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Original article

Outcomes of combination therapy with dexamethasone implant and bevacizumab in macular edema related to vascular occlusions

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ABSTRACT

Aim: To evaluate the anatomical and visual outcomes as well as the safety of combination therapy with dexamethasone intravitreal implant (0.7 mg) and bevacizumab in macular edema secondary to vascular occlusions.

Methods: In this interventional, prospective case series all patients received dexamethasone implant and bevacizumab in a single sitting. Patients diagnosed with retinal venous occlusion were monitored for changes in visual acuity and macular thickness. All patients underwent detailed ocular examination, best corrected visual acuity (BCVA), and optical coherence tomography examination at baseline and at Week 1, Month 1, and monthly thereafter for 6 months.

Results: Twenty four eyes of 24 treatment-naïve patients (central retinal venous occlusion, $n = 9$; branch retinal venous occlusion, $n = 15$) were identified. BCVA improved in 23 patients (95.83%) during the study period. Mean BCVA gained was 0.313 ± 0.26 (85.3% of final gain) and 0.367 ± 0.34 at Week 1 and Month 6, respectively. The percentage of patients who gained $\geq$2 lines were 52% at Week 1 and 68% at Month 6. The mean macular thickness reduced by 350.9 μm at Week 1 and the maximum treatment effect was seen at Month 2 (379.1 μm). Recurrence of macular edema was seen in 37.5% (9/24) of the eyes. Reinjection was needed, on average, at approximately 3.7 months from the first injection.

Conclusion: This study demonstrates that the combination therapy of bevacizumab and dexamethasone implant given simultaneously is safe and synergistic resulting in significantly early and sustained visual recovery and decreased macular edema in patients having retinal vein occlusions.

1. Introduction

Retinal vein occlusion (RVO) is a major cause of vision loss due to vascular diseases of the retina. In population-based studies of middle-aged and older adults, the prevalence of RVO as a whole ranged from 0.7% to 1.6%, making it the second most common retinal vascular disorder, following diabetic retinopathy.[1,2]

Macular edema is among the most prevalent causes of vision loss in both branch and central retinal venous occlusion (BRVO and CRVO).[3] Even though the pathogenesis of macular edema in RVOs is not yet fully understood, the presence of inflammatory cytokines as well as vascular permeability factors, such as interleukin-6, prostaglandins, vascular endothelial growth factors (VEGFs), and the consecutive breakdown of the blood–retina barrier due to endothelial cell dysregulation are postulated to cause macular edema.[4–6]

Until recently, our treatment strategy for patients with RVO was mainly based on the results of BRVO and CRVO trials suggesting deferred focal laser for macular edema in BRVO patients with best corrected visual acuity (BCVA) below 20/40.[7,8] Peripheral laser was recommended only for severe ischemia in RVO to treat/prevent anterior or posterior segment neovascularization, especially in CRVO; however, macular laser photocoagulation had no benefit at all in improving the macular function in eyes with CRVO. Recent randomized control trials have independently investigated and demonstrated the potential benefits of intravitreal therapy with the corticosteroids triamcinolone acetonide (the Standard Care vs Corticosteroid for Retinal Vein Occlusion trial),[9,10] ranibizumab (Lucentis; Genentech, Inc., BRAVO/CRUISE studies),[11–14] bevacizumab (Avastin; Genentech, Inc),[15–17] and dexamethasone intravitreal implant [dexamethasone implant; Allergan, Inc, Irvine,

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CA, USA; Global Evaluation of implaNtable dExamethasone in retinal Vein occlusion with macular edemA (GENEVA) study group][18,19] in RVO. However, the studies show that there were major concerns about intraocular pressure (IOP) increase in patients treated with triamcinolone acetonide whereas repeated treatments with anti-VEGF agents are often required to control macular edema, prevent visual loss, and increase the chances of visual improvement.

The action of bevacizumab starts at 24 hours and the action persists for 3–4 weeks,[20,21] whereas with the dexamethasone implant, the duration of peak action is at 2 months.[22] It has been noted that anti-VEGF and dexamethasone implant have a synergistic action (where dexamethasone implant was injected after 2 weeks of bevacizumab), increasing visual acuity and prolonging the time between injections, compared with either medication alone.[23] We carried out this study to determine whether dexamethasone implant and bevacizumab act synergistically when injected simultaneously in a single sitting in reducing the macular thickness and improving the visual acuity as well as to assess the safety profile of the combination in these patients.

2. Materials and methods

This prospective case series is a nonrandomized, noncomparative open-label, single-center investigation carried out at a tertiary eye care center after obtaining approval from the Institutional Review Board/Ethics Committee and informed consent from all patients.

Treatment-naïve individuals who were at least 18 years of age, with a BCVA of 20/40 or worse, and macular edema $\geq$ 300 μm on optical coherence tomography (OCT) secondary to RVO were recruited. Patients having clinically significant media opacity, history of vitrectomy and/or rubeotic or advanced glaucoma (defined as cup-to-disk ratio of 0.8 or worse), ocular hypertension (requiring $>$ 1 medication to control IOP) in the study eye, a history of steroid-induced IOP increase in either eye, aphakia, currently using or anticipating the use of systemic steroids or anticoagulants during the study, with known allergy/hypersensitivity to the study medication or their components, and previous use of dexamethasone implant were excluded.

