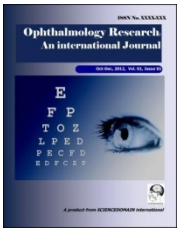


Ophthalmology Research: An International Journal
2(6): 325-335, 2014, Article no. OR.2014.6.006

SCIENCEDOMAIN *international*
www.sciencedomain.org

Intravitreal Dexamethasone Implant Plus Prompt Grid Laser for Macular Edema Due to Retinal Vein Occlusion

Justin B. Hellman[1*], Joshua K. Fernandes[2], Ravi D. Patel[2] and Seenu M. Hariprasad[2]

[1]Pritzker School of Medicine, University of Chicago, Chicago, Illinois, USA.
[2]Department of Ophthalmology and Visual Science, University of Chicago, Chicago, Illinois, USA.

Authors' contributions

This work was carried out in collaboration between all authors. Author SMH designed the study, wrote the protocol, and saw all of the patients. Author JBH managed the literature searches, analyzed the data, prepared the tables and graphs, and wrote the introduction. Author JKF wrote the materials/methods and the results sections. Author RDP wrote the discussion section of the paper. All authors read, edited and approved the final manuscript.

Original Research Article

Received 8th April 2014
Accepted 23rd April 2014
Published 7th June 2014

ABSTRACT

Purpose: To evaluate the use of intravitreal dexamethasone implant followed by prompt grid laser for macular edema secondary to retinal vein occlusion (RVO).
Methods: Prospective, non-controlled, 12-month interventional case series of fifteen patients with vision loss due to macular edema secondary to RVO. Patients received an intravitreal injection with a 0.7mg dexamethasone implant followed by prompt macular grid laser within 2-4 weeks. Retreatment was offered in 3-month intervals. Primary outcome measures were change in mean log MAR best-corrected visual acuity (BCVA) and central macular thickness (CMT) at 12 months. Secondary outcome was safety at 12 months.
Results: Fifteen eyes of fifteen patients (7 BRVO and 8 CRVO) were evaluated in the case series. The baseline mean log MAR BCVA of all patients was 1.14±0.71 with a significant improvement to 0.70±0.65 ($p<0.01$) at month 12. Patients had a baseline mean CMT of 513.6±168.5 µm with a significant improvement to 300.2±104.1 µm ($p<0.01$) at month 12. Safety analysis demonstrated three patients with an increase in IOP>10 mmHg

**Corresponding author: E-mail: retina@uchicago.edu, justin@tentacle.net;*

and four patients with cataract progression.
Conclusions: Intravitreal dexamethasone implant followed by prompt grid laser appears to be potentially safe and efficacious for treatment of select patients with macular edema secondary to RVO and should be considered as a treatment option, particularly in patients recalcitrant to monotherapy.

Keywords: Dexamethasone; laser; macular edema; ozurdex; retina; retinal vein occlusion.

1. INTRODUCTION

Retinal vein occlusion (RVO) is the second most common retinal vascular disorder after diabetic retinopathy, affecting nearly 180,000 eyes each year [1-2]. RVO may involve the branch, hemicentral, or central retinal veins in various combinations and with varying degrees of ischemia and hemorrhage [1–5]. Branch retinal vein occlusion (BRVO) involving a single vein is the most common type (prevalence of 0.6%-1.1%), whereas central retinal vein occlusion (CRVO) is less common (prevalence of 0.1%-0.4%) [1-2].

Macular edema (ME) is a common cause of vision loss in RVO [3-5]. The pathogenesis of ME in RVO is not completely understood but may result from a variety of factors including hydrostatic effects from increased venous pressure [6], inflammatory cytokines [7], dysregulation of endothelial tight junction proteins [6,8-9], or increased amounts of vascular permeability factors such as vascular endothelial growth factor (VEGF) [8-9].

Until recently, the standard for treatment of ME associated with RVO was based on the results of the Branch Vein Occlusion Study (BVOS) [10] and Central Vein Occlusion Study (CVOS) [11]. In BVOS, patients with BRVO and secondary ME were randomized to grid laser or observation. After 3 years, the laser group gained an average of 1.33 lines compared with 0.23 lines in the observation group (P=0.001). Laser treatment was recommended after waiting 3 months to assess for spontaneous resolution of ME and to allow clearance of hemorrhages for laser treatment [10]. In CVOS, patients with CRVO and ME were randomized to grid laser or observation. While there was a reduction in ME on fluorescein angiogram at 1-year, there was no difference in visual acuity between the two groups over 3-years. However, there was a suggestion of potential benefit from laser in patients less than 60 years of age, which could not be confirmed due to a small sample size [11].

