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Original Research Article

Visual outcome in patients of branch retinal vein occlusion (BRVO) with macular edema after one injection of intravitreal biosimilar ranibizumab

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ABSTRACT

Purpose: This study aims to determine the effects of intravitreal biosimilar ranibizumab injection on best corrected visual acuity (BCVA) and central macular thickness (CMT) in patients of branch retinal vein occlusion (BRVO) with macular edema.

Materials and Methods: A retrospective, unmasked, and data-based study was conducted on 50 patients of BRVO with macular edema, who presented to our OPD over a period of 2 years. Cases in our study received one intravitreal injection of biosimilar Ranibizumab (0.5 mg/0.05 ml) at presentation and were followed up one month after injection. The data was collected from patients and available records. The data regarding BCVA and CMT (by Optical Coherence Tomography) before and 1 month after treatment was recorded and analyzed statistically.

Results: In this study, we included fifty eyes of fifty patients. The mean patients' age (in years) was 53.08 ± 9.58. There were 24 (48%) male and 26 (52%) female patients. The baseline mean BCVA ± SD (logMAR) was 0.79 ± 0.16 and mean CMT ± SD (in μm) was 688.14 ± 98.41 before treatment. Mean BCVA (logMAR) and mean CMT (in μm) after one biosimilar ranibizumab injection, at 1-month follow-up, were 0.33 ± 0.13 and 307.18 ± 34.97 respectively. We used paired t-test to compare mean BCVA and mean CMT before and after injection, and we found a statistically significant difference (p-value of <0.001) for both. None of the patients experienced any significant ocular and systemic adverse effects on post-op day 1, and at 1 month.

Conclusion: Intravitreal biosimilar ranibizumab is an effective and safe therapy for patients of BRVO with macular edema and results in improvement of BCVA and decrease in CMT. Biosimilar injection has also reduced the cost of treatment leading to an increase in patients' compliance.

1. Introduction

Retinal vein occlusion (RVO) accounts for the second most common cause of retinal vascular disorder after diabetic retinopathy.[1] BRVO is a type of venous occlusion that can involve any division of the central retinal vein.

BRVO has an incidence of 0.44%-1.6% and is the most common type of RVO. Worldwide, 13.9 million people have had BRVO (4.42 per 1,000 persons). It has been observed that race has an association with BRVO, but there is no sex predilection. It has a higher prevalence in Asians and Hispanics than in other ethnic groups.[2]

Based on arteriovenous crossing, BRVO has been classified into 1) major BRVO, 2) hemispheric retinal vein occlusion, and 3) macular BRVO.[3] Superotemporal

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quadrant (58.1-66%) is most commonly involved, next in order is inferotemporal quadrant (29%), and nasal quadrants (12.9%) are least commonly involved.[4]

Both ophthalmic and systemic risk factors are known, including old age, hypertension dyslipidemia, ocular hypertension, and glaucoma.[5] In patients with age < 50 years, BRVO is not commonly seen, and in such patients, an association with BMI is significant.[6]

BRVO commonly occurs at arteriovenous crossings. A rigid artery mechanically compresses the vein at arteriovenous crossings, resulting in turbulence of blood flow, which results in damage to intima, media, and endothelium of the vein leading to its occlusion.[4]

The loss of vision caused by BRVO may be immediate, due to decreased blood perfusion leading to retinal hypoxia. Often temporal delay is present, when it is complicated by macular edema. An additional diminution in visual acuity may be caused due to the edema, which often exceeds the primary ischemic damage. Hence, macular edema remains an important target for treatment.[7] Treatment for macular edema in the past was focal photocoagulation and recently, it is intravitreal triamcinolone.[8,9] These treatment options had little success. Vitreous samples from patients with BRVO when compared with controls, have shown raised levels of vascular endothelial growth factor (VEGF), interleukin-6 (IL-6), interleukin-8 (IL-8), and monocyte chemoattractant protein-1.[10] A study has previously described that VEGF levels are remarkably elevated in vitreous humor post BRVO.[11] Underlying ischaemia and retinal hypoxia due to vascular occlusion are the causes of increased secretion of vascular endothelial-derived growth factor (VEGF), which contributes to macular edema and neovascularization leading to vision loss. Various anti-VEGF agents including ranibizumab, bevacizumab, and aflibercept are available for treatment of any macular edema.[12]

Multiple injections and multiple visits over very long time periods pose a serious strain on these patients financially. To encourage the treatment and to reduce the number of drop-outs, we are stressing over more flexible dosing schedules. Treatment has been revolutionized after the introduction of the biosimilar of ranibizumab as it has reduced the price of the injection, hence allowing a larger population to continue with long-term treatment. The Razumab® (the world's first biosimilar of ranibizumab by Intas Pharmaceuticals Ltd.) has been approved by the Drug Controller General of India (DCGI) in 2015 after a phase 3 trial.[13] With biosimilars, we intend to achieve comparable efficacy and mechanism of action. They are duplicates of the original molecule and are very close in structure and function to the biologic drug. In India, the estimated price of a vial of Razumab is 175 USD whereas the cost of an injection of ranibizumab is 322 USD.[14]

Hence, we conduct this study to determine the outcome of biosimilar ranibizumab in patients having macular edema secondary to BRVO.

