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Retrospective analysis of outcomes of biosimilar ranibizumab (BSR) in treating cystoid macular oedema (CME) in ischaemic central retinal venous occlusion (CRVO)

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ABSTRACT

Objectives: The objective of this study was to understand the efficacy of biosimilar ranibizumab (BSR) in treating cystoid macular oedema in ischaemic central retinal venous occlusion (CRVO) in developing countries like India.

Materials and Methods: Data from ten patients diagnosed with ischaemic CRVO were analysed in the form of a central foveal thickness (CFT), visual acuity and pupillary reaction after three doses of intravitreal BSR at the end of 1 month, 3 months and 6 months.

Results: There was a significant reduction in CFT after 1, 3 and 6 months post 1st dose of BSR ($P < 0.05$) with moderately improved visual acuity after 3 and 6 months of post 1st dose of BSR ($P < 0.05$).

Conclusion: BSR has been found to be a low-cost alternative to conventional therapy in treating ischaemic CRVO with macular oedema.

Keywords: Ischaemic CRVO, Vascular endothelial growth factor, Cystoid macular oedema, Anti-vascular endothelial growth factor, Biosimilar ranibizumab

INTRODUCTION

Retinal vein thrombosis is strongly associated with age-related local and systemic factors. Central retinal venous occlusion (CRVO) is a retinal vascular condition that affects an estimated 16 million people worldwide.[1] The second most common retinal vascular disease is retinal vein occlusion after diabetic retinopathy. CRVO is classified into ischaemic CRVO and non-ischaemic CRVO.[2] Atherosclerotic changes of the central retinal artery cause occlusion of central retinal veins as the central retinal vein and artery possess a common sheath at crossing points, which are posterior to lamina cribrosa. The pathophysiology of CRVO involves ischemia through occlusion of the lumen of the central retinal vein, which triggers and upregulates expression of vascular endothelial growth factor (VEGF) on messenger Ribonucleic acid (mRNA), which, further tends to increased levels of VEGF in the vitreous along with other inflammatory mediators such as interleukin 6 and 8 and monokine.[3-5] Elevated levels of VEGF play a key role in causing macular oedema and neovascularisation, which subsequently leads to vision loss. Therefore, inhibition of VEGF with anti-VEGF like ranibizumab is important in managing macular oedema secondary to CRVO.[6] Ischaemic CRVO tends to cause ischaemic macular oedema and neovascular glaucoma, which are poor responders to treatment. Few studies are there that show the effectiveness of ranibizumab in ischaemic CRVO. Ranibizumab is a humanised monoclonal antibody that binds and inactivates VEGF-A and VEGF-B. The innovator ranibizumab molecule has a major obstacle for public use in terms of its high cost. Furthermore, the fact that CRVO is a disease which might require intravitreal ranibizumab injections at regular intervals further enhances the treatment cost. In India, an average innovator ranibizumab costs around 322 USD in contrast to biosimilar ranibizumab (BSR), will costs around 175 USD.[7] BSR molecules are very similar to an innovator biological product in terms of clinical efficacy, immunogenicity and biosafety. This study is conducted to evaluate the efficacy of BSR in treating cystoid macular

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oedema (CME) in patients of ischaemic CRVO in developing countries like India, especially in government hospitals.

MATERIALS AND METHODS

A retrospective observational study was carried out among all the patients diagnosed with ischaemic CRVO over 6 months.

Diagnostic criteria for ischaemic CRVO include visual acuity (<6/60), >grade 2 relative afferent pupillary defect pupillary reaction, and multiple capillary non-perfusion areas (>10 Disc diameter) on fundus fluorescein angiography.[2]

Inclusion criteria include patients aged ≥18 years with macular oedema who fulfil the diagnostic criteria of ischaemic CRVO and who have followed up for 6 months.

Patients having a history of recent myocardial infarction and stroke within the past 1 year, had a history of intravitreal injection in the past 3 months and with any other ocular comorbidities such as dense cataract, glaucoma and optic disc disorders were excluded from this study.

In our study, ten cases diagnosed with ischaemic CRVO having CME were treated with three doses of intravitreal BSR injection (Ranieyes™ – Lupin Pharma-No Financial Disclosure) (0.05 mL) 1 month apart. The landing cost of BSR to the patient in our institute is 6000 rupees per injection. The patient was followed up after 1 month, 3 months and 6 months post 1st dose injection. At all the visits, efficacy was evaluated in the form of the patient's central foveal thickness (CFT) on spectral domain optical coherence tomography (OCT) and visual acuity.

Ocular side effects, such as periocular pain and any signs of inflammatory reactions like redness, were checked at each follow-up visit. Systemic adverse effects such as myocardial infarction and stroke were checked at every visit and the end of 6 months.

