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Original Research Article

Assessment of efficacy and safety of intravitreal ranibizumab in patients with macular edema secondary to retinal vein occlusion

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ABSTRACT

Background: The aim of the study was to assess the efficacy and safety of individualized repeated injection of intravitreal anti-VEGF ranibizumab for preserving or improving vision (BCVA) and central foveal thickness (CFT) in macular edema secondary to retinal vein occlusion (RVO).

Materials and Methods: 25 eyes of 25 patients with RVO were included. General and systemic examination was done. IOP measurement, slit lamp, fundus examination, BCVA assessment and OCT was done. CFT was measured to assess macular edema. Injection intravitreal ranibizumab (0.5mg/0.05ml) was given in the affected eye, every 6 weeks, till week 18, if CFT>250 μm. Total 3 injections were given in each patient. Final follow-up visit was at week 36.

Results: Hypertension (72%), DM (20%) and altered lipid profile (16%) were associated comorbidities. There was significant reduction in mean CFT from baseline visit (516.08±35.21) to week 18 visit (203.32±4.97) with P<0.0001. There was no significant statistical difference between week 18 CFT and week 36 CFT (P=0.44). There was significant reduction in mean CFT from baseline visit (516.08±35.21) to week 36(251.60±23.17) with P<0.0001.

There was significant improvement in mean BCVA from baseline visit (0.87±0.03) to week 18 visit (0.27±0.03). There was no significant statistical difference between week 18 BCVA and week 36 BCVA (P=0.76). There was a significant reduction in mean BCVA from baseline visit (0.87±0.03) to week 36(0.35±0.05) with P<0.0001.At week 36 follow up visit, 4 patients had recurrence of macular edema. 2 had uncontrolled hypertension, 2 had combined uncontrolled hypertension and DM. 21(84%) patients had stable CFT and BCVA. No significant ocular or systemic side-effects were seen.

Conclusion: Individualized repeated intravitreal injection of ranibizumab showed improvement in BCVA and CFT in patients with macular edema secondary to RVO. For long term maintenance, control of systemic comorbidities is essential.

1. Introduction

Retinal vein occlusion (RVO), the second most common cause of retinal vascular disease after diabetic retinopathy, is a significant cause of unilateral and painless loss of vision. Based on the localization of venous occlusion, the most frequently occurring types are branch retinal vein occlusion (BRVO), defined as occlusion of a branch of the retinal vein system, and central retinal vein occlusion (CRVO), defined as occlusion located in the central retinal vein.

RVO is a significant cause of vision loss with an overall incidence of 0.21% among patients aged ≥40 years. The prevalence of RVO varies from 0.7 to 1.6%. An estimated 16 million people globally develop RVO, with BRVO comprising 80% of cases.[1] BRVO is more common than CRVO, and may result in intraocular inflammatory changes; it affects approximately 1% of the population. The estimated prevalence of BRVO ranges from 0.6 to 1.1%. It can cause severe vision loss through macular edema, retinal neovascularization, and retinal detachment.[2]

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Treatment options for managing macular edema with RVO include macular grid laser photocoagulation and anti-vascular endothelial growth factor (VEGF inhibitors).[3,4] In RVO patients, the VEGF concentration in the ocular fluid is increased, which correlates with the severity of macular edema. Ranibizumab binds to and inhibits VEGF, a key driver of macular edema in RVO. The treatment of retinal vascular diseases, including RVO, has been revolutionized with the introduction of intravitreal pharmacotherapy.[5,6]

2. Aims and Objectives

To assess the efficacy and safety of individualized injection of intravitreal anti-VEGF ranibizumab for preserving or improving vision (BCVA) and central foveal thickness (CFT) in macular edema secondary to retinal vein occlusion.

3. Materials and Methods

After getting ethical approval from Institutional Review Board, an interventional, prospective study was carried out from March 2019- June 2020 in outpatient Department of Ophthalmology in a tertiary care hospital. We enrolled total 25 eyes of 25 subjects of age between 20-75 years.

