Taiwan Journal of Ophthalmology xxx (2014) 1–5

Contents lists available at ScienceDirect

Taiwan Journal of Ophthalmology

journal homepage: www.e-tjo.com

Original article

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

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ARTICLE INFO

Article history:
Received 16 December 2013
Received in revised form
27 March 2014
Accepted 28 March 2014
Available online xxx

Keywords:
bevacizumab
branch retinal vein occlusion
central retinal vein occlusion
dexamethasone implant
macular edema

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.

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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, CA, USA; Global Evaluation of implaNtable dExamethasone in retinal Vein occlusion with macular edemA (GENEVA) study

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http://dx.doi.org/10.1016/j.tjo.2014.03.008
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Please cite this article in press as: Nagpal M, et al., Outcomes of combination therapy with dexamethasone implant and bevacizumab in macular edema related to vascular occlusions, Taiwan Journal of Ophthalmology (2014), http://dx.doi.org/10.1016/j.tjo.2014.03.008

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.

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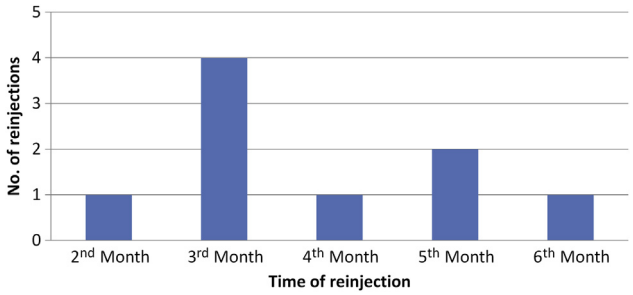

Fig. 1. Distribution of time for reinjection.

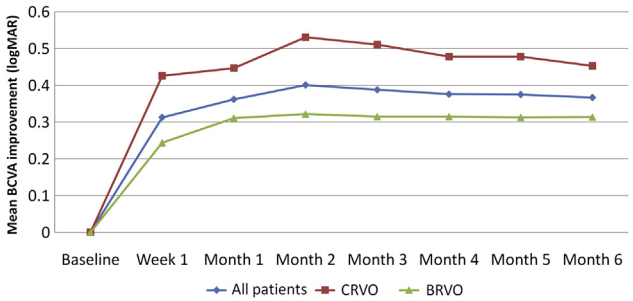

Fig. 2. Mean best corrected visual acuity (BCVA) improvement over time. BRVO = branch retinal venous occlusion; CRVO = central retinal venous occlusion.

0.511 ± 0.4, 0.478 ± 0.38, 0.478 ± 0.38, and 0.453 ± 0.38 and in the BRVO subgroup it was 0.244 ± 0.22, 0.311 ± 0.27, 0.322 ± 0.26, 0.315 ± 0.31, 0.315 ± 0.31, 0.313 ± 0.31, and 0.314 ± 0.31 at Week 1, Month 1, Month 2, Month 3, Month 4, Month 5, and Month 6, respectively (Fig. 2). The maximum mean BCVA gain of total gain at 6 months was noted at Week 1 (94% in CRVO and 77.7% in BRVO) and the maximum treatment effect in terms of visual gain was seen at Month 2 in both the subgroups (Fig. 2). The percentage of patients who gained ≥2 lines compared with baseline were 40% and 66.6% in BRVO cases as compared with 77.8% and 88.9% in CRVO cases at Week 1 and Month 6, respectively.

The overall mean OCT thickness at baseline and all follow ups are detailed in Table 2. The overall mean reduction in OCT thickness (in μm) noted was 350.92 ± 236.3, 367.29 ± 235.2, 379.12 ± 238.2, 334 ± 231.3, 348.54 ± 251.1, 354.17 ± 240.3, and 322.5 ± 228.2 at Week 1, Month 1, Month 2, Month 3, Month 4, Month 5, and Month 6, respectively (Fig. 3). The maximum OCT thickness reduction was noted at Week 1, macular thickness improved by 350.9 μm, and the maximum treatment effect was seen at Month 2 (379.1 μm). The OCT measurements showed a statistically significant reduction in central retinal thickness at all follow ups ($p > 0.05$).

3.2. Subgroup analysis

The mean OCT thickness of subgroups CRVO and BRVO at baseline and all follow ups is shown in Table 2. In both the subgroups, the maximum amount of reduction in OCT thickness was noted at Week 1 and the maximum treatment effect was seen at Month 2 (Fig. 3).