RESULTS

Table 1 shows significantly improved visual acuity at 3 and 6 months post-first injection (i.e., $P < 0.05$). After 1st dose of BSR, there was no significant improvement in visual acuity (i.e., $P = 0.07$).

Table 2 shows a significant reduction in the mean CFT (i.e., $P < 0.05$) after 1, 3 and 6 months post 1st dose of BSR.

The landing cost of BSR is 6000 rupees per injection and that of innovator ranibizumab is 20,000 per injection to the patients in our institute. In our study, three doses of ranibizumab were given, which cost around 18,000 rupees for three doses of BSR and 60,000 rupees for three doses of innovator ranibizumab which clearly shows that BSR is cheaper and a low-cost alternative as compared to innovator ranibizumab in a government hospital like our institute.

Table 1: Comparison of BCVA pre-ranibizumab (BCVA0), 1-month post 1st dose (BCVA1), 3 months post 1st dose (BCVA2), and 6 months post 1st dose (BCVA3).

Patient	BCVA 0	BCVA 1	BCVA 2	BCVA 3
1	1.77	1	0.6	0.18
2	1.77	1.47	1.3	0.78
3	1.85	1.77	1	0.48
4	1.77	1.3	1	0.3
5	1.17	1	0.78	0.3
6	1.9	1.85	1.3	1
7	1.17	1.3	1.77	1.85
8	1.17	1	0.6	0.18
9	1.3	1.47	1	1.47
10	1.77	1.3	0.77	0.3

BCVA 0 baseline, BCVA1-1 month post 1st dose, BCVA2-3 months post 1st dose, BCVA3-6 months post 1st dose. BCVA: Best-corrected visual acuity

Table 2: Comparison of CFT pre-ranibizumab injection (CFT0), 1-month post 1st dose (CFT1), 3 months post 1st dose (CFT2) and 6 months post 1st dose (CFT3).

Patient	CFT0	CFT1	CFT2	CFT3
1	655	548	147	110
2	567	229	209	185
3	730	502	245	156
4	402	317	220	200
5	575	385	282	192
6	635	512	324	258
7	522	402	478	560
8	382	258	200	123
9	450	530	321	580
10	453	330	254	146

CFT0 baseline, CFT1-1-month post 1st dose, CFT2-3 months post 1st dose and CFT3-6 months post 1st dose. CFT: Central foveal thickness

No ocular side effects such as periocular pain, any signs of inflammation such as redness were noted or no systemic adverse events such as thromboembolic events, stroke and myocardial infarction were noted during the study period.

DISCUSSION

Anti-VEGF agents have been found to be beneficial in patients with ischaemic CRVO in treating macular oedema and improving vision. It, further, prevents vision loss which results in better prognosis and outcomes. Ranibizumab, a humanised monoclonal antibody fragment, binds at the receptor site and, thus, prevents interaction of VEGF present on the endothelial surface, which will further decrease the proliferation of endothelial cells, vascular leakage and neovascularisation.[8,9] Innovator ranibizumab is a high-cost molecule that has been a concern for use in healthcare. To overcome this, BSR, a molecule similar to the reference product, is derived, which has comparable pharmacokinetics,

pharmacodynamics, immunogenicity, safety and efficacy to the biological reference product.[10,11] In the present study, the mean CFT shows significant reduction (i.e., $P < 0.05$) after 1, 3 and 6 months post 1st dose of BSR with significantly improved visual acuity after 3 and 6 months post 1st dose of BSR (i.e., $P < 0.05$). After 1 month of BSR, there was no significant improvement in visual acuity (i.e., $P = 0.07$).

In the real life assessment of safety and effectiveness of razumab 2 (RE-ENACT 2) study, the visual acuity and CFT improvement, as measured by logarithm of the minimum angle of resolution (logMAR) best corrected visual acuity (BCVA) and OCT-domain, respectively, was significant with BSR starting at week 4 and throughout 48 weeks (i.e., 12 months), which was similar to our study conducted for over 6 months except for the statistical improvement which was not seen in BCVA after 1st dose of BSR injection.[12-14]

A Phase 3, multicenter, randomized, sham injection-controlled study of the efficacy and safety of ranibizumab injection compared with sham in patients with macular edema secondary to CRVO. The CRUISE studies also demonstrated similar results with significant improvements in BCVA sustained over 12 months in patients with CRVO.[15]

As in ischaemic CRVO, photoreceptor cells are damaged so in spite of a decrease in macular oedema; there would only be a qualitative visual improvement and not quantitative visual improvement. The standard cost of the innovator ranibizumab (three injections) to the patients is around 60,000 rupees as compared to BSR (three injections) which is around 18,000 rupees.[16] Thus, BSR has shown to be a cost-effective alternative for economically poor people attending tertiary care centres and thus preventing ischaemic maculopathy and neovascular glaucoma, which is a complication of untreated ischaemic CRVO.