3.1. Inclusion criteria

1. Patients giving written informed consent.
2. Patients with age between 20-75 years.
3. Patients attending Ophthalmology OPD, newly diagnosed with retinal vein occlusion (BRVO or CRVO) with macular edema (CFT >250μm).

3.2. Exclusion criteria

1. Patients denying written informed consent.
2. Patients age if less than 20 years and more than 75 years.
3. Patients who were known cases of glaucoma.
4. Patients with other diseases of retina i.e. Diabetic retinopathy, ARMD (CNVM) and other ocular comorbidities.
5. History of previous intravitreal injection.
6. History of previous laser photocoagulation.
7. One-eyed patients.
8. Procedure

Written informed consent was taken. All enrolled patients were underwent for detailed history and clinical examination including chief complaints, history of present illness, past history, personal history, family history, drug history followed by general examination & vitals monitoring. All the patients underwent screening for complete blood count, renal function tests, serum electrolytes, random blood sugar level, lipid profile, blood pressure and electrocardiogram. The presence of systemic diseases was evaluated by general physician. Systemic hypertension, diabetes mellitus and dyslipidemia were defined as pre-existing diseases for which patients were treated. Best corrected visual acuity (BCVA) was taken using ETDRS chart. Subjects were examined by slit lamp for anterior segment of eyes to look for any neovascularization. IOP measurement in each was done using Haag-Streit Goldmann's Applanation Tonometry (GAT) with fluorescein stain. After that each patient underwent fundus examination with 90D indirect ophthalmoscopy. OCT was performed using Topcon Spectral-Domain, 3D OCT 1 machine. Under aseptic precautions in ophthalmology operation theatre first intravitreal injection Ranibizumab (0.5mg/0.05ml) was given in the affected eye. Follow-up examination was done after 1 and $\frac{1}{2}$ months. On evaluation, if required (CFT > 250μm), 2^{nd} intravitreal injection Ranibizumab (0.5mg/0.05ml) was given. Follow-up examination was done after 3 months from first injection.

On evaluation, if required (CFT> 250μm), 3^{rd} intravitreal injection Ranibizumab (0.5mg/0.05ml) was given. Follow-up examination was done after 4 and $\frac{1}{2}$ months. Final follow-up examination was done after 9 months from 1^{st} injection.

4. Results

The study was conducted in Department of Ophthalmology in a tertiary care hospital on 25 eyes of 25 patients with retinal vein occlusion either CRVO or BRVO from March 2019 to June 2020.

This study included 25 patients. 19 (76%) patients were equal to or more than 50 years age. 6 (24%) patients were below 50 years age. 11 (44%) patients were male and 14 (56%) patients were female. Out of 25 patients, 16 (64%) patients were diagnosed with BRVO and 9 (36%) patients were diagnosed with CRVO. Out of the 16 BRVO patients, 10 (40%) had ST-BRVO and 6 (24%) had IT-BRVO.

Hypertension (72%; 18/25), diabetes (20%; 5/25) and altered lipid profile (16%; 4/25) were the most common comorbidities found in these patients. There was no patient without any systemic comorbidity.

It was observed that patients with retinal vein occlusion, younger than 50 years of age were more commonly associated with hypertension and altered lipid profile. No patient less than 50 years of age had associated diabetes mellitus. Whereas patients with retinal vein occlusion, equal to or older than 50 years of age had associated hypertension, altered lipid profile as well as diabetes mellitus.

4.1. Central foveal thickness (CFT)

The mean (±SE) pretreatment baseline CFT was 516.08 ± 35.21 μm, which decreased to 389.76 ± 26.13 μm by first follow-up visit (week 6) showing a significant improvement ($p<0.0001$) in the disease condition. The CFT during second

follow-up visit (week 12) was decreased to 278.44 ± 7.24 μm which was also significant (P<0.0001). The CFT during third follow-up visit (week 18) was decreased to 203.32 ± 4.97 μm which was also significant (P<0.0001). The CFT during final follow-up visit (week 36) was 251.60 ± 23.17 μm (P=0.44).