During the 6-month follow up, 16.6% (4/24) patients experienced an increase in IOP and were controlled with antiglaucoma topical medications alone. One patient had superficial retinal hemorrhage that can be due to the direct impact of implant on retina. No other adverse events such as vitreous hemorrhage, retinal detachment, or endophthalmitis were noted. No accelerated cataract formation was noted in phakic eyes.

4. Discussion

Because of increasing awareness of the role of inflammatory mediators in the pathogenesis of macular edema secondary to RVO, these patients have a better chance of visual recovery with intravitreal application of corticosteroids[18,19] and anti-VEGF drugs.[11–17] Both pharmacological approaches address important issues in the pathogenesis of retinal vascular occlusion, such as the expression of VEGF in the vitreous and inflammatory processes.[4–6]

Anti-VEGF drugs (ranibizumab/bevacizumab) have a beneficial effect on visual function and reduce central macular thickness in BRVO and CRVO eyes.[11–17] However, with respect to their shorter half-life, numerous injections are required to achieve and maintain this therapeutic effect.

Dexamethasone is a potent, water-soluble corticosteroid that can be delivered into the vitreous cavity either by injection of a dexamethasone solution with a very short half-life or by the approved dexamethasone implant using a customized applicator system. The dexamethasone implant is composed of a biodegradable co-polymer of lactic acid and glycolic acid containing micronized dexamethasone. The drug–co-polymer complex gradually releases the total dose of dexamethasone over a series of up to 6 months and has a beneficial effect on visual acuity and retinal thickness in patients with macular edema associated with RVO.[18,19]

The aim of this study was to determine the combined effect of a sustained-release corticosteroid injection with an anti-VEGF and also whether the combination provides early and sustained improvement in visual acuity and reduction in OCT thickness over a period of 6 months.

This study shows that the combination of dexamethasone implant and bevacizumab therapy injected simultaneously is synergistic in increasing visual acuity, decreasing the retinal thickness, and lengthening the time between injections as compared with either medication alone.[11–19] In a study carried out by Singer et al[23] in which RVO patients were injected with bevacizumab at baseline, followed by dexamethasone intravitreal implant injection 2 weeks

Table 2
Mean BCVA/OCT thickness (baseline and all follow ups) divided by disease types.

	Baseline	Week 1	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6
Mean BCVA (in logMAR units)								
All points	0.723 ± 0.45	0.410 ± 0.33	0.361 ± 0.31	0.322 ± 0.3	0.334 ± 0.27	0.347 ± 0.27	0.348 ± 0.28	0.356 ± 0.3
CRVO	0.744 ± 0.59	0.318 ± 0.33	0.298 ± 0.31	0.213 ± 0.23	0.233 ± 0.22	0.267 ± 0.23	0.267 ± 0.26	0.291 ± 0.32
BRVO	0.709 ± 0.37	0.465 ± 0.33	0.399 ± 0.31	0.387 ± 0.32	0.395 ± 0.29	0.395 ± 0.29	0.396 ± 0.29	0.395 ± 0.29
Mean central retinal thickness (in μm)								
All points	605.1 ± 251.2	254.2 ± 56.8	237.8 ± 44.3	235.0 ± 43.9	271.1 ± 103.1	256.6 ± 75.2	250.9 ± 57.4	282.6 ± 114.3
CRVO	754.4 ± 178.9	280.0 ± 69.3	262.5 ± 44.3	264.0 ± 44.4	274.0 ± 71.7	283.7 ± 95.3	262.1 ± 39.1	295.0 ± 111.8
BRVO	515.5 ± 249.9	238.7 ± 43.3	223.0 ± 38.4	217.6 ± 34.2	269.4 ± 120.4	240.3 ± 57.8	244.3 ± 66.5	275.2 ± 119.0

Data are presented as mean ± SD.
BCVA = best corrected visual acuity; BRVO = branch retinal venous occlusion; CRVO = central retinal venous occlusion; OCT = optical coherence tomography.

