Indian Journal of Clinical and Experimental Ophthalmology 2023;9(3):329–333

Content available at: https://www.ipinnovative.com/open-access-journals

Indian Journal of Clinical and Experimental Ophthalmology

Journal homepage: www.ijceo.org

Original Research Article

Safety and efficacy of ranibizumab biosimilar (Razumab®) as a cost-effective alternative to the innovator molecule for macular disorders in real-world

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ARTICLE INFO

Article history:
Received 17-09-2022
Accepted 15-06-2023
Available online 29-09-2023

Keywords:
Biosimilars
Ranibizumab
Realworld
Razumab
Antivascular endothelial growth factor

ABSTRACT

Purpose: To report the clinical efficacy and safety of the intravitreal ranibizumab biosimilar molecule, Razumab® (IVRz) as an economic alternative to the innovator molecule (Lucentis®) in macular diseases under real-world conditions.

Materials and Methods: A single- center, prospective study of 100 consecutive eyes undergoing three-monthly IVRz between April 2020 to March 2021 for a variety of macular disorders including diabetic macular edema (DME), neovascular age-related macular degeneration (nAMD), retinal vein occlusion (RVO), and myopic choroidal neovascular membrane (mCNVM). The main outcome measures were changes in best-corrected visual acuity (BCVA), central subfield thickness (CST), intraretinal-fluid (IRF), and subretinal-fluid (SRF) along with a safety analysis at weeks 4, 8, and 12 respectively.

Results: Of the 100 eyes of 100 patients undergoing IVRz, a majority had DME (39 eyes; 39%) followed by RVO (34 eyes; 34%), nAMD (21 eyes; 21%), and mCNVM (6 eyes; 6%). Mean BCVA improved from baseline to weeks 4, 8, and 12 ($P<0.001$). A significant reduction in CST from the baseline was also noted at all the visits ($P<0.001$). On qualitative analysis, resolution of SRF and IRF was observed in 61.47% and 61.71% of eyes respectively. No serious ocular or systemic adverse events were noted.

Conclusions: Our real-world data suggests that IVRz therapy is safe and efficacious for the management of varied macular pathologies. The cost-effectiveness and systemic and ocular safety of this regulatory-approved biosimilar makes it a suitable alternative to the branded drug. Further comparative studies into the benefit-cost analysis of these biosimilar and branded agents are warranted to better understand the health economics of anti-vascular endothelial growth factor (anti-VEGF) therapy in chorioretinal disorders.

1. Introduction

Biologics are biotechnology-based therapeutic proteins derived from living organisms.[1] Recent advances in pharmacotherapy with biologics that inhibit the actions of vascular endothelial growth factor (anti-VEGFs) have transformed the management of various chorioretinal disorders including neovascular age-related macular degeneration (nAMD), diabetic macular edema (DME), and macular edema due to retinal vein occlusions (RVO).[2] Currently, the anti-VEGF drugs including ranibizumab (Lucentis®; Genentech, S. San Francisco, CA/Roche, Basel, Switzerland), aflibercept (Eylea®, Regeneron, Tarrytown, NY), and brolucizumab (Beovu®; Novartis, Basel, Switzerland) are approved by the US Food and Drug Administration (FDA) and are widely used in various chorioretinal pathologies.[3–5] At the same time, bevacizumab (Avastin®; Genentech, S. San Francisco, CA/Roche, Basel, Switzerland) which is an economical anti-VEGF alternative is also routinely adopted by retinal physicians as an off-label drug.[6] However, its use is limited due to a lack of regulatory approval and uncertainties

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https://doi.org/10.18231/j.ijceo.2023.062

related to the medicolegal and safety aspects.[6]