A retrospective study design with a small sample size and a short-term follow-up of 6 months was limitations of this study.

CONCLUSION

BSR is a low-cost alternative to conventional therapy in treating ischaemic CRVO to reduce CFT with moderate visual gain, especially in a tertiary care centre.

Ethical approval

The Institutional Review Board approval is not required because the study is a retrospective observational study.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

REFERENCES

1. Rogers S, McIntosh RL, Cheung N, Lim L, Wang JJ, Mitchell P, *et al*. The prevalence of retinal vein occlusion: Pooled data from population studies from the United States, Europe, Asia, and Australia. Ophthalmology 2010;117:313-9.
2. Hayreh SS. Classification of central retinal vein occlusion. Ophthalmology 1983;90:458-74.
3. Aiello LP, Avery RL, Arrigg PG, Keyt BA, Jampel HD, Shah ST, *et al*. Vascular endothelial growth factor in ocular fluid of patients with diabetic retinopathy and other retinal disorders. N Engl J Med 1994;331:1480-7.
4. Noma H, Funatsu H, Yamasaki M, Tsukamoto H, Mimura T, Sone T, *et al*. Pathogenesis of macular edema with branch retinal vein occlusion and intraocular levels of vascular endothelial growth factor and interleukin-6. Am J Ophthalmol 2005;140:256-61.
5. Pe'er J, Folberg R, Itin A, Gnessin H, Hemo I, Keshet E. Vascular endothelial growth factor upregulation in human central retinal vein occlusion. Ophthalmology 1998;105:412-6.
6. Huang JM, Khurana RN, Ghanekar A, Wang PW, Day BM, Blodi BA, *et al*. Disease-modifying effects of ranibizumab for central retinal vein occlusion. Graefes Arch Clin Exp Ophthalmol 2022;260:799-805.
7. Ratra D, Roy K, Giridhar S, Madaan S. Comparison between ranibizumab biosimilar, innovator ranibizumab and bevacizumab in a real-world situation. Ophthalmol Ther 2022; 11:135-49.
8. Sharma S, Khan M, Chaturvedi A. A multicenter, retrospective study (RE-ENACT on Razumab™ (World's first biosimilar ranibizumab) in retinal vein occlusion. Ophthalmol Ther 2020;9:625-39.
9. Boyd SR, Zachary I, Chakravarthy U, Allen GJ, Wisdom GB, Cree IA, *et al*. Correlation of increased vascular endothelial growth factor with neovascularization and permeability in ischemic central vein occlusion. Arch Ophthalmol 2002;120:1644-50.
10. Azad R, Vivek K, Sharma Y, Chandra P, Sain S, Venkataraman A. Ranibizumab as an adjunct to laser for macular edema secondary to branch retinal vein occlusion. Indian J Ophthalmol 2012;60:263-6.
11. Sameera VV, Apoorva AG, Joshi S, Guruprasad AS. Safety

and efficacy of Razumab-the new biosimilar in India: Our experience. Kerala J Ophthalmol 2016;28:180-5.
12. Sangroongruangsri S, Ratanapakorn T, Wu O, Anothaisintawee T, Chaikledkaew U. Comparative efficacy of bevacizumab, ranibizumab, and aflibercept for treatment of macular edema secondary to retinal vein occlusion: A systematic review and network meta-analysis. Expert Rev Clin Pharmacol 2018;11:903-16.
13. Sharma S, Khan MA, Chaturvedi A, RE-ENACT Study Investigators Group. Real-Life clinical effectiveness of Razumab® (the world's first biosimilar of ranibizumab) in retinal vein occlusion: A subgroup analysis of the pooled retrospective RE-ENACT study. Ophthalmologica 2018;241:24-31.
14. Sharma S, RE-ENACT 2 Study Investigators Group, Khan M, Chaturvedi A. A multicenter, retrospective study (RE-ENACT 2) on Razumab™ (world's first biosimilar ranibizumab) in retinal vein occlusion. Ophthalmol Ther 2020; 9:625-39.
15. Campochiaro PA, Heier JS, Feiner L, Gray S, Saroj N, Rundle AC, *et al*. Ranibizumab for macular edema following branch retinal vein occlusion: Six-month primary end point results of a phase III study. Ophthalmology 2010; 117:1102-12.e1.
16. Narayanan R, Sheng Y. Significant reduction in the cost of care for retinal diseases in India due to the approval of biosimilars: Lessons for health systems. IHOPE J Ophthalmol 2024;3:1-2.

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