During the past three years, several pivotal randomized controlled trials have shown that the intravitreal anti-VEGF agent ranibizumab [12-15] and the corticosteroids triamcinolone acetonide [16-17] and dexamethasone [18-19] can be of benefit in the treatment of ME associated with RVO. The use of corticosteroids is based on their ability to exhibit anti-inflammatory properties, reduce vascular permeability, inhibit fibrin deposition, stabilize endothelial cell tight junctions, and inhibit the synthesis of VEGF, prostaglandins, and other cytokines [6-9].

A sustained delivery, bioerodible dexamethasone intravitreal implant (Ozurdex^{TM}; Allergan, Inc., Irvine, CA, USA) has been shown in the GENEVA phase III randomized controlled trials to reduce ME and improve visual acuity in patients with BRVO and CRVO [18-19]. The time to achieve a visual acuity gain of 3 lines or more was shorter in the dexamethasone implant

group (41% at 180 days) than the sham group (23%) [18]. Repeated injection with the dexamethasone implant was well tolerated for up to 12 months [19].

While there are now multiple recognized treatment options for ME secondary to RVO, there have not been randomized, controlled trials evaluating combination therapy for this condition. Given that the complex pathogenesis of ME associated with RVO may result from multiple mechanisms, combining currently available monotherapies may provide an additional or synergistic approach to treating this disease.

This 12-month prospective interventional case series evaluated a combination therapy approach using an intravitreal dexamethasone implant followed by prompt grid laser for patients with ME secondary to RVO.

2. MATERIALS AND METHODS

A prospective non-controlled study was designed to assess a combination therapy approach with an intravitreal dexamethasone implant followed by prompt grid laser for patients with ME secondary to RVO. The study was approved by the institutional review board of the University of Chicago. All patients provided informed consent before participation in the study.

Patients who were at least 18 years of age and had decreased visual acuity as a result of ME secondary to RVO were enrolled in the study and followed in the retina clinic of one author (S.M.H.) at the University of Chicago Medical Center. The criteria for defining ME were identical to those in the GENEVA trial. Patients were required to have a central macular thickness (CMT) ≥ 300 μm as measured by macular spectral-domain optical coherence tomography (SD-OCT) and clinically detectable ME causing decreased visual acuity [19]. Patients could not have received any intravitreal agent for at least 60 days or macular laser for at least 90 days prior to enrollment. There was no limit to the duration of the RVO, duration of ME, or baseline visual acuity. Only patients that completed 12 months of follow-up were included. Exclusion criteria included presence of other concurrent eye conditions that could affect adverse outcomes, visual acuity, or ME. This included active retinal or optic disc neovascularization, aphakia or anterior chamber lens, clinically significant media opacity, presence of rubeosis iridis, active choroidal neovascularization, glaucoma or ocular hypertension requiring multiple medications, active infection, diabetic retinopathy, or any uncontrolled systemic disease. Patients who were using systemic steroids or anticoagulants or had a history of choroidal neovascularization or steroid-induced increase in intraocular pressure were also excluded.

Patients were given complete vitreoretinal exams, macular SD-OCT (Cirrus, Carl Zeiss, Dublin, CA), and fluorescein angiography (FA) (Topcon Medical Systems, Inc, Oakland NJ with software by OIS, Herndon, VA) on the day of enrollment (day 0) and at 1, 3, 6, 9, and 12 months. Patients were treated with a combination therapy approach, which consisted of an intravitreal injection with a 0.7mg dexamethasone implant at day 0 followed by macular grid laser photocoagulation (Lumenis Vision, Yokneam, Israel), en-face SD-OCT, and FA guidance within 2-4 weeks after injection. Laser photocoagulation with a green argon laser was applied in a grid pattern to all areas of diffuse leakage within two disc diameters of the center of the fovea, not including the foveal avascular zone. Laser parameters included a 100 μm spot size, a burn duration of 0.1 seconds, and a barely visible (light grey) burn intensity. Patients were retreated with an additional combination treatment in 3-month

intervals at months 3, 6, and 9. If no residual ME was detected by SD-OCT or logMAR best-corrected visual acuity (BCVA) < 0.3, treatment was deferred until the following visit.

