Efficacy of Ranibizumab in the Treatment of Macular Edema Secondary to Retinal Vein Occlusion

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ABSTRACT

Objective: Branch retinal vein occlusion (BRVO), a major cause of vision loss, is a significant ocular health concern. The frequency of macular edema due to BRVO is a critical area of study because of its profound impact on patient quality of life. This study investigated the effectiveness of ranibizumab, a monoclonal antibody fragment and VEGF inhibitor, in the treatment of macular edema in patients with BRVO.

Material and Methods: Twelve patients (12 eyes) diagnosed with macular edema secondary to BRVO were included in this study. Patients were selected on the basis of specific visual acuity and macular thickness criteria, excluding those with other ocular conditions or systemic diseases. 0.05 milligrams of ranibizumab was administered intravitreally to each patient. Ophthalmological assessments were conducted both before and after the injection and at 1, 2, 3, and 6-month intervals following medication administration.

Results: The average follow-up duration was 5.5±1.16 months (ranging from 2 to 6 months). The average central macular thickness before the injection was 542.66±191.44 µm, which decreased to 320.50±101.44 µm at 1-month post-injection, 283.66±125.01 µm at 2 months, 299.40±91.52 µm at 3 months, and 260.90±144.97 µm at 6 months. The reduction in central macular thickness at all time points was statistically significant (p<0.01). The mean Early Treatment Diabetic Retinopathy Study (ETDRS) letter score was 55.83±23.91 before the injection and improved to 71.25±17.07 at 1 month, 74.33±15.97 at 2 months, 66.7±21.60 at 3 months, and 71.2±17.38 at 6 months post-injection. The increase in visual acuity at 1, 2, 3, and 6 months after the injection was statistically significant compared to the pre-injection ETDRS letter scores (p<0.05). An improvement of two or more lines in visual acuity was observed in 58.3% of cases at 1 month, 58.3% at 2 months, 50% at 3 months, and 80% at 6 months (one line equivalent to five letters).

Conclusion: Intravitreal Ranibizumab injections have been found to be effective and reliable in the early stages of treating macular edema due to branch retinal vein occlusion.

Keywords: Ranibizumab, Macular Edema, Retinal Vein Occlusion, Visual Acuity, VEGF Inhibition

INTRODUCTION

Macular edema is a principal factor in vision impairment in individuals with branch retinal vein occlusion (BRVO). The precise contribution of hydrodynamic alterations resulting from blockage of the impact of chemical mediators on edema remains unclear (1). Retinal vein occlusion is the second leading cause of retinal vascular disease in diabetic retinopathy (DR). BRVO occurs when the retinal branch vein is blocked and affects a specific quadrant of the retina. During the ophthalmoscopic evaluation, the patient may exhibit retinal and possibly macular edema, along with both superficial and deep retinal hemorrhages and venous enlargement in the impacted area (1, 2). Age and systemic vascular conditions are the most commonly identified risk factors for BRVO (2, 3).
Hypertension has emerged as a critical predisposing factor of BRVOs. Persistent hypertension contributes to the thickening of the retinal arterioles. Since the retinal arterioles and veins are enveloped by shared adventitia at their crossings, this thickening can lead to the narrowing of the retinal veins, potentially triggering occlusion (3, 4). Complications associated with branch retinal vein occlusion (BRVO) mirror those observed in central retinal vein occlusion (CRVO), albeit on a more confined scale due to the retinal segmentation affected by specific branch vein occlusion. After occlusion, there is an increase in luminal pressure downstream, leading to heightened transudation of blood and plasma, an increase in interstitial fluid pressure, and diminished capillary perfusion, culminating in ischemia. Unlike CRVO, the extent of the ischemic retina in patients with BRVO is typically smaller, making iris neovascularization and neovascular glaucoma uncommon. However, retinal neovascularization near the ischemic zone can still occur, potentially resulting in vitreous hemorrhage, which might require scatter photocoagulation treatment. Macular edema predominantly accounts for vision deterioration, although non-perfusion of perifoveal capillaries also plays a significant role. The application of grid laser photocoagulation to the underperfused retina adjacent to the fovea alleviates macular edema and enhances visual acuity (3, 5).