Table 1: Mean CFT at baseline, week 6, week 12, week 18 and week 36

Examination time	Mean CFT (μm)
Baseline	516.08 ± 35.21
Week 6	389.76 ± 26.13
Week 12	278.44 ± 7.24
Week 18	203.32 ± 4.97
Week 36	251.60 ± 23.17

4.2. Best corrected visual acuity (BCVA)

The mean (±SE) pretreatment baseline logMAR BCVA was 0.87 ± 0.03. The BCVA improved to 0.68 ± 0.03 by first follow-up visit (week 6) which was significant (P<0.0001). The BCVA improved to 0.48 ± 0.02 by second follow-up visit (week 12) which was significant (P<0.0001). The BCVA improved to 0.27 ± 0.03 by third follow-up visit (week 18) which was significant (P<0.0001). The BCVA during final follow-up visit (week 36) was 0.35 ± 0.05 (P=0.76).

Table 2: Mean BCVA at baseline, week 6, week 12, week 18 and week 36

Examination time	Mean BCVA
Baseline	0.87 ± 0.03
Week 6	0.68 ± 0.03
Week 12	0.48 ± 0.02
Week 18	0.27 ± 0.03
Week 36	0.35 ± 0.05

4.3. Intraocular pressure (IOP) post-injection

On measurement of intraocular pressure 30 minutes post-injection, after 1^{st} injection IOP was slightly raised in 2 patients (24 mmHg in one patient and 26 mmHg in another patient). After 2^{nd} injection IOP was slightly raised in 2 patients (26 mmHg in one patient and 24 mmHg in another patient). After 3^{rd} injection IOP was slightly raised in 2 patients (22 mmHg in one patient and 26 mmHg in another patient). They were not the same patients. All 6 patients had normal pre-injection IOP. In these patients Tab. Acetazolamide (250mg) was given QDS for 1 day. IOP was normal during follow-up examination.

4.4. Slit lamp examination (SLE) post-injection

Overall after injection, there were 2 incidences of congestion and 2 incidences of subconjunctival haemorrhage. Slit lamp examination findings were normal during follow-up examination.

Out of 25 patients, 4 patients had recurrence of macular edema and associated reduction in BCVA at week 36 follow-up. Out of these, 2 patients had uncontrolled hypertension and 2 patients had uncontrolled diabetes with uncontrolled hypertension. All 4 patients were above 50 years age.

5. Discussion

Initially during baseline visit, all the patients had some associated comorbidity. Hypertension (72%; 18/25), diabetes (20%; 5/25) and altered lipid profile (raised LDL cholesterol and raised triglycerides) (16%; 4/25) were the most common comorbidities found in these patients. These associations are consistent with other studies.[7] Diabetes mellitus was found to be an association in patients equal to or more than 50 years of age whereas hypertension and altered lipid profile was found to be associated with both younger and older patients. Control of all the comorbidities was done in addition to administration of intravitreal ranibizumab.

Patients equal to or more than 50 years (76%) age were more common than patients aged less than 50 years (24%). This finding is consistent with other studies.[8] The number of female (56%) patients was higher than the number of male patients (44%) in this study. Out of 25 RVO patients, 9 patients (36%) had CRVO, 10 patients (40%) had ST-BRVO and 6 patients (24%) had IT-BRVO. BRVO was more common than CRVO. ST-BRVO was commonest amongst all.

The results showed that there was significant reduction in mean CFT from baseline visit (516.08 ± 35.21) to week 18 visit (203.32 ± 4.97) with P<0.0001. The CFT reached normal range at week 18. There was no significant statistical difference between week 18 CFT and week 36 CFT (P=0.44). There was a significant reduction in mean CFT from baseline visit (516.08 ± 35.21) to week 36 CFT (251.60 ± 23.17) with P<0.0001.

The results showed significant improvement in mean BCVA from baseline visit (0.87 ± 0.03) to week 18 visit (0.27 ± 0.03). There was no significant statistical difference between week 18 BCVA and week 36 BCVA (P=0.76). There was a significant reduction in mean BCVA from baseline visit (0.87 ± 0.03) to week 36 BCVA (0.35 ± 0.05) with P<0.0001.