Primary outcome measures included change in mean logMAR BCVA and CMT by SD-OCT at 12 months. The secondary outcome measure was safety of using an intravitreal dexamethasone implant in combination with grid laser in 3-month treatment intervals. Safety measures included the incidence and severity of ocular and non-ocular adverse events. For statistical analysis, Snellen BCVA was converted to logMAR BCVA according to standardized methods [20]. The change in BCVA and CMT from baseline was assessed at each visit using a paired t-test with $p<0.05$ considered statistically significant. Stata™ software (StataCorp LP, College Station, TX) was used for statistical analysis.

3. RESULTS

3.1 Study Population

Nineteen patients were enrolled in the study. Two patients were lost to follow-up and one patient passed away due to unrelated causes. One patient was excluded due to development of a vitreous hemorrhage secondary to neovascularization 3 months after enrollment. Thus, fifteen patients (7 BRVO and 8 CRVO) completed the 12-month follow-up period. Five of the eight CRVO patients were ischemic. Patient demographics and baseline characteristics are shown in Table 1. The mean time from diagnosis of RVO to enrollment was 7.32 months with a mean duration of ME of 5.85 months (range 0.25–24 months). Nine patients (60%) had residual or recurrent ME associated with decreased BCVA despite one or more prior monotherapies including intravitreal bevacizumab, intravitreal triamcinolone acetonide, or grid laser (Table 1).

Table 1. Patient demographic and baseline characteristics (n=15)

Mean age (years)	69.7 (range 45-92)
Gender	
Male	4(26.7%)
Female	11(73.3%)
Diagnosis in study eye	
BRVO	7(46.7%)
CRVO	8(53.3%)
Duration of macular edema	
<90 days	5(33.3%)
90-179 days	4(26.7%)
180-269 days	3(20.0%)
269-365 days	0(0.0%)
>365 days	3(20.0%)
Prior Treatment	9(60.0%)
Macular grid laser	6(40.0%)
Intravitreal triamcinolone acetonide	4(26.7%)
Intravitreal bevacizumab	4(26.7%)

BRVO=branch retinal vein occlusion; CRVO=central retinal vein occlusion

3.2 Description of Treatment

Ten patients received the full treatment schedule of four intravitreal dexamethasone implants followed by prompt grid laser at day 0 then month 3, 6, and 9. Three patients had treatment deferred at one visit. Two patients received one implant at day 0 followed by one prompt grid laser and did not require further treatment. The number of grid laser treatment spots applied per session ranged from 14-26 for BRVO and 18-37 for CRVO patients. The grid laser power ranged from 50-65mW for BRVO and 55-85mW for CRVO patients.

3.3 Change from Baseline BCVA

A primary outcome measure was mean change from baseline BCVA at month 12. The combined results of patients with BRVO and CRVO demonstrated a baseline mean logMAR BCVA of 1.14±0.71 (range 0.18-2.00) with a statistically significant improvement to 0.70±0.65 ($p<0.05$) at month 12 (Table 2). The greatest change in mean BCVA occurred between day 0 and month 3 (logMAR BCVA 0.77±0.64, $p=0.008$) and was relatively maintained over the 12 month follow up period (Fig. 1A).

Table 2. Mean logMAR BCVA in patients with BRVO and CRVO

	Mean logMAR BCVA±SD/p value*		
	Combined (BRVO+CRVO) (n=15)	**BRVO (n=7)**	**CRVO (n=8)**
Baseline	1.14±0.71	0.83±0.58	1.41±0.74
1 month	0.92±0.67/p=0.02	0.65±0.43/p=0.04	1.16±0.78/p=0.15
3 month	0.77±0.64/p=0.008	0.52±0.37/p=0.02	1.00±0.77/p=0.09
6 month	0.73±0.64/p=0.004	0.51±0.50/p=0.01	0.93±0.71/p=0.05
9 month	0.75±0.62/p=0.008	0.53±0.48/p=0.02	0.95±0.69/p=0.08
12 month	0.70±0.65/p=0.004	0.43±0.40/p=0.02	0.93±0.77/p=0.07

*BCVA=best-corrected visual acuity; BRVO=branch retinal vein occlusion; CRVO=central retinal vein occlusion; SD=standard deviation. *P values are derived from paired t-tests comparing the mean baseline BCVA versus the mean BCVA at the specified follow up visit*