The occurrence of retinal ischemia exacerbates the condition, leading to the release of vascular endothelial growth factor (VEGF), which not only prompts neovascular complications, but also amplifies vascular permeability. Thus, VEGF release is believed to significantly contribute to the development of macular edema in patients with BRVO. In this context, ranibizumab (commercially known as Lucentis among other names), a monoclonal antibody fragment derived from the parent molecule bevacizumab and tailored for eye applications, plays a pivotal role. It mechanism centers on inhibits VEGF-A, a pivotal agent in both angiogenesis and escalation of vascular permeability, which are key processes in the pathogenesis of numerous ocular conditions such as age-related macular degeneration (AMD), BRVO-induced macular edema, and diabetic macular edema (DME) (6, 7).

This study aimed to explore VEGF’s role in macular edema in patients with BRVO by evaluating intraocular ranibizumab.

**MATERIAL and METHODS**

**Study Design**

This retrospective clinical study assessed the efficacy of intravitreal ranibizumab (Lucentis) injections for treating macular edema secondary to BRVO. The study spanned from March 2010 to October 2013, and involved patients treated at the Haseki Training and Research Hospital, Ophthalmology Clinic.

**Study Patients**

Twelve patients (12 eyes) diagnosed with macular edema due to BRVO were included in the study. The inclusion criteria were diagnosis based on dilated fundus examination, Optical Coherence Tomography (OCT), and Fluorescein Angiography (FA). Eligible patients had central macular thickness (CMT) ≥250 µm, initial best-corrected visual acuity (BCVA) measured by the Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity score ≤85 (Snellen equivalent) (20/40), and no evidence of neovascularization or ischemia on FA. Exclusion criteria included active neovascularization, presence of cataracts, primary open-angle glaucoma (excluding those causing visual impairment), uncontrolled hypertension, and a history of cerebrovascular disease.

**Study Procedure**

Informed consent, detailing potential complications, was obtained from all participants before the intravitreal ranibizumab injection. The patients underwent comprehensive ophthalmological evaluations pre-injection and at 1, 2, 3, and 6-months post-injection. Assessments included BCVA using the Snellen chart, anterior segment examination via slit-lamp biomicroscopy, pupil dilation with tropicamide followed by fundus examination with 78D and 90D lenses, intraocular pressure measurement, and evaluation of foveal ischemia and neovascularization through 10% sodium fluorescein FA. CMT was measured using optopol spectral-domain OCT at baseline and during follow-up visits.

Intravitreal Ranibizumab was administered under sterile conditions in the operating room. The eyelids and surrounding areas were disinfected with 10% povidone-iodine. After topical anesthesia, the eye was washed with 5% povidone-iodine. The injection site was marked 3.5 mm from the limbus for phakic eyes and 3 mm for pseudophakic eyes, preferring the inferotemporal quadrant. A 30-gauge needle was used to inject 0.05 ml (0.05 mg) of ranibizumab into the vitreous cavity. Post-injection, patients were prescribed antibiotic drops and ointment for one week and were examined the following day for infection and intraocular pressure increase. Follow-up visits were conducted monthly, and additional injections were administered as needed.

**Ethical Consideration**

The study was conducted in accordance with the Declaration of Helsinki, and the ethical review board of Haseki Training and Research Hospital approved the study protocol by the local hospital administration. Informed consent was obtained from all the participants before their inclusion in the study.

**Statistical Analysis**

Visual acuity and central macular thickness changes before and after injection were analyzed. IBM SPSS Statistics 21 software was used for statistical analysis. The paired sample t-test was used to compare quantitative data. The results were considered statistically significant at a 95% confidence interval (CI), with a p-value <0.05.

**RESULTS**

Demographic and disease-related characteristics of patients treated with intravitreal ranibizumab injections for macular edema secondary to BRVO.

