Original Article

Efficacy of combined intravitreal bevacizumab and triamcinolone for branch retinal vein occlusion

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Purpose: To evaluate the efficacy of combined treatment with intravitreal bevacizumab (IVB) and triamcinolone acetate (IVT) for patients with macular edema secondary to branch retinal vein occlusion (BRVO). **Materials and Methods:** Retrospective analysis of 20 eyes injected with 1.25 mg IVB and 2 mg IVT for clinically identified BRVO within 8 weeks of onset. All patients lacked concomitant ocular pathology and completed 6 months' follow-up. Clinical examination including LogMAR visual acuity (VA) and central macular thickness (CMT) by spectralis optical coherence tomography (OCT) was performed preoperatively and at 1, 3 and 6 months post-operatively. **Results**: Mean patient age was 61.3 years with a mean BRVO diagnosis time of 3 weeks at presentation. VA improved from logMAR 1.08 preoperatively to Mean logMAR VA of 0.55 ± 0.17 at 1 month ($P < 0.001$), 0.56 ± 0.21 at 3 months ($P < 0.001$), and 0.38 ± 0.1 at 6 months ($P < 0.001$) Mean CMT improved from 482 ± 107 µm preoperatively to 319 ± 53 µm at 1 month ($P < 0.001$), 344 ± 89 µm at 3 months ($P < 0.001$), and 241 ± 29 µm at 6 months ($P < 0.001$). Mean IOP preoperatively was 16.5 mmHg, 21 mmHg at 1 month, and 15 mmHg at 6 months. Six out of 20 patients (30%) were re-injected with IVB and IVT at 3 months. **Conclusions:** Early combined treatment with IVB and IVT is effective in improving anatomic and functional outcomes in patients with macular edema secondary to BRVO.

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Retinal venous occlusive disease affects at least 16 million people worldwide, and is the second-most common retinal vasculopathy causing visual loss.[1,2]

Hypertension, atherosclerotic, inflammatory, and thrombophilic conditions may predispose to retinal endothelial vascular damage, leading to compromised venous flow and downstream ischemia. Endothelial vascular damage may be mediated by a combination of free radical production, inflammation, or micro-environmental changes from growth factors.[2]

Ischemia from BRVO leads to inflammation, retinal tissue injury, and increased vascular permeability. Triamcinolone acetonide has demonstrated efficacy in stabilizing the blood-retinal barrier by decreasing cell membrane permeability, inhibiting polymorphonuclear infiltration to injured tissues, blocking macrophage recruitment and phagocytosis, and down-regulating inflammatory cytokines such as interleukin-5, 6, 8, tumor necrosis factor, and prostaglandins. Studies have also suggested the efficacy of corticosteroids in downregulating the expression of vascular endothelial growth factor (VEGF).[3]

Retinal ischemia catalyzes the production of VEGF while delaying expression of VEGF's most potent endogenous inhibitor, pigment epithelial derived factor (PEDF).[4] VEGF promotes retinal neovascularization while also breaking down the blood-retinal barrier, contributing to macular edema. VEGF also causes endothelial cell hypertrophy that can narrow the capillary lumen, worsening retinal ischemia, and further aggravating macular edema.[5] This has been further demonstrated in a study correlating elevated VEGF levels in BRVO eyes with BRVO to increased capillary non-perfusion and macular edema.[5] Thus, VEGF is believed to be a key molecular player in both the pathogenesis of BRVO-related macular edema.

Macular edema secondary to BRVO has been treated using a number of therapies. The Branch Retinal Vein Occlusion study group is credited with establishing argon laser photocoagulation as the standard of care in 1984.[6] Although argon laser treatment remains the gold standard treatment, frequently significant hemorrhage involving the macula prevents effective laser treatment initially following a BRVO. The advent of anti-angiogenic agents has helped evolve the treatment of macular edema in BRVO with multiple studies demonstrating the independent efficacy of anti-angiogenic agents and IVT.[7-10] Most recently, the anti-VEGF agent ranibizumab and the dexamethasone-containing Ozurdex implant have been approved by the FDA for the treatment of macular edema secondary to BRVO and CRVO.