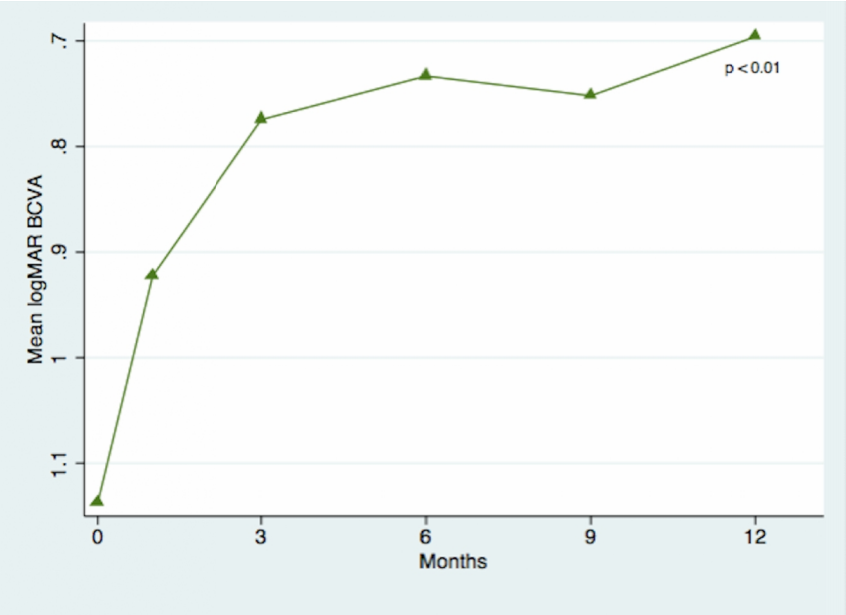
Subgroup analysis of BRVO patients demonstrated a baseline mean logMAR BCVA of 0.83±0.58 with a statistically significant improvement to 0.43±0.40 ($p=0.02$) at month 12. CRVO patients demonstrated a baseline mean logMAR BCVA of 1.41±0.74 with an improvement to 0.93±0.77 at month 12, but this improvement did not gain statistical significance ($p=0.07$). For the subgroup of five patients with CRVO who were ischemic, the mean baseline logMAR BCVA was 1.72±0.17 with an improvement to 1.34±0.31 ($p=0.14$). Similar to the combined results, the BRVO and CRVO subgroups showed the greatest change in BCVA between day 0 and month 3, which was relatively maintained over the remaining follow up period (Fig. 1B).

3.4 Change from Baseline CMT

An additional primary outcome measure was mean change from baseline CMT as demonstrated by SD-OCT at month 12. The combined results of patients with BRVO and CRVO demonstrated a baseline mean CMT of 513.6±168.5 μm with a statistically significant improvement to 300.2±104.1μm ($p=0.0002$) at month 12 (Table 3 and Fig. 2). Similar

statistically significant findings were seen in BRVO, CRVO, and CRVO ischemic subgroup analysis.

A



B

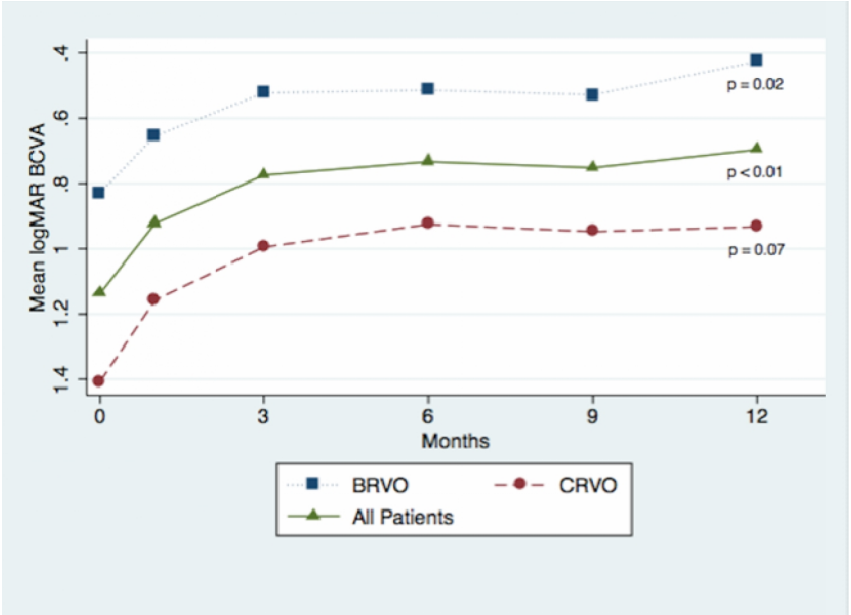


Fig. 1. Mean change from baseline logMAR BCVA. A: Combined (BRVO+CRVO). B: Subgroup analysis of BRVO and CRVO relative to combined. BCVA=best-corrected visual acuity; BRVO=branch retinal vein occlusion; CRVO=central retinal vein occlusion. P values are derived from paired t-tests comparing the mean baseline BCVA versus the mean BCVA at the specified follow up visit

