t*-test comparing the final IOP between the two groups yielded a t-statistic of −0.78 and a p-value of 0.455, indicating that the difference in IOP increase between the groups is not statistically significant ($p > 0.05$). Details of IOP are noted in Table 3.

Table 1 Distribution of Injections as per Diagnosis

Diagnosis	Group	Eyes	Injections	Mean Injections Per Eye (±SD)	p-value
Wet AMD	Innovator	4203	16.616	3.95 ± 0.56	0.045
Wet AMD	Biosimilar	4892	17.989	3.68 ± 0.61	
DME	Innovator	5899	17.324	2.94 ± 0.23	0.183
DME	Biosimilar	5600	16.912	3.02 ± 0.33	
BRVO	Innovator	4795	6713	1.40 ± 0.09	>0.05
BRVO	Biosimilar	3936	5306	1.35 ± 0.23	
Myopic CNVM	Innovator	559	782	1.40 ± 0.23	>0.05
Myopic CNVM	Biosimilar	378	509	1.35 ± 0.19	
Miscellaneous	Innovator	780	1505	1.93 ± 0.41	–
Miscellaneous	Biosimilar	599	612	1.02 ± 0.22	

Table 2 Age of Patients as per Diagnosis

Diagnosis	Group	Mean Age (±SD)
Wet AMD	Innovator	67.32 ± 13.13
Wet AMD	Biosimilar	66.16 ± 14.28
DME	Innovator	56.44 ± 10.12
DME	Biosimilar	58.44 ± 12.37
BRVO	Innovator	57.66 ± 11.42
BRVO	Biosimilar	60.66 ± 13.22
Myopic CNVM	Innovator	29.21 ± 6.89
Myopic CNVM	Biosimilar	27.30 ± 7.33

Table 3 Intra Ocular Pressure (IOP) as per Diagnosis

Diagnosis	Group	Baseline IOP (±SD)	Final IOP (±SD)	p-value
Wet AMD	Innovator	17.2 ± 1.99	18.15 ± 3.63	0.325
Wet AMD	Biosimilar	18.3 ± 2.65	19.15 ± 3.63	
DME	Innovator	18.6 ± 4.14	19.34 ± 2.44	0.244
DME	Biosimilar	17.9 ± 3.54	20.64 ± 4.44	

In both the groups, majority of the adverse events (AEs) were mild or moderate and resolved within the period of observation. In the Innovator Ranibizumab group, the most common ocular side effects were: ocular pain, observed in 2521 eyes. Serious complications included two cases of endophthalmitis that required vitrectomy, as well as 62 cases of retinal pigment epithelial (RPE) tears. In the Biosimilar Ranibizumab group, common ocular side effects were similar, with ocular pain reported in 2021 eyes. Serious complications in this group included two eyes developing endophthalmitis, out of which one required vitrectomy. The other patient was managed with intravitreal antibiotics. There were 79 eyes that developed RPE tears. Details of adverse events are noted in Table 4.

In the Innovator Ranibizumab group, the most common systemic side effects included raised blood pressure in 350 cases. More severe systemic issues were observed, including 9 myocardial infarctions with a mean age of 66.34 years, and 18 cerebrovascular accidents with a mean age of 78.88 years. In the Biosimilar Ranibizumab group, the most

Table 4 Ocular Side Effects

Side Effect	Group	Cases	p-value
Ocular Pain	Innovator	2521	–
Ocular Pain	Biosimilar	2021	–
Watering	Innovator	1020	0.731
Watering	Biosimilar	987	
Transient Blurring	Innovator	997	0.611
Transient Blurring	Biosimilar	1023	
Subconjunctival Hemorrhage	Innovator	1043	–
Subconjunctival Hemorrhage	Biosimilar	1101	–
RPE Tear	Innovator	62	0.054
RPE Tear	Biosimilar	79	
Endophthalmitis	Innovator	2	–
Endophthalmitis	Biosimilar	2	
AC cells/flare	Innovator	32	0.005
AC cells/flare	Biosimilar	56	
Hypopyon	Innovator	5	0.2
Hypopyon	Biosimilar	9	
Lens injury	Innovator	6	–
Lens injury	Biosimilar	8	–

https://doi.org/10.2147/OPTH.S515479

Table 5 Systemic Side Effects

Adverse Event	Group	Cases	p-value
Raised BP	Innovator	350	0.8995
Raised BP	Biosimilar	389	
Headache	Innovator	169	0.0002
Headache	Biosimilar	231	
Backache	Innovator	187	0.113
Backache	Biosimilar	219	
Myocardial Infarction	Innovator	9	0.5140
Myocardial Infarction	Biosimilar	12	
Cerebrovascular Accident	Innovator	18	0.5904
Cerebrovascular Accident	Biosimilar	15	

common systemic side effects were raised blood pressure in 389 cases. Headache was noted in 231 patients in the this cohort and the difference with the innovator group was statistically significant. Severe systemic events in the biosimilar cohort included 12 myocardial infarctions with a mean age of 63.45 years, and 15 cerebrovascular accidents with a mean age of 72.38 years. Details of systemic adverse events are noted in Table 5.