Based on the literature, repeated intravitreal injection therapy over the long term is recommended for the optimal management of macular pathologies. However, because of the higher overall treatment costs, an anti-VEGF agent which is affordable, effective, safe, and broadly accessible is required to effectively treat these retinal conditions. Biosimilar drugs, which closely resemble the approved biological agents in structure and function, may offer a solution to this problem.[7] Razumab®, the world's first regulated biosimilar of Ranibizumab, was developed by Intas Pharmaceuticals Ltd., Ahmedabad, India, and approved in 2015 by the highest Indian regulatory body, the Drug Controller General of India (DCGI).[2]

The RE-ENACT studies have provided the initial phase 3 data related to the safety and efficacy of Razumab in nAMD and RVO.[8–11] However, the outcomes of these controlled trials may not truly reflect the outcomes in a real-world setting. Additionally, with changing global healthcare scenario in the backdrop of the COVID-19 pandemic, the impact of the preference for biosimilars over branded agents remains unexplored. To better understand this aspect, we present the real-world data of intravitreal Razumab (IVRz) therapy for various macular pathologies, in Indian patients who chose the biosimilar agent over the branded ranibizumab molecule.

2. Materials and Methods

This was a single-center, prospective study of patients undergoing IVRz from the beginning of the COVID-19 pandemic in India (April 2020) till March 2021. The study was conducted in accordance with the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board. Written informed consent for treatment and data collection was obtained from each patient.

2.1. Patient recruitment and treatment

Eligible patients having treatment-naïve or previously treated chorioretinal pathologies such as diabetic macular edema (DME), neovascular age-related macular degeneration (nAMD), retinal vein occlusion (RVO), and myopic choroidal neovascular membrane (mCNVM) were advised to undergo three loading doses of intravitreal ranibizumab therapy. Exclusion criteria included any signs of ocular infection, history of vitreous surgery, any episode of cerebrovascular accident or myocardial infarction within the past three months, or any media opacity prohibiting detailed fundus examination and spectral-domain optical coherence tomography (SD-OCT).

Treatment with both varieties of ranibizumab molecules, i.e., the innovator drug (Lucentis® [marketed in India as Accentrix®]) and the regulatory approved biosimilar drug (Razumab®) was offered to the patients. Non-affording patients who chose to undergo IVRz therapy due to financial constraints were included in the study. All the patients lacked insurance coverage for intravitreal therapy. The IVRz (0.5 mg in 0.05 mL) treatment was performed in a sterile operation theater. Pre-injection, povidone-iodine 5% was applied to the periocular region. Post-injection, topical moxifloxacin 0.5% was given for one week. The patients were reviewed at weeks 1, 4, 8, and 12 respectively. IVRz was repeated at weeks 4, and 8, and assessment of the best-corrected visual acuity (BCVA), intraocular pressure by Goldmann applanation tonometry, clinical evaluation of the anterior and posterior segments, and SD-OCT (Optovue, Fremont, CA) imaging was performed at baseline and all the subsequent visits.

2.2. Outcome measures

The primary outcome measures included the mean change in BCVA and the central subfield thickness (CST) from the baseline till weeks 4, 8, and 12. Automated central subfield thickness (CSFT) was calculated using the 25-line raster scan protocol. Additionally, changes in the IOP, intraretinal fluid (IRF), and subretinal fluid (SRF) along with a safety analysis were performed too.

2.3. Statistical analysis

The Statistical analysis was performed by SPSS 23.0 version (SPSS Inc., Chicago, IL, USA). For purposes of statistical analysis, all Snellen visual acuity data were converted to LogMAR values. Continuous variables were described as mean and variation of each observation from the mean value (Standard deviation) represented as mean ± SD or median and interquartile range if they failed to follow a normal distribution. The differences during follow-up were compared with paired t-tests. A p-value of <0.05 was considered to be statistically significant.