It was observed that 4 patients (33%) had hypertension, and 3 (25%) had a history of type 2 diabetes mellitus. Medical treatment-controlled glaucoma was present in 3 patients (25%). An equal distribution was observed in the occurrence of BRVO; half of the cases involved the right eye, whereas the other half involved the left eye. Similarly, the obstruction
was localized to the supertemporal branch in 6 patients (50%) and to the inferotemporal branch in the remaining 6 patients (50%). Focal laser photocoagulation was previously administered approximately 8 months earlier in the area of the occluded branch vein in 2 cases. The gender distribution was even, with 6 females (50%) and 6 males (50%), and the mean age was 56.41±12.61 years. Regarding systemic diseases, 5 patients (41%) had no associated systemic conditions, 4 (33%) had hypertension, 3 (25%) had diabetes mellitus, and 3 (25%) had glaucoma. Prior focal laser treatment was reported in 2 cases (16%). The mean baseline central macular thickness was 542.66±191.44 µm, and the mean baseline visual acuity score (Snellen equivalent) was 55.83 ± 23.91, corresponding to approximately 20/125.

The measurements of central macular thickness before and after the intravitreal Ranibizumab injections

In the analysis of central macular thickness, OCT data from 12 patients at the 1-month mark, 12 patients at the 2-month mark, 10 patients at the 3-month mark, and 10 patients at the 6-month mark were evaluated. The average central macular thickness was determined to be 542.66±191.44 µm pre-injection, 320.50±101.44 µm at 1 month, 283.66±125.01 µm at 2 months, 299.40±91.52 µm at 3 months, and 260.90±144.97 µm at 6 months. Compared with the pre-injection central macular thickness, the reductions observed at 1, 2, 3, and 6-months post-injection were statistically significant (p<0.01)(Table 1).

Quantitative insights into macular thickness reduction after injection.

A consistent and significant decrease in central macular thickness was observed post-treatment over the monitored period. Prior to injection, the average central macular thickness substantially decreased over the subsequent months. Specifically, there was a 36.54±19.90% reduction observed at the 1-month follow-up, a 42.14±29.73% reduction at the 2-month follow-up, a 41.45±24.08% reduction at the 3-month follow-up, and a notable 53.99±16.16% reduction at the 6-month follow-up (Figure 1).

Following the administration of intravitreal ranibizumab, a reduction in central macular thickness was observed in all cases (100%, n=12) at the 1-month evaluation. However, only four of these cases (33.3%) had a central macular thickness below 250 µm at the end of the first month. By the 2-month mark, 6 patients (50%) had a central macular thickness below 250 µm; at 3 months, this was observed in 3 patients (30%), and by the 6-month interval, 7 patients (70%) maintained a central macular thickness below the 250 µm threshold.

Figure 2 shows OCT images of the patient with BRVO before and after treatment with intravitreal ranibizumab injections.

The measurements of visual acuity before and after the intravitreal Ranibizumab injections

The ETDRS letter scores were assessed before and after ranibizumab injections. Before the injection, the mean ETDRS letter scores were 55.83±23.91. Following the injection, a notable improvement was observed: 71.25±17.07 at 1 month, 74.33±15.97 at 2 months, 66.7±21.60 at 3 months, and 71.2±17.38 at 6 months. The increase in visual acuity from the baseline ETDRS letter score to that at 1, 2, 3, and 6-months post-injection was statistically significant (p<0.05) (Table 2).

When examining the monthly changes in visual acuity improvement, it was observed that an increase of two or more lines in visual acuity occurred in 58.3% of patients at 1 month, remained at 58.3% at 2 months, was present in 50% at 3 months, and increased to 80% at 6 months (with one line equivalent to five letters). Postinjection, a decrease of one line in visual acuity was seen in 16.6% of patients at 1 month, while a decrease in visual acuity was only noted in one case at 6 months. There was no change in visual acuity in 8.6% of the patients at 1 month, 41.6% at 2 months, 40% at 3 months, and 50% at 6 months.

Throughout the study procedure and 6-month follow-up period, no major adverse effects related to the procedure or treatment were observed. Patients’ complaints of pain associated with the injection prior to the procedure resolved quickly.