Discussion

The current study assessed the ocular adverse effects associated with biosimilar and innovator ranibizumab, emphasizing their safety profiles in real-world clinical settings. Data were evaluated based on the number of eyes that experienced various side effects in both groups and was derived from routine clinical practice involving adults across a wide age range and with diverse comorbidities. While anti-VEGF therapies are generally well tolerated for managing retinal diseases, ocular adverse events (AEs) remain a recognized risk associated with intravitreal injections.[9,12] Careful assessment of potential adverse effects on ocular and systemic health is particularly critical for older patients, who constitute a large proportion of individuals receiving anti-VEGF injections for chorioretinal vascular conditions.

The most frequently reported ocular side effects— ocular pain, transient blurring of vision, and subconjunctival/ conjunctival haemorrhage —occurred at similar rates across both groups in our study. However, a significantly higher incidence of anterior chamber (AC) cells/flare was observed in the biosimilar group compared to the innovator group (56 vs 32 eyes, $p = 0.0055$). On the other hand, while the biosimilar group reported a slightly higher occurrence of hypopyon (9 vs 5 eyes), this difference was not statistically significant ($p = 0.2888$). IOP rise has been noted in some studies with anti VEGF agents,[16,17] however, in our study, the IOP profiles of patients in both groups were comparable at both baseline and final follow-up. The safety profiles observed in this study closely align with findings from large-scale studies such as the LUMINOUS study etc.[16–19]

Procedure-related complications, such as hyphema and vitreous haemorrhage, were observed in both groups in similar numbers and generally resolved with conservative treatment. Cases of lens injury during the injection procedure led to cataract development, necessitating subsequent phacoemulsification. Chi-square tests were conducted for each adverse event to assess statistical significance. The results consistently indicated non-significant p-values, confirming that the safety profiles of biosimilar and innovator ranibizumab are comparable. These complications are consistent with observations from other real-world studies.[16–19]

Retinal pigment epithelial (RPE) tears have been reported following the administration of intravitreal anti-VEGF agents. In our study, the incidence of RPE tears in both groups was consistent with findings from other investigations, where less than 1% of patients experienced RPE tear.[16–20] The occurrence of RPE tears is typically linked to pre-existing

ocular conditions rather than the intravitreal agent or the injection procedure itself. Although its exact mechanism remains uncertain, contributing factors may include the baseline size of the PED and mechanical stress exerted on the RPE. These tears may arise spontaneously or during anti-VEGF treatment, which is considered a potential risk factor.[21]

Endophthalmitis, though rare and serious, was observed at the same rate (2 eyes in each group) across both cohorts. Meta-analyses of clinical trials and real-world data indicate endophthalmitis rates ranging from 0.02% to 0.05%.[22,23] The strict adherence to pre-injection asepsis protocols and the common practice of administering intravitreal injections in operating theatres in India likely contribute to the reduced incidence of endophthalmitis in the country.[24] Cluster endophthalmitis has been reported in India with the use of multidose vials of off-label bevacizumab (BVZ).[25] Avoiding the use of multidose vials could significantly mitigate the risk of endophthalmitis and provide a strong rationale for transitioning to biosimilar ranibizumab.

Although this study compared the safety profiles of biosimilar ranibizumab and its innovator counterpart, it did not include testing for anti-drug antibodies (ADA) due to the practical limitations of routine clinical practice. Safety was assessed clinically, in line with the methodology typically employed in real-world safety data evaluations.[26,27] A comprehensive review by Sharma et al on biosimilar ranibizumab (Razumab) highlighted that its efficacy and safety have been consistently demonstrated across multiple prospective and retrospective studies. Interestingly, the incidence of ocular AEs and serious adverse events (SAEs) in our study was lower than those reported in randomized controlled trials (RCTs), a trend also noted in other studies.[9,10,12–14,16–19]