3. Results

3.1. Baseline characteristics

A total of 100 eyes of 100 patients underwent IVRz therapy during the one-year study period. Of these, 94 eyes were treatment-naïve while the other 6 eyes were previously treated with other anti-VEGF agents, intravitreal steroids, or laser photocoagulation. The mean age of the patients was 58.05 ± 12.777 years, with a majority being males (53 patients; 53%). The most common indication for IVRz was DME (39 eyes; 39%), followed by RVO (34 eyes;34%), nAMD (21 eyes; 21%), and mCNVM (6 eyes; 6%). Table 1 represents the baseline characteristics of the study population.

Table 1: Demographic characteristics of the study population

Characteristic	Number of eyes/patients (Total 100)
Age (years) Mean (+SD)	58.05 (12.777)
Gender	
Males	53 (53%)
Females	47 (47%)
Treatment Status	
Treatment-naive	94 (94%)
Previously treated	6 (6%)
Treatment Status	
DME	39 (39%)
nAMD	34 (34%)
RVO	21 (21%)
mCNVM	6(6%)

SD – Standard deviation; DME – Diabetic Macular Edema; nAMD – Neovascular age related Macular Degeneration; RVO – Retinal Vein Occlusion; mCNVM – Myopic choroidal neovascular membrane

3.2. Visual acuity

The mean BCVA of all the study eyes improved significantly at weeks 4 (Mean LogMAR BCVA: 0.62 ± 0.554; P < 0.0001), 8 (Mean LogMAR BCVA: 0.42 ± 0.389; P < 0.0001), and 12 (Mean LogMAR BCVA: 0.32 ± 0.267; P < 0.0001) respectively from the baseline (Mean LogMAR BCVA: 1.03 ± 0.807). Subgroup analysis based on the primary indication for the treatment also showed significant visual improvement at all the visits in each disease category. Table 2 lists the detailed visual acuity outcomes of the entire cohort and each disease subtype.

3.3. SD-OCT analysis

At baseline, the mean CST of the study eyes was 554.36 ± 165.575 μm. Post-IVRz therapy, the CST significantly reduced at weeks 4 (Mean CST: 402.58 ± 133.286 μm; P < 0.001), 8 (Mean CST: 318.89 ± 104.295 μm; P < 0.001) and 12 (Mean CST: 281.34 ± 73.5246 μm; P < 0.001) respectively. In each disease category, subgroup analysis based on the primary indication for treatment revealed a significant reduction in CST at all visits.

For all indications, the percentage of patients with SRF was reduced from 85.00% at baseline to 23.53% at 12 weeks (P = 0.04838). Similarly, the percentage of patients with IRF was significantly reduced to 25.29% at 12 weeks compared to 87.00% at baseline for the entire study cohort (P = 0.0401). Table 3 outlines the detailed SD-OCT outcomes of the study population.

3.4. Safety analysis

There were no reports of serious ocular complications such as endophthalmitis, retinal detachment, uveitis, retinal pigment epithelial tears, or raised intraocular pressure (IOP). The mean IOP at baseline was 14.13 ± 2.795 mmHg and at 12 weeks was14.87 ± 2.884 mmHg. Furthermore, no systemic adverse events were observed during the study, including thromboembolic episodes such as stroke or myocardial infarction. The safety profile of Razumab was as good as with Lucentis with no adverse events noted in the course of the study.

4. Discussion

In this real-world study on the efficacy and safety of IVRz as an economical alternative to the branded agent Lucentis, significant improvement in visual acuity and tomographic biomarkers was seen as early as four weeks after the initial injection of IVRz and maintained upto 12 weeks. The effectiveness of IVRz was seen across a variety of chorioretinal diseases including DME, nAMD, RVO, and mCNVM. Additionally, no new safety concerns or systemic adverse events were noted.

