Original Article

To Determine the Effectiveness of Ranibizumab in Patients with Branch and Central Retinal Vein Occlusion: A Hospital Based Study

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Ronak Afza Memon[1], Fariha Sherwali[2], Shehnillah Shujaat[3], Waqas Ali[4], Asra Talpur[5]
[1-5]Sindh Institute of Ophthalmology & Visual Sciences, Hyderabad

ABSTRACT

Purpose: To determine the effectiveness of ranibizumab in patients with branch and central retinal vein occlusion in a tertiary care hospital.

Study Design: Interventional case series.

Place and Duration of Study: Sindh Institute of Ophthalmology and Visual Sciences, Hyderabad. from July 2023 to March 2024.

Methods: Patients of either gender and aged at least 20 years, diagnosed with macular edema (ME) secondary to CRVO or BRVO and best corrected visual acuity (BCVA) of less than 6/9 were included in the study. Patients with known retinal diseases, infection or previous treatment with laser photocoagulation, or a history of anti-VEGF injections or corticosteroids in the last 6 months were excluded. Three intravitreal ranibizumab injections were given at monthly intervals. The effectiveness of ranibizumab injection was investigated by measuring the difference in mean central macular thickness and BCVA at 0, 3,6 and 9 months. Data was analyzed using SPSS version 25.

Results: Total 188 patients were included with mean age of 57.53±10.74 years. Majority were males (63.8%) and 59% had disease in the right eye. Injections were administered to 158 patients (84%)for three months, while 30 (16%) patients required injections for six months. The mean central macular thickness was 541.54±146.99 before injection, and 270.99±82.10, 240.02±22.50, 234.73±18.06 at 3, 6,and 9months,respectively. The mean BCVA (LogMAR) was1.21±0.57 before injection, 0.30±0.27 at 3 months, 0.21±0.16 at 6 months and 0.17±0.14at 9 months.

Conclusion: Ranibizumab is effective in decreasing central macular thickness and improving BCVA in patients with macular edema following retinal vein occlusion.

Keywords: Ranibizumab, central retinal vein occlusion, branch retinal vein occlusion, anti-VEGF drug, best corrected visual acuity, central macular thickness, macular edema.

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Correspondence: Ronak Afza Memon
Sindh Institute of Ophthalmology & Visual Sciences, Hyderabad
Email: ronakafzamemon@yahoo.com

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INTRODUCTION

Retinal vein occlusion (RVO) is the second most common retinal disorder, causing painless vision loss following diabetic retinopathy, significantly impacting visual acuity and quality of life.[1,2] The worldwide incidence of RVO ranges from 0.08% to 2.3% and in Pakistan, around 1% of the population suffers from this disease.[3-4] RVO arises from the formation of

atherosclerotic plaques within retinal vessels, causing resistance in blood flow and triggering endothelial damage, hypercoagulability, and thrombus formation. RVO can be categorized based on the anatomical location of thrombus formation into central (CRVO) or branch (BRVO) retinal vein occlusion, with the latter being more common.[3] Both types can lead to complications like macular edema, and neovascularization, which if left untreated can progress to glaucoma, vitreous hemorrhage, and tractional retinal detachment, causing visual loss.[4]

RVO induces hypoxia and hypo-perfusion, prompting the release of several inflammatory markers like vascular endothelial growth factor (VEGF) and interleukin 6.[5] This cascade increases vessel permeability, compromising the blood-retinal barrier. Consequently, fluid accumulates, leading to increased macular thickness and edema, thereby reducing the visual acuity of the patient.[6,7]

Over the past decade, several treatment modalities have been implemented to address RVO. These include laser photocoagulation, corticosteroids, and the administration of intravitreal VEGF inhibitors.[8] Among these, the use of anti-VEGF drugs such as bevacizumab, ranibizumab, and aflibercept have shown superior results compared to other management options. VEGF inhibitors work by reducing vascular leakage and improving retinal perfusion. This helps alleviate symptoms such as macular edema and ischemia, preserving vision in patients with RVO.[9]

Ranibizumab is an effective option for RVO, supported by pivotal clinical trials like the BRAVO and CRUISE studies, affirming its safety and efficacy for use in patients.[9,10] Ranibizumab is a recombinant, humanized monoclonal antibody Fab fragment that is administered monthly in a 0.5 mg intravitreal dose, effectively neutralizing all existing forms of VEGF-A.[10] Ranibizumab helps to decrease macular edema and retinal hemorrhages, thus improving visual acuity.[11,12]

While clinical trials may provide valuable evidence about the effectiveness of ranibizumab, their findings may not always directly translate into practical application. This study was conducted to present hospital based real life results to see the effectiveness of ranibizumab in reducing central macular thickness (CMT) and improving best-corrected visual acuity (BCVA) in patients.