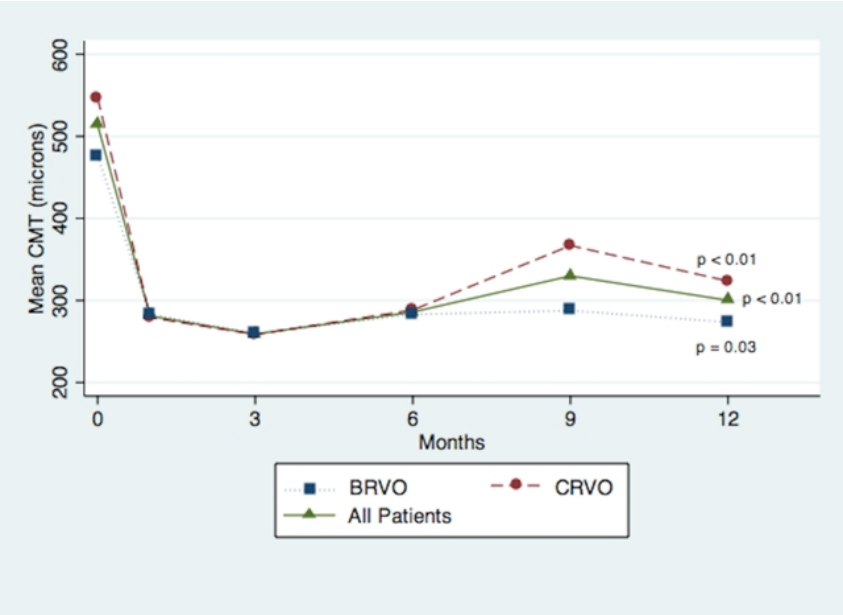


Fig. 2. Mean change from baseline CMT. CMT=central macular thickness; BRVO=branch retinal vein occlusion; CRVO=central retinal vein occlusion. P values are derived from paired t-tests comparing the mean baseline CMT versus the mean CMT at the specified follow up visit

3.5 Safety

Analysis of adverse events over the 12 month follow-up period demonstrated one patient with a vitreous hemorrhage at month 3, which resulted in exclusion from the study. The vitreous hemorrhage, based on the timeline, was felt to be due to neovascularization from CRVO and not due to the injection or laser treatment. There were no incidents of endophthalmitis, retinal detachment, or other serious ocular adverse events. Three patients had an increase in IOP>10 mmHg from baseline but were controlled with one topical IOP-lowering medication. Four patients showed a progression of cataract and underwent cataract extraction during the 12-month period, with an average time period of 4 months from entering the study to surgery. No patient experienced a non-ocular complication that was attributable to the study treatment.

4. DISCUSSION

We report the 12-month results of a prospective, non-controlled study evaluating the safety and efficacy of a combination therapy approach for patients with ME secondary to RVO. To the authors' knowledge, this is the first report of the use of an intravitreal dexamethasone implant in combination with prompt grid laser for treatment of ME secondary to RVO.

The primary outcome measure of our study was the efficacy of this combination therapy. The combined results of BRVO and CRVO patients demonstrated statistically significant improvements in mean BCVA as well as anatomic improvements in mean CMT at every follow up visit over the 12-month period. The improvement in mean BCVA was the most

important outcome. It is significant to note that nine out of fifteen (60%) patients in our study had residual or recurrent ME at enrollment despite prior monotherapies. This suggests that combination therapy can be a good option to improve visual acuity in patients where monotherapy has failed to do so. In addition, there were three patients that required only three combination treatments and two patients that required a single combination treatment over the 12-month follow-up. This suggests a possible role for combination therapy in reducing the number of treatments in certain patients. At 6 months the GENEVA trial showed a mean change in central retinal thickness of only 119±203 μm with an intravitreal dexamethasone implant alone, which was not statistically different than the sham group. Our results suggest that the addition of macular grid laser can create a greater change in CMT than intravitreal dexamethasone implant alone (Table 3). It should be noted that many of our patients received dexamethasone every three months while those in the GENEVA trial received it every six months.