Anti-VEGF agents and steroids have been used in conjunction in studies with AMD, but this has not been studied as extensively in BRVO. Anti-VEGF agents and steroids appear to have some overlap in their functions of blood-retinal barrier consolidation and VEGF down regulation, but their precise biologic role in combination has not been clearly elucidated. The purpose of this study is to evaluate the efficacy of combined IVB and IVT in patients with macular edema secondary to BRVO.

Materials and Methods

We retrospectively analyzed 20 eyes of 20 patients that were treated from October 2008 to April 2010. Intravitreal bevacizumab (1.25 mg) and intravitreal triamcinolone (2 mg) were simultaneously administered to all patients with clinically identified BRVO and secondary macular edema. The patients were treated within 1-8 weeks of BRVO diagnosis. Exclusion

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criteria were concomitant ocular pathology, e.g., diabetic retinopathy or glaucoma, and inability to complete 6-months' follow-up. All patients were treatment naïve prior to our intervention.

The risks and benefits of the off-label use of IVB and IVT were discussed with patients prior to administration of the injections and informed consent was obtained. The combined injections were administered in a standard sterile fashion including betadyne preparation and use of a lid speculum in a designated injection room in an ophthalmology clinic. Intravitreal bevacizumab (1.25 mg) was injected first 3.5-mm posterior to the limbus, and then an anterior chamber paracentesis was performed, and then intravitreal triamcinolone (2 mg) was injected.

Patient characteristics reviewed were age, gender, previous ocular interventions (i.e. laser photocoagulation), duration of vein occlusion prior to intravitreal administration, and number of intraocular injections. Clinical endpoints included intraocular pressure (IOP in mmHg), visual acuity (VA in logMAR) and central macular thickness (CMT in μm) as measured by Spectralis optical coherence tomography (OCT) at 1, 3, and 6 months post injections. Patients were examined at postoperative day 1 and postoperative months 1, 3, and 6. Change in visual acuity and CMT were evaluated using a paired *t*-test. Patients were re-injected with the same combination of IVB and IVT doses at subsequent office visits if there was a two-line drop in visual acuity or if macular edema had increased.

Results

The mean age of patients was 61.3 ± 7.6 years (mean ± SD). Six patients were female and fourteen were male. Seventeen patients (85%) had a diagnosis of hypertension, 11 patients had a diagnosis of hyperlipidemia (55%), and six (30%) patients had a diagnosis of diabetes mellitus. The mean duration of BRVO prior to intravitreal injection was 3 weeks ± 1.6.

The initial visual acuity was logMAR 1.08 ± 0.35 [Table 1]. Mean logMAR VA at 1, 3, and 6 months was 0.55 ± 0.17 ($P < 0.001$), 0.56 ± 0.21 ($P < 0.001$), and 0.38 ± 0.1 ($P < 0.001$) [Fig. 1]. Mean initial CMT was 482 ± 107 μm. Mean CMT at 1, 3, and 6 months was 319 ± 53 μm ($P < 0.001$), 344 ± 89 μm ($P < 0.001$), and 241 ± 29 μm ($P < 0.001$) [Fig. 2]. Intraocular pressure initially was 16.5 ± 3.2 mmHg. IOP was 21 ± 4.4 mmHg at 1 month, 16.3 ± 2.1 mmHg at 3 months, and 15.4 ± 1.8 mmHg at 6 months [Fig. 3]. IOP transiently increased 1 month after injection in 6 patients (30%), but returned to baseline levels with one topical beta-blocker. Each of these 6 patients were successfully withdrawn from the topical medication at 6 months with restoration of IOP to baseline levels. Six out of 20 patients (30%) were noted to experience worsening visual acuity or increasing macular edema at the 3-month mark, required re-injection, resulting in a mean number of re-injections per patient of 0.35 ± 0.48. There were no cases of endophthalmitis in this series.