METHODS

This was a single center interventional study conducted at Sindh Institute of Ophthalmology and Visual Sciences, Hyderabad. from July 2023 to March 2024, after getting approval from the ethical review committee **(SIOVS/EXEC.DIR/5445)**. The study population included all patients coming to the outpatient department who met the inclusion criteria (patients above the age of 20 years, diagnosed with macular edema secondary to CRVO or BRVO, and BCVA of less than 6/9). The study excluded all patients with other known retinal diseases such as Diabetic Retinopathy, ocular infection or inflammation, media opacity, history of vitreoretinal surgery or laser photocoagulation and treatment with anti-VEGF drug or corticosteroids in past 6 months. Informed consent was sought from all patients with an assurance of complete confidentiality.

The sample size was calculated by taking mean macular thickness of 479.9±216.25µm at baseline and 284.9±171.35 µm at 48 weeks using power of error (d)=90%.[13] The total calculated sample size was 44 participants using Open Epi software with 95% confidence level. A non-probability convenient sampling technique was employed in this study.

Every recruited patient had their visual acuity and CMT measured prior to injection. Slit lamp examination was done, and intraocular pressures were noted. All injections were given in the operating theater under aseptic conditions. Topical anesthetic was instilled, and the eyelid and periocular surfaces were cleaned with 5% povidone-iodine, followed by the instillation of a drop into the conjunctival sac. After obtaining consent from patients, intravitreal ranibizumab was injected at a dose of 0.5 mg / 0.05 ml using an insulin syringe with a 30-gauge needle, 3.5-4mm from the limbus. Patients were prescribed topical antibiotics (Moxifloxacin eye drops) to be used four times a day for one week. Follow-up appointments were scheduled for day 1, followed by one week and one month. The effectiveness of ranibizumab injections was evaluated by comparing the mean CMT and BCVA at 0, 3, 6, and 9months. Monthly assessments included BCVA and fundus examinations, while optical coherence tomography (OCT) was conducted at 3, 6, and 9 months.

The Statistical Package for Social Sciences (SPSS) version 25 was used for data compilation and analysis. Frequency and percentages were computed for qualitative variables like gender, diagnosis, and eye

involved. Quantitative variables were presented as mean SD; like age, CMT and BCVA. One-way Repeated Measures ANOVA was applied to compare CMT and BCVA from baseline to 9 months. When Mauchly's test failed to detect sphericity, the Greenhouse–Geisser adjustment was used. Pairwise comparisons were also made using Bonferroni corrections. P-value ≤ 0.05 was considered as significant.

RESULTS

One hundred and eighty-eight patients were included. The characteristics of the sample studied are shown in Table 1. There were 80(42.6%) patients with BRVO and 108(57.4%) with CRVO. Mostpatients111(59%) had right eye involved. The majority of the 158 (84%) patients were administered injections for three months into the study, while a smaller proportion of 30 (16%) patients required monthly injections for the six months.

The mean CMT was 541.54±146.99 before injection, 270.99±82.10 after 3 months, 240.02±22.50 after 6 months, and 234.73±18.06 after 9 months. The BCVA was 1.21±0.57 before injection, 0.30±0.27 at 3 months, 0.21±0.16 at 6,and 0.17±0.14 at 9 months. The BCVA (log Mar) comparison on follow-up also revealed improvement in vision. The detailed frequency distribution is presented in Table 1.

Repeated measures ANOVA test revealed that there was significant difference in CMT from baseline to 9 months (p<0.001) whereas pairwise comparisons showed significant difference among all the pairs of means (Table 2). Repeated measures ANOVA analysis for BCVA (log Mar) also showed significant differences (p<0.001) as depicted in Table 2.

Table1: *Characteristics of the population under study.*

Characteristics of sample	n(%)
Age in years	57.53±10.74
Gender	
Male	120(63.8)
Female	68(36.2)
Age group	
≤55 years	82(43.6)
>55 years	106(56.4)
Diagnosis	
BRVO	80(42.6)
CRVO	108(57.4)
Eye	
Right	111(59)
Left	77(41)
Central retinal thickness	
Before injection	541.54±146.99
3 months after the injection	270.99±82.10
6 months after the injection	240.04±22.50
9 months after the injection	234.73±18.06
BCVA (LogMAR)	
Before injection	1.21±0.57
3 months after the injection	0.30±0.27
6 months after the injection	0.21±0.16
9 months after the injection	0.17±0.14

DISCUSSION

In the current study, intravitreal treatment with ranibizumab was effective in improving vision in patients by RVO. We enrolled 188 patients, a significantly larger sample size than in previous studies.[14,15] enabling a more diverse analysis. This variance in sample size may be due to our shorter

Table2: *Pairwise comparison of CMT and BCVA (log MAR) from baseline to 9 months.*