The COVID-19 pandemic which began in 2019 has changed the face of healthcare delivery and health economics on a global scale. Virus containment measures including periodic lockdowns have been adopted universally by all governments. The global economic fallout has been catastrophic, resulting in widespread job losses.[12] The situation was particularly grim in developing countries such as India and also in underdeveloped nations.[13,14] Health care has always been a challenge in a country like India, where the majority of the population lives in slums and rural areas and is below the poverty line.[13,14] A major health challenge in India is the high out-of-pocket expenditure (OOPE) on health, which accounts for 62.6% of total health expenditure.[15] India has one of the highest OOPE on health in the world, nearly three times the global average of 20.5 percent.[15]

Razumab was approved for intravitreal use in n-AMD and RVO by the DGCI in 2015. The approval was based on positive results from a 12-week phase 3 clinical trial (RE-ENACT), which demonstrated efficacy in 103 eyes with nAMD and 160 eyes with RVO.[8,9] Following that, at 48 weeks, the RE-ENACT-2 trial in nAMD demonstrated significant improvement in BCVA, CST, IRF, and SRF.[10] Similarly, the comparable RE-ENACT-2 trial in RVO established Razumab to be an effective treatment option in RVO by demonstrating significant visual acuity gains and reduction in the CST at 48 weeks.[11] We also similarly observed notable improvement in the visual parameters and SD-OCT, including a reduction in the CST, IRF, and SRF.

In India, the cost of the biosimilar Razumab ($125) is less than half of the branded agent (Branded Accentrix; $320). It is also very economical as compared to the other FDA-approved molecules, including Eylea ($760), and Beovu (Branded Pagenax; $350).[2] Bevacizumab is also widely used as an economical anti-VEGF agent, although its use is off-label for chorioretinal pathologies.[6] It is currently

Table 2: Visual outcomes of the study population

	Mean LogMAR BCVA				
Diagnosis	Baseline	4 weeks	8 weeks	12 weeks	P - Value
Entire Cohort	1.03 ± 0.807	0.62 ± 0.554	0.42 ± 0.389	0.32 ± 0.267	< 0.0001
DME	0.67 ± 0.252	0.48 ± 0.269	0.33 ± 0.239	0.26 ± 0.2	< 0.0001
nAMD	1.39 ± 1.067	0.93 ± 0.893	0.67 ± 0.623	0.50 ± 0.332	0.0002
CRVO	1.66 ± 1.051	0.57 ± 0.356	0.50 ± 0.367	0.37 ± 0.303	< 0.0001
BRVO	0.86 ± 0.582	0.53 ± 0.225	0.32 ± 0.21	0.23 ± 0.201	< 0.0001
mCNVM	1.26 ± 0.922	0.94 ± 1.049	0.34 ± 0.305	0.24 ± 0.249	0.0195

BCVA – Best-corrected visual acuity; DME – Diabetic Macular Edema; nAMD – Neovascular age related Macular Degeneration; CRVO – Central Retinal Vein Occlusion; BRVO – Branch Retinal Vein Occlusion; mCNVM – Myopic choroidal neovascular membrane

Table 3: Spectral-domain optical coherence tomographic (SD-OCT) outcomes of the study population

	Mean CST (μm)				
Diagnosis	**Baseline**	**4 weeks**	**8 weeks**	**12 weeks**	**P - Value**
Entire Cohort	554.36 ± 165.575	402.58 ± 133.286	318.89 ± 104.295	281.34 ± 73.524	< 0.001
DME	547.67 ± 142.804	400.08 ± 116.321	330.74 ± 124.192	288.69 ± 91.290	< 0.0001
nAMD	540.29 ± 118.879	396.43 ± 109.807	306.62 ± 79.012	284.19 ± 66.252	< 0.0001
CRVO	568.50 ± 268.297	443.43 ± 160.850	362.64 ± 120.684	292.79 ± 58.194	< 0.0015
BRVO	591.70 ± 147.885	392.95 ± 149.965	284.70 ± 47.563	261.15 ± 57.077	< 0.0001
mCNVM	489.67 ± 220.68	377.17 ± 204.778	296.67 ± 119.833	264.17 ± 46.344	0.026