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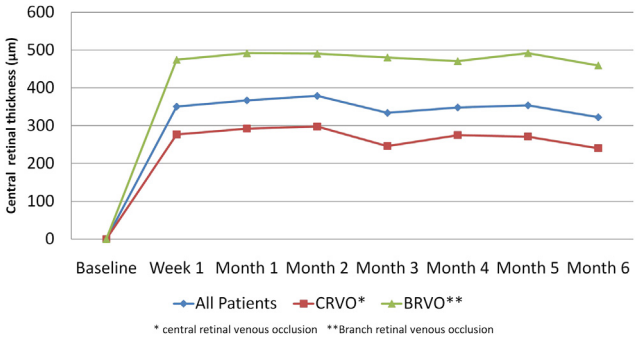

Fig. 3. Mean optical coherence tomography retinal thickness improvement over time. BCVA = best corrected visual acuity; BRVO = branch retinal venous occlusion; CRVO = central retinal venous occlusion.

later, only 38% (13/34) of patients on bevacizumab at Week 2 had central retinal thickness < 300 μm. This number increased to 68% at Week 4 (23/34) once the dexamethasone implant was added. Compared with these results, in our study, at Week 1, 71% (17/24) had central retinal thickness < 300 μm, which further improved to 83% (20/24) at Month 1. Of note, the mean pretreatment central retinal thickness in our study was 605 μm as compared with only 513 μm in the aforementioned study, which demonstrates the early and better benefits of this combination therapy.

The previously mentioned study[23] also noted BCVA improvement in 97% of cases, of which 55% of cases had a maximum visual acuity gain of three lines of the Snellen visual acuity chart and 82% required reinjection around the average time of 125.9 ± 25.5 days. Our study showed similar results with BCVA improvement noted in 95.8% patients with 54% having maximum visual acuity gain ≥3 lines and only 37.5% required reinjection at an average time of 3.7 months. If one compares our results in terms of visual acuity improvement with other RVO studies with monotherapy, differences become very apparent. In the GENEVA/dexamethasone implant studies,[18,19] only 29.3% of patients gained three lines of vision. In the bevacizumab study by Stahl et al,[15] all patients experienced a mean 2.4 line increase in visual acuity when compared with baseline versus the current study, in which the mean gain is 2.94 lines. Mayer et al[24] found that pretreatment with three doses of bevacizumab followed by a single dexamethasone implant was not effective in prolonging the interval until recurrence of macular edema as compared with monotherapy using the dexamethasone implant in the first instance. The average recurrence time for edema was noted to be approximately 3.55 months, and increased IOP was noted in 55.1% of the cases.

Looking at the safety profile, the current study had 16.6% (4/24) of patients with increased IOP and is similar to the GENEVA/dexamethasone implant study[18,19] and Singer et al study[23] in which increased IOP was noted in 12.6% and 18% of patients, respectively. No other adverse events such as vitreous hemorrhage, retinal detachment, or endophthalmitis were noted.

We performed the study to take advantage of the different modalities available to treat RVO. The aim of our combination study was to have early and sustained visual and anatomical recovery by taking advantage of bevacizumab's early onset of action and dexamethasone implant's gradual release, thereby minimizing the number of injections during the study period. In our study, 85.3% of the final mean BCVA gain was achieved as early as Week 1 and the maximum effect was seen at Month 2. In addition, the maximum mean reduction in retinal thickness noted was 379.1 μm at Month 2, of which 350.9-μm mean reduction was noted by Week 1. The GENEVA/dexamethasone implant[18,19] data show maximum effect in terms of visual acuity gained at 2 months with a residual effect at 3 months and decreasing effect at 6 months.

Limitations of this study are as follows: This is a noncomparative study with a small sample size and relatively short follow-up duration. The visual acuity was measured using the Snellen visual acuity chart, which may not have the same consistency as the Early Treatment of Diabetic Retinopathy Study chart. Although we could conclude that the combination helps in early and better visual recovery, a longer period of review will be needed to document the sustainability of the treatment benefit.

Although there will be continued debate over which combination is best, what will be the number of injections required for a patient, and timing of the injections, our trial is among the first to investigate the combination of an anti-VEGF treatment and the dexamethasone slow-release implant injected simultaneously. This combined tailored treatment approach of bevacizumab and dexamethasone implant can be a new option to treat macular edema due to vein occlusions where bevacizumab helps to achieve early reduction of macular thickness on OCT, and dexamethasone implant maintains the effect for a prolonged period, thereby stretching out the interval between the injections, thus avoiding frequent visits.

Conflicts of interest

The authors do not have any proprietary and financial interests.

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