Table 3. Mean CMT in patients with BRVO and CRVO

	Mean CMT (μm)±SD/p value*		
	Combined (BRVO + CRVO) (n=15)	**BRVO (n=7)**	**CRVO (n=8)**
Baseline	513.6±168.5	475.7±174.3	546.8±167.5
1 month	281.1±68.5/p=0.0001	283.1±57.9/p=0.02	279.3±80.7/p=0.003
3 month	259.0±46.9/p=0.0001	259.6±52.8/p=0.03	258.5±44.8/p=0.002
6 month	285.9±41.5/p=0.0002	283.0±35.7/p=0.02	288.4±48.3/p=0.006
9 month	329.9±146.4/p=0.0007	287.6±61.5/p=0.009	366.9±196.4/p=0.08
12 month	300.2±104.1/p=0.0002	273.4±46.5/p=0.03	323.6±135.9/p=0.006

*CMT=central macular thickness; BRVO=branch retinal vein occlusion; CRVO=central retinal vein occlusion; SD=standard deviation. *P values are derived from paired t-tests comparing the mean baseline CMT versus the mean CMT at the specified follow up visit*

Our study also challenged the standard established by CVOS that grid laser is not recommended for treatment of ME secondary to CRVO [11]. In CVOS, the majority of patients in the laser group had very diffuse ME at baseline (61/77 patients ≥ 5 disc areas of ME) and the median number of laser spots applied during all sessions was 143 (range 37-798 spots) [11]. In our study, pretreatment with an intravitreal dexamethasone implant rapidly and significantly reduced the thickness and geographic treatment area of the macula (evident in the CMT results within one month) prior to application of grid laser. This approach allowed for more precise laser burn placement, reduced number of spots and power, and decreased area of the macula requiring treatment. Though we were unable to demonstrate a statistically significant improvement in mean BCVA among CRVO patients at 12 months, there was an overall trend towards significance (p=0.07) and a larger sample size and/or a slightly younger patient population may have shown one. The use of grid laser in combination with an intravitreal agent such as dexamethasone for patients with CRVO and diffuse ME is intriguing and warrants further investigation.

The safety of an intravitreal dexamethasone implant for treatment of ME secondary to RVO has been well studied in the FDA registered GENEVA trial [18-19]. However, additional treatments including grid laser were prohibited in the trial's primary outcome analysis. Non-study rescue treatments were only given at the discretion of the investigator and were used in a separate intent-to-treat analysis. Thus, the secondary outcome of our study was to evaluate the safety of the dexamethasone implant in combination with prompt grid laser. We also investigated the safety of dosing the dexamethasone implant in 3-month retreatment

intervals given that a significant number of patients in the GENEVA trial were undertreated when the dexamethasone implant was dosed in 6-month intervals.

Our study demonstrated a similar safety profile compared with the 12-month results of the GENEVA trial [19]. There was only one serious ocular adverse event (i.e. vitreous hemorrhage) in our study, which was not felt to be due to the treatment. The most common ocular adverse event was cataract progression. Four patients (26%) in our study versus 29.8% of phakic eyes in the retreated dexamethasone 0.7/0.7 mg group of GENEVA showed a progression of cataract [19]. All four of our patients underwent cataract extraction while only 1.3% of phakic eyes in the GENEVA retreated dexamethasone 0.7/0.7mg group underwent cataract extraction [19]. The decision to undergo cataract surgery was at the discretion of the investigators in both our study and the GENEVA trial, thus it is difficult to draw any conclusion from this difference since rates of cataract progression were similar in both studies. The second most common ocular adverse event was increase in IOP. Three patients (20%) had an increase in IOP>10 mmHg from baseline, but all were controlled with one topical IOP-lowering medication. This finding was better than the 32.8% of eyes in the GENEVA retreated dexamethasone 0.7/0.7mg group that had at least a 10 mmHg increase in IOP from baseline [19]. The only non-ocular adverse event in our study was a patient that passed away six months after enrollment, but this was determined to be unrelated to the study treatment.