Table 1. Changes in Mean Central Macular Thickness at Various Time Points Post-Injection

<table>
<thead>
<tr>
<th>Time Point</th>
<th>Mean CMT (µm) (Mean±SD)</th>
<th>p-value (Pre-injection vs. Time Point)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-injection</td>
<td>542.66±191.44</td>
<td>N/A</td>
</tr>
<tr>
<td>1-month control</td>
<td>320.50±101.44</td>
<td>0.003*</td>
</tr>
<tr>
<td>2-month control</td>
<td>283.66±125.01</td>
<td>0.003*</td>
</tr>
<tr>
<td>3-month control</td>
<td>299.40±91.52</td>
<td>0.003*</td>
</tr>
<tr>
<td>6-month control</td>
<td>260.90±144.97</td>
<td>&lt;0.000*</td>
</tr>
</tbody>
</table>

Paired sample t-test: *p<0.002
CMT: central macular thickness.
Table 2. Changes in ETDRS scores at Various Time Points Post-Injection

<table>
<thead>
<tr>
<th>Time Point</th>
<th>ETDRS Score (Mean±SD) (Snellen)</th>
<th>p-value (Pre-injection vs. Time Point)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-injection</td>
<td>55.83±23.91 (20/160)</td>
<td>N/A</td>
</tr>
<tr>
<td>1-month control</td>
<td>71.25±17.07 (20/80)</td>
<td>0.012*</td>
</tr>
<tr>
<td>2-month control</td>
<td>74.33±15.97 (20/63)</td>
<td>0.010*</td>
</tr>
<tr>
<td>3-month control</td>
<td>66.7±21.60 (20/100)</td>
<td>0.044*</td>
</tr>
<tr>
<td>6-month control</td>
<td>71.2±17.38 (20/80)</td>
<td>0.006*</td>
</tr>
</tbody>
</table>

Paired sample t test *: p<0.05
ETDRS: Early Treatment Diabetic Retinopathy Study visual acuity

Figure 1. Impact of Treatment on Central Macular Thickness: A Temporal Analysis
The first graph demonstrates a significant decrease in thickness from the pre-injection value through the 6-month checkpoint. Correspondingly, the second graph highlights the percentage decrease at each time interval, showing a substantial reduction, particularly noted by the 6-month mark.

Figure 2. OCT images of a patient with macular edema following BRVO, before and after intravitreal Ranibizumab injection at 1, 2, 3, and 6 months. BRVO: brunch retinal vein occlusion, OCT: optical coherence tomography
DISCUSSION

The present study evaluated a regimen of intravitreal ranibizumab (0.5 mg) injections in patients experiencing visual impairment due to macular edema secondary to BRVO. Our findings indicate that ranibizumab treatment leads to a consistent decrease in macular thickness at all observed time points, from day 1—the first examination following the baseline Ranibizumab 0.5 mg injection—through to month 6. By month 6, all patients had achieved a BCVA of 71 letters or more (Snellen equivalent, 20/40). There was a statistically significant reduction in the mean CMT from baseline, underscoring ranibizumab’s efficacy in improving anatomical and functional outcomes in patients with BRVO.

The study cohort had a high prevalence of systemic conditions commonly associated with BRVO, including hypertension in 33% of the patients and type 2 diabetes mellitus in 25%. These findings align with the existing literature identifying these conditions as significant risk factors for BRVO (8). The presence of medically controlled glaucoma in 25% of patients further supports previous reports, suggesting a possible link between glaucoma and retinal vascular occlusion (9).

Analysis of CMT changes following intravitreal ranibizumab injections for macular edema secondary to BRVO demonstrated a significant reduction in CMT at all evaluated post-treatment time points. The initial average CMT of 542.66±191.44 µm reflects the expected pathology in BRVO, where macular edema is prevalent.

By the 1-month follow-up, the CMT had decreased to 320.50±101.44 µm, and continued to decline to 283.66±125.01 µm at 2 months, indicating a rapid and significant response to Ranibizumab treatment. This immediate reduction in macular thickness is a promising indicator of the drug’s effectiveness in reducing fluid accumulation in the macula, which is a primary factor in the visual impairment associated with BRVO.

Although a slight increase in average CMT to 299.40±91.52 µm was noted at the 3-month mark, this change was not a reversal but a stabilization, as the thickness remained significantly lower than baseline levels. This pattern suggests that, while the initial response to treatment is robust, some cases may require additional monitoring and possibly further intervention to maintain therapeutic gains.

By the 6-month interval, CMT further decreased to 260.90±144.97 µm, the lowest average thickness across all time points, underscoring the sustained efficacy of Ranibizumab over the medium term. The statistical significance of these results (p<0.01) indicates a strong likelihood that the observed improvements are directly attributable to the intervention rather than to chance.