Discussion

Ehrlich *et al*., previously investigated the combined treatment of IVB and IVT in patients with BRVO.[11] In their study the authors found no advantage of combined IVT and IVB over IVB alone in the treatment of retinal vein occlusion. However, their study had important differences in the power of their study population and interval to intervention. Their study had a small "n" of only 8 eyes with BRVO, as they included both central and branch retinal vein occlusion patients. Their mean time from BRVO diagnosis to injection was 9 months. Although not clearly reported, these patients may have had macular edema for 9 months as well, with potential irreversible photoreceptor damage after chronic macular edema that would yield poorer visual outcomes.[12] In our study, early intervention (less than 8 weeks) was offered to patients. Our study further supported early intervention in that patients with the shortest identification-to-treatment time experienced the greatest gains in visual acuity. Additionally, our study included 8 patients with visual acuity worse than 20/200 who all had improvement of visual acuity to at least 20/100 (logMAR 0.70) by 6 months [Table 1 and 2], arguing against selection bias.[6] This may be attributable to prompt treatment rather than the agents used but further study is required.

An important benefit from the presented treatment protocol is the decreased need for multiple re-injections when compared

Table 1: Mean LogMAR visual acuity, central macular thickness, and intraocular pressure over 6 months

		1 m	3 m	6 m
LogMAR VA	1.08±0.35	0.55±0.17	0.56±0.21	0.38±0.1
CMT in um	482±107	319±53	344±89	241±29
IOP mmHg	16.5±3.2	21±4.4	16.3±2.1	15.4±1.8

VA: Visual acuity, CMT: Central macular thickness, IOP: Intraocular pressure, m: Months

Table 2: Identification to treatment time in weeks, Initial LogMAR visual acuity, and LogMAR visual acuity at 6 months, Improvement in LogMAR visual acuity from treatment time to 6 months

Patient no.	Identification to treatment time (w)	Initial LogMAR VA	LogMAR VA at 6 months	Improvement in LogMAR VA
1	1	1	0.30	0.70
2	1	0.70	0.30	0.40
3	1	1.30	0.48	0.82
4	2	1.85	0.30	1.55
5	3	1	0.30	0.70
6	3	1.85	0.48	1.37
7	1	0.60	0.48	0.12
8	3	0.70	0.18	0.52
9	1	0.60	0.30	0.30
10	4	1	0.48	0.52
11	8	1.85	0.70	1.15
12	3	1	0.30	0.70
13	2	0.70	0.60	0.10
14	4	1	0.18	0.82
15	1	1.85	0.30	1.55
16	1	0.60	0.30	0.30
17	3	1	0.30	0.70
18	8	1.30	0.70	0.60
19	6	1	0.40	0.60
20	4	0.70	0.18	0.52

W: Weeks, VA: Visual acuity

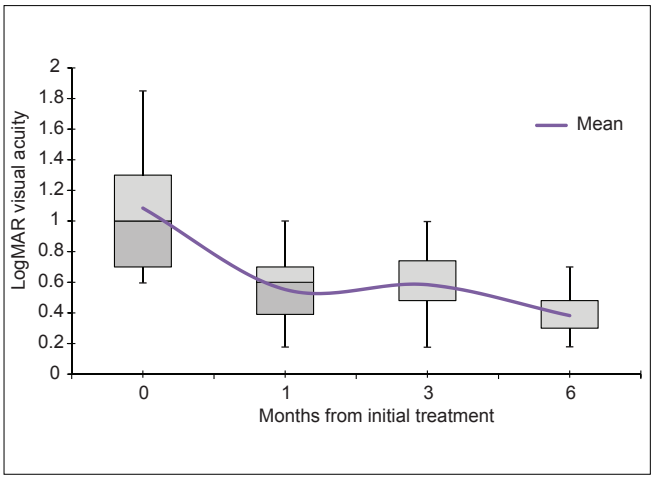

Figure 1: Mean gain in visual acuity over 6 months for eyes with macular edema secondary to branch retinal vein occlusion treated with combined intravitreal bevacizumab and triamcinolone acetate. Whiskers on box plots represent the minimum and maximum values