During the final follow-up visit, 4 (16%) patients out of 25 had recurrence of macular edema and reduction in BCVA. Out of these 4 patients, 2 patients had uncontrolled hypertension and 2 patients had uncontrolled hypertension with uncontrolled diabetes mellitus. Other 21 (84%) patients

had stable CFT and BCVA. In the 4 patients with recurrence of macular edema, injection intravitreal ranibizumab was administered with control of systemic comorbidities. Thus, control of systemic comorbities is essential for long term stability of CFT and BCVA.

The efficacy and safety of ranibizumab in the treatment of macular edema in patients with RVO by improvement in visual function and macular edema has been established in several studies.[9–11] Ranibizumab not only prevents vision loss but also improves visual acuity.[12] A significant improvement in BCVA was reported in the pivotal BRAVO and CRUISE studies with ranibizumab treatment in patients with RVO, which was sustained over 12 months.[12,13] Ranibizumab was associated with improved BCVA till 6 months in macular edema after BRVO in a prospective observational study, suggesting a positive correlation of the short-term effects of ranibizumab with long-term improvements.[14]

Another study, conducted by Chui and Petrunya,[15] showed that a significant improvement in visual function and a persistent reduction in macular edema secondary to BRVO is achieved after 1 ranibizumab injection per month over a 3-month period.

Ganglion cell damage is associated with the thickness of the central macula. A very thin or thick retina, thick subretinal tissue, atrophy, and scarring are associated with worse visual acuity.[16] Ganglion cell damage results from traction to the ganglion cell due to greater CFT. To avoid any permanent structural damage to retina, specifically the macula, early intervention by intravitreal injection of Ranibizumab is necessary.[17] This study demonstrated a significant decrease in CFT with ranibizumab treatment, indicating improved disease outcomes without any permanent structural damage to retina. Similar results have been shown for ranibizumab, with a significant reduction in CFT as early as at week 4 and lasting over 3 months after the injection in a study involving 32 patients.[18] Another multicenter study showed a significant decrease in CFT at 6 months after ranibizumab treatment.[19]

There was slight rise in intraocular pressure in 6 patients overall which was controlled with oral Tab. Acetazolamide (250mg) QDS for a day. Overall there were 2 incidences of conjunctival congestion and 2 incidences of subconjunctival haemorrhage. These incidences were trivial and not associated with any long-term adverse effects.

Improvements in BCVA and CFT were observed for all the patients of this study irrespective of BRVO or CRVO. The statistically nonsignificant changes in mean logMAR BCVA (P=0.76) and mean CFT (P=0.44) from week 18 to week 36 suggest that there was maintenance of mean CFT and mean BCVA during the period. There was recurrence of macular edema in 4 patients probably due to uncontrolled systemic comorbid conditions. Other 21 patients showed stable BCVA and CFT even at week 36 follow-up.

The limitations of our study are that the sample size is small and no other drug was used for comparison with ranibizumab.

Overall, this study demonstrates the effects of ranibizumab in functional and anatomical visual improvements in BCVA and CFT, and the degree of improvement was similar to that reported in several studies with ranibizumab administration.

6. Conclusion

1. In this study, statistically significant improvement was observed in CFT and BCVA, in patients with macular edema secondary to retinal vein occlusion after administration of intravitreal ranibizumab irrespective of age and gender.
2. Patients equal to or older than 50 years of age were more commonly affected by retinal vein occlusion than younger patients.
3. Systemic control of comorbidities and lifestyle modification is essential for maintenance of effect of ranibizumab over long-term. Uncontrolled comorbid conditions lead to recurrence of macular edema and reduction in BCVA.
4. Thus, our study concludes that intravitreal ranibizumab is effective and safe for treatment in patients with retinal vein occlusion over short-term. Ranibizumab is also effective over long-term period provided that the systemic comorbidities are under control.

7. Source of Funding

None.

8. Conflict of Interest

The authors declare that there is no conflict of interest.

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