All patients were evaluated at baseline and every subsequent visit with BCVA, slit-lamp examination, indirect ophthalmoscopic examination, IOP measurement, and OCT (Spectralis OCT, Heidelberg Engineering, Heidelberg, Germany). Each participant received bevacizumab injection and dexamethasone implant (0.7 mg) at baseline in a single sitting. Patients were seen on the 7th day, 1st month, and every month thereafter.

Outcomes were evaluated for visual, anatomical, and safety parameters. Improvement in BCVA was defined as the ability to read $\geq$2 lines on the Snellen visual acuity chart from baseline. Anatomical outcomes were evaluated by measuring the central retinal thickness on Spectralis OCT. By taking a reference scan every time it was ensured that the follow-up scan was passing through the same region. Our criteria for retreatment included loss of BCVA $\geq$ 1 line on the Snellen visual acuity chart and/or an increase in retinal thickness on OCT $>$ 100 μm. Dexamethasone implant was used as the drug of reinjection. Safety parameters included increased risk of IOP increase, endophthalmitis, vitreous hemorrhage, or retinal detachment. A relevant increase in IOP was defined as an increase $>$5 mm of Hg compared with the baseline.

The dexamethasone implant was inserted through the pars plana (inferotemporal quadrant) under topical anesthesia. All entries were created in a biplanar fashion using trocar fixation plate (pressure plate forceps) from ASICO (Westmont, IL, USA). Initially, the dexamethasone implant injection is administered at a 30° angle until the applicator bevel and then perpendicular to globe up to the silicone sleeve. At this point, the actuator button was pressed until an audible click was heard. The implant could be seen ejected out of the needle tip under direct microscope visualization. The needle was withdrawn in the same direction and the entry/exit wound was massaged with a steel-made scleral indenter.

Following the dexamethasone implant, intravitreal bevacizumab (1.25 mg/0.05 cc) was injected at a different site with a 30-g needle 3.5 mm in pseudophakic and 4 mm in phakic eyes posterior to the limbus. Povidone-iodine was instilled in the conjunctiva prior to and after the injection. Following the intravitreal injections, patients were monitored for signs of inflammation, endophthalmitis, and elevation in IOP. All these patients were treated with a topical antibiotic four times daily for 5–7 days. For statistical analysis, the BCVA value (Snellen visual acuity chart) was converted into logMAR and paired *t* test was applied.

3. Results

Twenty four eyes of 24 patients ($n = 24$) were analyzed in this study. The population consisted of 16 males (66.66%) and eight females (33.33%), with a mean age of 54.75 years. Nine of these patients were diagnosed with CRVO, whereas another 15 were diagnosed with BRVO (Table 1).

There was a recurrence of macular edema in 41% (9/24) of eyes, which satisfied the criteria of retreatment prior to Month 6. Analyses of this subgroup revealed that four were CRVO and five were BRVO patients. Reinjection was needed, on average, at approximately 3.7 months from the first injection (Fig. 1). Dexamethasone implant was used as the drug of reinjection.

The visual acuity results showed that 95.8% (23/24) of patients gained vision during the 6 months of observation, whereas 4.2% (1/24) had no change. The overall mean baseline BCVA and at all follow ups are shown in Table 2. The mean BCVA (logMAR) gained was 0.313 ± 0.26, 0.362 ± 0.29, 0.401 ± 0.34, 0.388 ± 0.35, 0.376 ± 0.34, 0.375 ± 0.52, and 0.367 ± 0.34 for visits at Week 1, Month 1, Month 2, Month 3, Month 4, Month 5, and Month 6, respectively, and the values were statistically significant in all follow ups (Fig. 2). The mean BCVA gain was maximum at Week 1 (85.3% of final mean BCVA gain) and the maximum treatment effect in terms of visual gain was seen at Month 2 (Fig. 2). The percentage of patients who gained $\geq$2 lines compared with baseline were 52% at Week 1 and 68% at Month 6.

3.1. Subgroup analysis

Improvement in BCVA values was noted in all cases of CRVO (9/9) and in 14 of 15 cases in BRVO. In the single patient, who did not show improvement, the duration of disease was 4 months. The mean BCVA (baseline and in all follow ups) values in CRVO and BRVO cases are shown in Table 2. The mean BCVA (logMAR) gain in the CRVO subgroup was 0.426 ± 0.3, 0.447 ± 0.32, 0.531 ± 0.42,

Table 1
Demographic characteristics of the study population.

Number of patients		$n = 24$
Sex	Male	16 (66.67)
	Female	08 (33.33)
Type of retinal venous occlusion	CRVO	09 (37.5)
	BRVO	15 (62.5)
Mean age (y)		54.9 ± 12.5
Study horizon		6 mo
No. of patients requiring reinjection		09 (37.5)
Average time of reinjection		3.7 ± 1.5 mo

Data are presented as *n* (%) or mean ± SD.
BRVO = branch retinal venous occlusion; CRVO = central retinal venous occlusion.