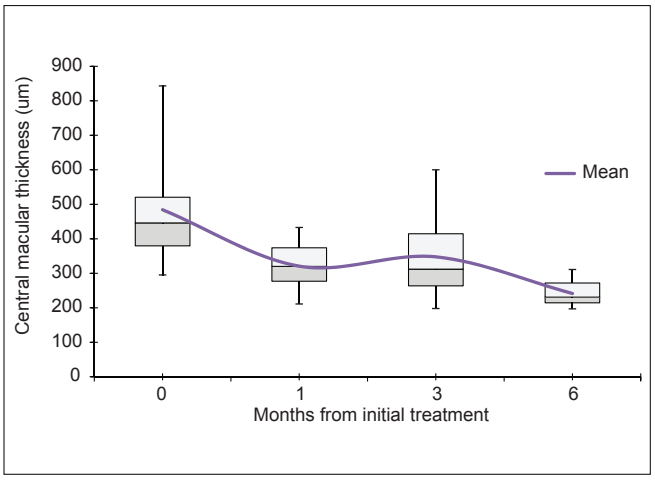

Figure 2: Mean decrease in central macular thickness over 6 months for eyes with macular edema secondary to branch retinal vein occlusion treated with combined intravitreal bevacizumab and triamcinolone acetate. Whiskers on box plots represent the minimum and maximum values

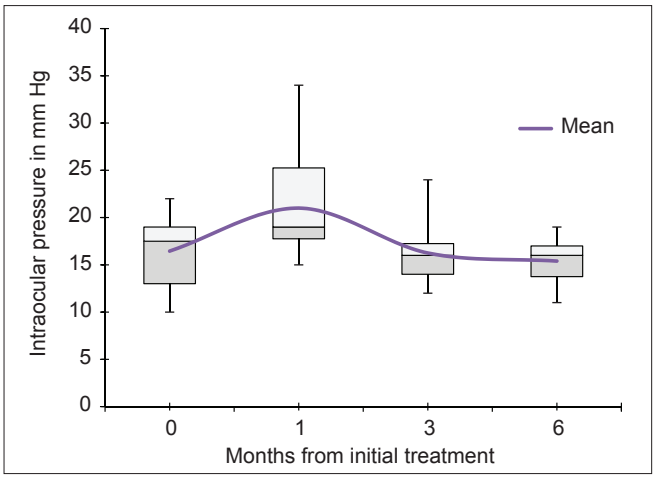

Figure 3: Transient increase and then return to baseline of mean intraocular pressure over 6 months for eyes with macular edema secondary to branch retinal vein occlusion treated with combined intravitreal bevacizumab and triamcinolone acetate. Whiskers on box plots represent the minimum and maximum values

to other studies describing the standard of care.[7,13,14] For example, Russo *et al*., reported that 67% of patients needed two or more injections of bevacizumab.[14] Prager *et al*., utilized three initial IVB injections at 1-month interval.[7] Eighty-six percent of eyes did not demonstrate resolution of macular edema as determined by OCT after 3 months, so an average of eight injections were required over 1 year. While visual acuity and CMT did improve at 12 months, frequent re-treatment was required to achieve this outcome. The authors acknowledged the problem of tachyphylaxis, citing a potential rebound phenomenon due to an up-regulation of VEGF receptors following IVB injection in patients with chronic retinal vein occlusion. In our study, we had a much lower rate of re-injection. Only 6 out of 20 patients required re-injection at 3 months, for a total of 0.35 ± 0.48 re-injections per patient over 6 months. These results may lend credence to the idea that combining drugs with different biologic mechanisms of action may overcome tachyphylaxis of a single agent (IVB), or simply that reducing the number of injections may achieve the visual outcomes prior to a tachyphylaxis threshold.