Non-ocular adverse events associated with anti-VEGF therapies, such as elevated blood pressure, myocardial infarction (MI), and stroke, have been reported in various studies.[28,29] In the LUMINOUS trial, the rates of non-ocular events potentially attributable to VEGF inhibition were low, with all events occurring at rates below 0.5%.[20] Similarly, the CATT (Comparison of Age-Related Macular Degeneration Treatments Trials) study noted a higher incidence of serious systemic adverse events with bevacizumab compared to ranibizumab during the first year.[19] Ranibizumab has been widely recognized as a relatively safe intravitreal drug, and its low systemic exposure and short half-life have been linked to the low frequency of non-ocular events observed in multiple studies.[28–31] In our study, raised blood pressure was one of the more common systemic side effects. Interestingly, headache occurred more frequently in the biosimilar group, a statistically significant finding that may warrant further investigation. Serious events such as MI and cerebrovascular accidents (CVA) were rare in both groups, with no statistically significant differences. These results align closely with those reported in large-scale trials like the CATT and HARBOR studies.[19,32]

An important aspect in Anti-VEGF therapy is the high cost of biologics. A retrospective single-center study from India revealed that over half of the patients were lost to follow-up, with 41% citing unaffordability as the primary reason.[33] Biosimilars have demonstrated 35–50% cost reductions across various therapeutic areas, providing more affordable and cost-effective treatment options for managing neovascular retinal diseases worldwide.[11,34] By maintaining therapeutic equivalence to their innovator counterparts, biosimilars significantly lower the cost per injection, improving accessibility and enhancing patient compliance. Adoption of biosimilars can generate substantial savings at institutional, regional, and national levels, which can be reinvested into healthcare systems to enhance patient care. A national budget impact model evaluating the financial implications of switching from innovator ranibizumab to its biosimilar for conditions such as wet age-related macular degeneration demonstrated significant cost savings for the UK's National Health Service (NHS). In resource-limited settings like India, the adoption of biosimilar ranibizumab could have an even more profound impact.

While there is increasing approval of the use of biosimilar antiVEGF by physicians, there is still some reservation on the use of biosimilars. In this aspect, it needs to be pointed out that besides real worlds experience that is gathering volume, the approval of the biosimilars have been possible because of well designed RCTs. A recent Cochrane meta-analysis emphasized that randomized controlled trials (RCTs) evaluating currently approved biosimilars of ranibizumab were of satisfactory methodological quality. The analysis concluded, with moderately high confidence, that the safety profiles of biosimilar and innovator ranibizumab exhibit minimal differences.[12] Other meta-analysis of RCTs focused on biosimilar ranibizumab have also reported no significant differences in safety outcomes when comparing biosimilar and reference ranibizumab treatments for neovascular age-related macular degeneration (nAMD).[27,32]

One of the major strengths of this study is its large sample size, which includes patients with diverse baseline characteristics and represents the use of biosimilar ranibizumab (RBZ) across multiple centres. Additionally, the inclusive nature of patient enrolment in this registry-based study ensures minimal selection bias. Despite the robustness of the real-world data provided by this study, several limitations must be acknowledged. The retrospective design inherently carries the risk of biases typical of such studies. The lack of a randomized controlled trial framework limits the ability to control for confounding variables effectively. Furthermore, reliance on clinical records from hospital networks may have resulted in incomplete documentation of adverse events or treatment outcomes. The exclusion of patients with less than three months of follow-up or incomplete records may also have led to an underestimation of adverse events. Another limitation stems from the nature of routine clinical evaluations, which do not typically involve comprehensive systemic assessments or exhaustive blood tests following intravitreal injections. This may have resulted in missed systemic data. The absence of detailed information on concurrent medications further limits the ability to evaluate their influence on treatment outcomes and adverse events. While the study provides valuable insights into real-world outcomes with biosimilar RBZ, these limitations highlight areas for future research and the need for prospective, controlled studies to confirm these observations. Lastly, evolving practices in ophthalmology and changes in healthcare delivery over time may impact the generalizability of these findings.

Conclusion

In conclusion, this study provides valuable real-world evidence on the safety of biosimilar ranibizumab across a large and diverse patient population. The use of biosimilars offers a cost-effective alternative for managing neovascular retinal diseases, addressing affordability challenges and improving access to care, particularly in resource-constrained settings. While the study highlights the potential of biosimilars to alleviate the economic burden associated with anti-VEGF therapy, it also underscores the need for largescale prospective, studies to further validate these findings.

Acknowledgments

Dr Debasish Bhattacharya MS, Chairman Disha Eye Hospital, Kolkata, India

Consent to Participate

The authors confirm that all research participants provided informed consent for involvement in this study.

Disclosure

The authors report no conflicts of interest in this work.

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