The substantial reduction in CMT and corresponding improvement in visual acuity align with the known pharmacological action of Ranibizumab as a VEGF inhibitor, which reduces vascular permeability and subsequent fluid leakage into the retinal layers. These outcomes corroborate the findings of other studies, affirming the role of ranibizumab as a cornerstone therapy for BRVO-induced macular edema (10, 11).

Furthermore, the consistency of these results with the broader literature not only reinforces the validity of ranibizumab’s use in clinical settings but also suggests that patients with BRVO can anticipate a significant decrease in macular edema and potential improvement in visual outcomes when treated appropriately (12).

The results indicated that improvements in ETDRS letter scores after intravitreal ranibizumab injections were significant, not only statistically but also clinically. Initial mean scores increased from 55.83 to over 71 by the 1-month follow-up and demonstrated a notable improvement in visual acuity, which was maintained with slight fluctuations throughout the 6-month period. The high percentage of patients experiencing an improvement of two or more lines in visual acuity, reaching 80% at the 6-month mark—underscores the efficacy of the treatment in a substantial proportion of the cohort. These outcomes were aligned and better than those of the CRYSTAL study, which reported that BCVA gains were similar with or without macular ischemia at baseline after ranibizumab injection at 12 months (13).

However, noting a slight dip in mean visual acuity at the 3-month point is interesting. This could indicate the need for subsequent injections to sustain initial visual gains or reflect natural fluctuations in the disease process. The presence of patients (16.6% at 1 month and one case at 6 months) with decreased visual acuity post-injection suggests a variable response to treatment, which warrants further investigation to identify any predictive factors for treatment response.

The absence of a change in visual acuity in a consistent subset of patients across all time points, especially 50% at 6 months, could suggest a ceiling effect of the treatment or the presence of irreversible retinal damage not amenable to anti-VEGF therapy. These findings align with existing literature that indicates that while anti-VEGF therapy is a significant advancement in the management of macular edema due to BRVO, not all patients recover full visual function, possibly because of the chronicity or severity of the disease at the time of treatment initiation (13, 14).

The lack of major adverse effects further supports the safety profile of intravitreal ranibizumab injections, consistent with its reputation as a well-tolerated treatment. The quick resolution of injection-related pain adds to its acceptability by patients, which is an important consideration in repeated treatments (15, 16).

In summary, intravitreal ranibizumab injection appears to be a promising therapeutic option for improving visual acuity in patients with macular edema secondary to BRVO. Significant visual gains, sustained improvements over six months, and minimal adverse effects underscore its potential as a first-line treatment. Further studies are warranted to optimize treatment intervals and explore long-term outcomes beyond the 6-month mark.

Study Limitations

This study has various limitations that warrant consideration, including a small sample size of 12 patients, which may limit the generalizability of the findings. Larger studies are needed to validate our results and provide more robust data regarding the efficacy and safety of intravitreal ranibizumab injections. Additionally, the follow-up period was limited to 6 months,
which may not be sufficient for understanding the durability of treatment effects and potential late-onset adverse events. Despite these limitations, this study provides valuable insights into ranibizumab’s early efficacy and safety profile for macular edema in patients with BRVO. Future research should address these limitations by incorporating larger randomized controlled trials with longer follow-up periods and a more diverse patient population.

CONCLUSION

In conclusion, this study demonstrated that intravitreal ranibizumab injections provide effective early outcomes in treating macular edema resulting from retinal vein branch occlusion. The minimal ocular and systemic side effects of intravitreal ranibizumab administration make it a safe and reliable therapeutic option. These findings support the continued use of ranibizumab as a primary treatment modality for this condition and underscore the importance of further research to optimize treatment protocols and patient outcomes. Further investigations will be crucial to fully establish the role of Ranibizumab in managing this challenging ocular condition, ensuring that treatment strategies remain clinically effective and tailored to individual patient needs.

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Author Contributions: ZT, NA, AFO: Study Design, Literature Search, Data collection, ZT: Manuscript preparation, final revisions. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval: The present study was conducted in strict accordance with the principles outlined in the Declaration of Helsinki. Informed consent was obtained from the participant of this study.

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