It is difficult to compare this study to the results of randomized control trials because these trials had slightly different inclusion criteria and were designed differently. However, when comparing anatomical results to the SCORE and BRAVO trials, mean improvement in central macular thickness in BRAVO with 6 injections +/- laser was 337 microns, and mean improvement in the SCORE trial at 8 months was 118 μm. In our study mean improvement in central macular thickness was 241 μm with just the initial two injections in 70% of patients. When comparing functional outcomes, in BRAVO 55% of patients had >3-line gain in vision, and in SCORE nearly 30% had >3-line gain, and in our study 85% had >3-line gain in vision. In comparing these trials it appears that our study had comparable ultimate anatomic outcomes, but a more robust functional outcome, which may support a synergistic impact of using combination treatment of IVB and IVT. This could also be because our mean time-to-treat was significantly shorter than BRAVO and SCORE, or could be simply because of a smaller sample size, and further randomized trials will be necessary to elucidate this.

It is challenging to discuss treatment mechanism given the retrospective design of the study, but the authors propose hypotheses based on our current understanding of these treatments. Intravitreal bevacizumab likely treats macular edema through countering VEGF-mediated permeability, and intravitreal triamcinolone likely reduces inflammation, limits extravasation from blood vessels, and stabilizes endothelial cells. Thus, their effects in reducing macular edema may be through different pathways. It is also known that intravitreal bevacizumab has a much shorter half-life compared to intravitreal triamcinolone. Combined IVB and IVT may allow a prolonged efficacy against macular edema through different pathways, explaining a reduced number of intravitreal injections required to achieve prompt and sustained decrease in macular edema. It follows that fewer administered injections will reduce the risk of elevated IOP associated with corticosteroids.

This study had some limitations, including its retrospective study design, limited sample size, and lack of a control arm. Yet, despite its small sample size, statistical significance was still achieved. Although a multicenter randomized controlled trial will ultimately help elucidate the precise role of this combination therapy in BRVO, it is important to remember that most clinical trials are preceded by multiple smaller studies that suggest a potential therapeutic effect. Very few studies exist on combined treatment, and these studies had limitations as described earlier, further highlighting the importance of this study. This study also had limited patient follow-up; however, an important therapeutic effect is demonstrated even in this limited follow-up that compares favorably with other randomized clinical trials, particularly at their short-term follow-up benchmarks.

It is important to note that there may be other therapeutic avenues of reducing patient injection burden, potentially by combining grid laser with either IVB or IVT versus IVB or IVT alone. However, no randomized controlled trials have clearly demonstrated this. Further, there are certain cases in which grid laser may be relatively contraindicated, such as patients that have macular ischemia, patients with significant intraretinal hemorrhages or media opacity limiting laser uptake, patients with age-related macular degeneration with significant drusen, patients with high myopia that may be predisposed to significant atrophic scar expansion, patients that have already undergone multiple previous lasers (either for the vein occlusion or for diabetic macular edema), or patients that are unable to maintain stable head position or posture for laser delivery.

The results of our study on concomitant administration of IVB and IVT for BRVO demonstrate an improvement in structural and visual outcomes in patients treated as early as possible (within 8 weeks of identification of vein occlusion). IOP transiently increased 1 month after injection in 6 patients (30%), but returned to baseline levels by 6 months with one topical beta blocker. No endophthalmitis, retinal detachment, or traumatic cataract occurred. No patient suffered from drug-related systemic adverse outcomes. Central macular thickness decreased in all patients and visual acuity improved in all patients by the 6-month mark. Interestingly, three treated patients in our study had improvement in visual acuity to 20/30 (logMAR 0.18) by 6 months, exceeding visual expectations of the natural history of BRVO.[15]

In summary, we report short-term results with concomitant administration of IVB and IVT for macular edema secondary to early onset BRVO. The prolonged anti-VEGF effect of combined IVB and IVT may be helpful in reducing the number of intravitreal injections required to achieve prompt and sustained decrease in macular edema. It may also help to reduce the risk of elevated IOP associated with corticosteroids if fewer injections are administered. IVB and IVT may be a particularly good option when argon laser photocoagulation cannot be administered. IVB and IVT may have a synergistic effect on minimizing the sequelae of vision threatening macular edema secondary to branch retinal vein occlusion, but further randomized clinical trials with control groups are needed.

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