BCVA – Best-corrected visual acuity; DME – Diabetic Macular Edema; nAMD – Neovascular age related Macular Degeneration; CRVO – Central Retinal Vein Occlusion; BRVO – Branch Retinal Vein Occlusion; mCNVM – Myopic choroidal neovascular membrane

available in a 4-mL vial, from which multiple doses for ophthalmic use are aliquoted. Because multiple pricks may be performed during aliquoting, this technique carries an inherent risk of infection, as well as viability concerns due to the difficulty in maintaining the cold chain and storing the vial. Following a few cases of endophthalmitis caused by its use, the US-FDA issued a warning about its ocular use.[6] Furthermore, due to safety concerns, the drug was temporarily banned in India.[6] Regulatory approved biosimilar such as Razumab is available as a single-use vial and hence can be considered as a safer and economical anti-VEGF agent. A comparative survey conducted by the Vitreoretinal Society of India (VRSI) showed that a vast majority of Indian retinal physicians are well aware of biosimilars and there is an increasing trend toward prescribing a ranibizumab biosimilar.[16] They were also largely satisfied with the biosimilar's safety and efficacy.[16] In our study, which included patients with a wide array of common chorioretinal pathologies such as DME, nAMD, RVO, and mCNVM, the safety and efficacy of IVRz were well established. In 100 eyes, significant improvement in visual and tomographic outcomes was noted after three loading doses of the ranibizumab biosimilar. Verma L et al retrospectively analyzed the clinical efficacy and safety of biosimilar Razumab in 153 eyes with AMD, DME, and RVO, and demonstrated significant clinical improvement with no ocular or systemic adverse events at three months.[17] The authors however did not perform a detailed tomographic evaluation including IRF and SRF resolution that was conducted in the current study.

Systemic safety remains an ongoing challenge with anti-VEGF therapy. The use of these agents in the eyes has been linked to a small increase in the risk of systemic thromboembolic events, which can be serious in some cases. Additionally, biosimilars can also cause immunologic reactions when injected intraocularly. In 2015, 2017, and 2019, there were reports of sterile endophthalmitis following Razumab injections.[18] In the first real-world data on the safety of 9406 IVRz, the rate of serious adverse events was 0.61%, which included one patient with infectious endophthalmitis, two with sterile vitritis, and 12 with non-fatal thromboembolic events.[19] However, we found no cases of serious ocular or systemic adverse events following Razumab injection in our study.

The major limitations of the current study include a limited follow-up and lack of comparative group undergoing intravitreal therapy with the branded ranibizumab, Lucentis. Despite these limitations, the results reported here represent the first real-world data regarding the safety and efficacy of the ranibizumab biosimilar (Razumab) as an economical alternative to the innovator molecule (Lucentis) in the backdrop of the COVID-19 pandemic. With the biologics', including Lucentis and Eylea, patents on the verge of expiry and biosimilar acceptance growing, countries may shift away from branded drugs and toward biosimilars.

5. Conclusion

To conclude, IVRz therapy appears to be safe and effective in the treatment of a variety of macular pathologies, according to our real-world data. Management with this

regulatory approved biosimilar agent can be considered for both treatment-naïve eyes and previously-treated ones as a cost-effective option to the other pricier anti-VEGF agents. This is especially true for patients who are financially strained due to the economic fallout of the COVID-19 pandemic. At the same time, further studies are warranted to evaluate the health economics of anti-VEGF therapy with biosimilar agents in comparison to branded agents. They may throw further insights into the benefit-cost analysis of these agents and help in the national healthcare policy formulations.

6. Source of Funding

None.

7. Conflict of Interest

None.

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Cite this article: Paliwal S, Deshpande R, Upadhyay P. Safety and efficacy of ranibizumab biosimilar (Razumab®) as a cost-effective alternative to the innovator molecule for macular disorders in real-world. *Indian J Clin Exp Ophthalmol* 2023;9(3):329-333.