2. Materials and Methods

This retrospective, unmasked study included all patients with BRVO-induced macular edema presenting between August 2020 and August 2022 to PGIMS Rohtak. Informed written consent describing the benefits, risks, and alternative treatment options was taken from the study subjects at the time of registration. The data was collected from patients and available records. The data regarding BCVA and CMT (by Optical Coherence Tomography) before and 1 month after treatment was recorded and analyzed statistically. All procedures performed on human participants were according to the ethical standards of the institutional research committee and with the Helsinki declaration.

We did a retrospective analysis in 50 eyes of 50 patients who presented in our outpatient department. Cases in our study received one intravitreal injection of biosimilar ranibizumab at presentation and were followed up one month after injection. Patients who also underwent other treatment modalities such as laser photocoagulation, and intraocular steroids were excluded from the study.

After topical anesthesia, under aseptic technique, 0.5mg/0.05 ml biosimilar ranibizumab was given intravitreally, 4 mm posterior to the limbus and 3.5 mm posterior to the limbus in phakic and pseudophakic eyes respectively. Examination of patients at baseline and follow-up included:

1. BCVA using Snellen charts.
2. Measurement of CMT using Spectral Domain Optical Coherence Tomography (SD-OCT).

BCVA values were converted into logMAR for statistical analysis.

We compiled and tabulated the data using the Microsoft Excel database and then exported it to statistical software for analysis, which was then done accordingly.

3. Results

3.1. Distribution of cases according to age

The mean patients' age (in years) was 53.08 ± 9.58.

Table 1: Distribution of cases according to the age of the patient. (N = 50)

Age of the patient (in years)	Mean ± SD	Range
	53.08 ± 9.58	36 – 71

3.2. Distribution of cases according to sex

There were 24 (48%) male and 26 (52%) female patients.

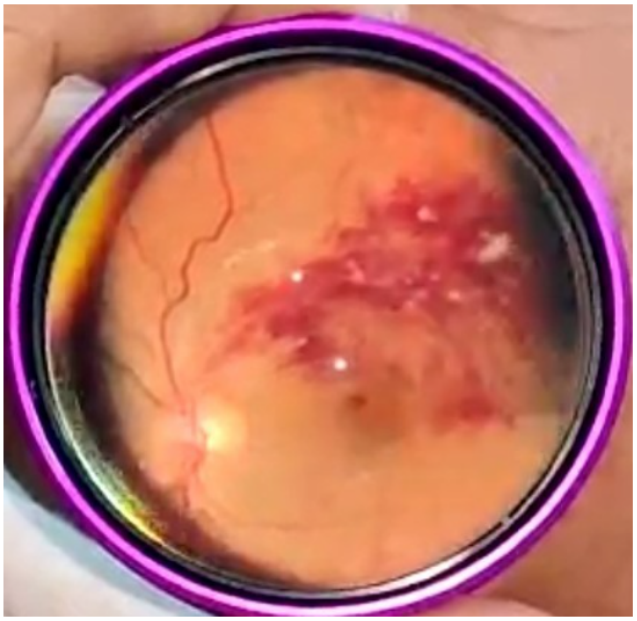

Fig. 1: Right eye inferotemporal BRVO with macular edema

Table 2: Distribution of cases according to the sex of the patient. (N = 50)

Sex of the patient	Number of cases
Male	24 (48%)
Female	26 (52%)

3.3. Distribution of cases according to diagnosis of the patient

32 (64%) patients had superotemporal BRVO whereas 18 (36%) patients had inferotemporal BRVO.

Table 3: Distribution of cases according to diagnosis of the patient. (N = 50)

Diagnosis of the patient	Number of cases
Superotemporal BRVO	32 (64.0%)
Inferotemporal BRVO	18 (36.0%)

3.4. Distribution of cases according to best corrected visual acuity

Before treatment, the baseline mean BCVA ± SD (logMAR) was 0.79 ± 0.16. The mean BCVA (logMAR) after one biosimilar ranibizumab injection, at 1 month follow-up, was 0.33 ± 0.13. When paired t-test was used to compare mean BCVA pre and post injection, a statistically significant difference was found with a p-value of <0.001.