Time		Mean Difference	Std. Error	p-value[a]	95% Confidence Interval for Difference[b] Lower Bound	Upper Bound
Central retinal thickness						
Baseline	3 months	270.548	9.303	<0.001	245.741	295.354
	6 months	301.5	10.342	<0.001	273.922	329.078
	9 months	306.803	10.347	<0.001	279.212	334.394
3 months	6 months	30.952	5.130	<0.001	17.271	44.633
	9 months	36.255	5.270	<0.001	22.204	50.307
6 months	9 months	5.303	0.683	<0.001	3.481	7.125
BCVA (LogMAR)						
Baseline	3 months	0.917	0.036	<0.001	0.821	1.013
	6 months	1.000	0.037	<0.001	0.902	1.098
	9 months	1.036	0.036	<0.001	0.939	1.133
3 months	6 months	0.083	0.013	<0.001	0.049	0.117
	9 months	0.119	0.016	<0.001	0.076	0.163
6 months	9 months	0.036	0.009	<0.001	0.012	0.060

a. The mean difference is significant at the 0.05 level. b. Adjustment for multiple comparisons: Bonferroni.

study duration of only nine months, while other studies had longer follow-up periods, increasing the likelihood of lost follow-up.

Most of our patients (56.4%) were elderly, aged over 55 years with a mean of 57.53 years, which aligns closely with the mean age of 58.53 years reported in an Indian study by Yadav et al.[2] Laouri and his co-authors also found a notably higher occurrence of RVO with increasing age and a decreased incidence in individuals under 50 years of age.[16]

The current study population consisted of men, with a higher incidence of CRVO (57.4%) compared to less than half (42.6%) of patients with BRVO. Existing literature shows contradictory findings, stating no difference in RVO prevalence between gender and BRVO being more common than CRVO.[17,18] However, this difference is attributed to the fact that RVO prevalence may vary between different races and ethnicities as these studies were conducted in different regions and enrolled patients with different characteristics and co-existing conditions.[1]

Our study corroborates previous literature, indicating a higher incidence of unilateral RVO compared to bilateral cases, with a predominance noted in the right eye over the left.[2,17]

In the present study, most patients (84%) received injections for three months, with only a few (16%) receiving injections for six months. We attribute this distribution to the possibility that some patients may require multiple injections for optimal results, and treatment timelines may vary depending on the early diagnosis.[19]

To assess the effectiveness of ranibizumab in vision improvement, our study evaluated reductions in mean CMT and enhancements in BCVA at 0-, 3-, 6-, and 9-months following injections. The mean CMT showed a decreasing pattern as the treatment progressed. BCVA was found to be 1.21±0.57 before injection, 0.30±0.27 after 3 months, 0.21±0.16 after 6 months, and 0.17±0.14 after 9 months, indicating improvement in vision. This is like findings by Brown et al, Maggio et al, and Umeya et al, that found significant improvement in vision, CMT, and BCVA after giving ranibizumab on a 6- and 12-month follow-up, respectively.[10,19,20] We noted a difference in mean central retinal thickness measurements over a span of 3- 6- and 9-months post-injection. Furthermore, we observed a marked decrease in mean CMT during this time. These findings align with existing literature investigating the efficacy of intravitreal ranibizumab in reducing CMT and improving vision.[21,22]

A notable improvement in BCVA was also seen after 3, 6, and 9 months of receiving injections, with a substantial increase in mean BCVA measurements post-injection. This is analogous to results demonstrated by the LUMINOUS study group, showing that visual acuity was increased in patients who were given 6–9 injections compared to those who received only 2–5 injections.[23]

The limitations of this study include failure to classify patients based on the etiology of RVO and whether the disease was ischemic or non-ischemic. Studies have shown that patients with ischemic RVO may deteriorate as soon as anti-VEGF therapy is withdrawn, showing a completely different long-term outcome than those with non-ischemic RVO; hence, differentiating between the two is important.[24] Additionally, our study is limited to a 9-month duration and does not highlight the future outcomes once therapy stops. Further studies with longer follow-ups should be conducted to gain a better understanding in the long term. Furthermore, we did not consider the timeline since diagnosis, as results may vary depending on how early or late the condition is diagnosed.

CONCLUSION

Administration of intravitreal ranibizumab injections at monthly intervals is an effective treatment for improving BCVA and decreasing the CMT in patients with central and branch retinal vein occlusion.

Funding: None.

Patient's Consent: Researchers followed the guidelines set forth in the Declaration of Helsinki.

Conflict of Interest: Authors declared no conflict of interest.

Ethical Approval: The study was approved by the Institutional review board/Ethical review board **(SIOVS/EXEC.DIR/5445)**.

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Authors Designation and Contribution

Ronak Afza Memon; Senior Registrar: *Concepts, Design, Literature search, Manuscript preparation.*

Fariha Sherwali; Assistant Professor: *Literature search, Statistical analysis.*

Shehnillah Shujaat; Assistant Professor: *Data acquisition, Manuscript editing.*

Waqas Ali; Senior Registrar: *Manuscript editing.*

Asra Talpur; Assistant Professor: *Manuscript review.*