Table 4: Comparison of mean BCVA (logMAR) before and after injection. (N = 50)

BCVA (logMAR)	Before injection	After injection	p-value
	0.79 ± 0.16	0.33 ± 0.13	<0.001

3.5. Distribution of cases according to central macular thickness

Before treatment, baseline mean CMT ± SD (in μm) was 688.14 ± 98.41. Mean CMT (in μm) after one biosimilar ranibizumab injection, at 1 month follow up, was 307.18 ± 34.97. Paired t-test was used to compare mean CMT pre and post injection and the difference found was statistically significant.

Table 5: Comparison of mean CMT before and after injection. (N = 50)

CMT	Before injection	After injection	p-value
	688.14 ± 98.41	307.18 ± 34.97	<0.001

3.6. Safety

Patients were followed-up on post-op day 1, and at 1 month. 5 patients were found to have an increase in intraocular pressure by 10-15% from baseline on post-op day 1. They were then advised an additional visit at 1 week and their IOP values were found to have returned to baseline values by then. None of them required treatment. None of them were found to have any other ocular (including cataract, RPE tear, glaucoma, vitreous hemorrhage, endophthalmitis, intraocular inflammation) and systemic adverse effects (including nasopharyngitis, hypertension, increased C-reactive protein level).

4. Discussion

The mean age (in years) of patients in our study was 53.08 ± 9.58, ranging from 36-71. In a study by Abegg et al. using bevacizumab for the treatment of macular edema caused by BRVO, median age of patients was 65 years, with a range of 48 to 87 years.[7] Rogers S et al. in their study found that the incidence of BRVO increased with age, with highest prevalence in 70-79-year-olds (1.276 per 100).[2]

Our study showed that baseline mean BCVA ± SD (logMAR) was 0.79 ± 0.16 and mean CMT ± SD (in μm) was 688.14 ± 98.41 before treatment. Mean BCVA (logMAR) and mean CMT (in μm) after one biosimilar ranibizumab injection, at 1 month follow up, were 0.33 ± 0.13 and 307.18 ± 34.97 respectively. We found that biosimilar ranibizumab injection when given intravitreally for BRVO-induced macular edema, resulted in rapid and significant (p<0.001) improvement of visual acuity along with a decline in CMT. Similar results were previously

obtained using intravitreal bevacizumab injection. In a study by Abegg et al, BCVA was found to be 0.68 ± 0.3 and 0.5 ± 0.35 logMAR, before and after administration of bevacizumab injection respectively ($p < 0.01$, paired t-test). Central retinal thickness values before and after injection were 454 ± 117 μm and 305 ± 129 μm, respectively ($p < 0.01$, paired t-test). The mean follow-up interval was found to be 30 ± 11 days. The number of injections was variable, unlike our study where a single injection was administered.[7]

Cekic et al.in their study suggested similar findings with intravitreal injection of triamcinolone.However, unlike triamcinolone, in our study, there were no severe and frequent ocular side effects such as an increase in intraocular pressure or development of cataract.[9]

Campochiaro et al. in their study on 397 patients with macular edema following BRVO, found that in the 0.3 mg and 0.5 mg ranibizumab groups, mean (95% confidence interval [CI]) change from baseline BCVA letter score at 6 months was 16.6 (14.7-18.5) and 18.3 (16.0-20.6) whereas, in the sham group, it was 7.3 (5.1-9.5) ($p<0.0001$ for each ranibizumab group vs sham). Central foveal thickness (CFT) showed a mean decrease of 337 microns (0.3 mg) and 345 microns (0.5 mg) in the ranibizumab groups and 158 microns in the sham group ($p<0.0001$ for each ranibizumab group vs sham). In their study, the follow-up period was 6 months whereas our study had a follow-up period of 1 month, and we did not have any sham group.[15]

The retrospective study RE-ENACT in 160 patients with retinal vein occlusion (RVO) receiving at least 3 Razumab® injections, found that baseline BCVA, according to the logMAR chart, was 0.76 (±0.04) which improved to 0.73 (±0.03) when observed at 4^{th} week after ranibizumab injection ($p = 0.0656$), and which subsequently improved to 0.55 (±0.02) at 8^{th} week ($p <.0001$). CMT showed improvement from a baseline mean value of 447.60 μm (±10.91 μm) to 431.84 μm (±10.92 μm) at 4^{th} week ($p = .0028$) and further improved to 339.28 μm, ±8.12 μm at 8^{th} week and 298.23 μm, ±6.68 μm at 12^{th} week. Patients with branch RVO and central RVO were found to have similar improvements.[16]

Half-life of intravitreal injections is short with 4.32 days of bevacizumab, 2.88 days of ranibizumab, and 18.6 days of triamcinolone.[17–19] Hence, repeated injections are needed.

Our study concludes that biosimilar ranibizumab is a cost-effective and safe treatment option for decreasing macular edema and leads to an improvement in visual acuity in patients of BRVO with minimal adverse effects.

5. Source of Funding

Nil.

6. Conflicts of Interest

There are no conflicts of interest.

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