There are several limitations to the conclusions that can be drawn from this study. Our small study size significantly limits the statistical power of the data analysis. The non-controlled study design limits our interpretation of the efficacy of the study treatment compared to observation, intravitreal dexamethasone, or grid laser alone and allows for potential bias. The broad inclusion and exclusion criteria of the study allowed for a significant number of patients with recalcitrant disease. Although patients couldn't have received any intravitreal agent for at least 60 days or macular laser for at least 90 days prior to enrollment, there remains the possibility that some of the effects that we saw were residual effects from previous treatments. There is also a confounding variable in the analysis of BCVA in the four patients who underwent cataract extraction during the study period. Although some would fault our study for including patients with both BRVO and CRVO, there is no definitive evidence that the pathophysiology of the macular edema is substantially different, and we followed the format of the GENEVA trial in including both sets of patients. Given these limitations, we should take caution in making comparisons of our findings with the large, randomized, controlled trials that support the use of various FDA-approved monotherapies for ME due to RVO [10,12-15,18-19].

5. CONCLUSION

In conclusion, combination therapy with an intravitreal dexamethasone implant followed by prompt grid laser appears to be a potentially safe treatment for patients with ME secondary to RVO that can improve visual acuity and reduce ME in select patients. Further randomized controlled studies with a larger patient cohort over a longer follow-up period are needed to confirm the role of this treatment approach.

CONSENT

All authors declare that written informed consent was obtained from the patients for publication of this case series.

ETHICAL APPROVAL

All authors hereby declare that this study has been examined and approved by the appropriate ethics committee and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

COMPETING INTERESTS

Declaration of Interest: Justin Hellman, None; Joshua K. Fernandes, None; Ravi D. Patel, None; Seenu M. Hariprasad, Alcon (Speaker, Consultant), Allergan (Speaker, Consultant), Genentech (Speaker), Ocular-Therapeutix (Consultant), Regeneron (Speaker), OD-OS (Consultant), Optos (Consultant), Bayer (Consultant), Alimera Sciences (Consultant), Bausch and Lomb (Consultant), Clearside Biomedical (Consultant). No financial support was received for this submission.

REFERENCES

1. Klein R, Moss SE, Meuer SM, Klein BE. The 15-year cumulative incidence of retinal vein occlusion: The Beaver Dam Eye Study. Arch Ophthalmol 2008;126:513-8.
2. Rogers S, McIntosh RL, Cheung N, et al. The prevalence of retinal vein occlusion: pooled data from population studies from the United States, Europe, Asia, and Australia. Ophthalmology 2010;117:313-9.
3. Hayreh SS. Prevalent misconceptions about acute retinal vascular occlusive disorders. Prog Retin Eye Res 2005;24:493-519.
4. Rogers SL, McIntosh RL, Lim L, et al. Natural history of branch retinal vein occlusion: an evidence-based systematic review. Ophthalmology 2010;117:1094-101.
5. McIntosh RL, Rogers SL, Lim L, et al. Natural history of central retinal vein occlusion: An evidence-based systematic review. Ophthalmology 2010;117:1113-23.
6. Antonetti DA, Wolpert EB, DeMaio L, Harhaj NS, Scaduto RC Jr. Hydrocortisone decreases retinal endothelial cell water and solute flux coincident with increased content and decreased phosphorylation of occludin. J Neurochem 2002;80:667-77.
7. Lee HB, Pulido JS, McCannel CA, Buettner H. Role of inflammation in retinal vein occlusion. Can J Opthalmol 2007;42:131-3.
8. Nauck M, Karakiulakis G, Perruchoud AP, Papakonstantinou E, Roth M. Corticosteroids inhibit the expression of the vascular endothelial growth factor gene in human vascular smooth muscle cells. Eur J Pharmacol 1998;341:309-15.
9. Wang K, Wang Y, Gao L, Li X, Li M, Guo J. Dexamethasone inhibits leukocyte accumulation and vascular permeability in retina of streptozotocin-induced diabetic rats via reducing vascular endothelial growth factor and intercellular adhesion molecule-1 expression. Biol Pharm Bull 2008;31:1541-6.
10. Argon laser photocoagulation for macular edema in branch vein occlusion. The Branch Vein Occlusion Study Group. Am J Ophthalmol 1984;98:271-82.
11. Evaluation of grid pattern photocoagulation for macular edema in central vein occlusion. The Central Vein Occlusion Study Group M report. Ophthalmology 1995;102:1425-33.
12. Campochiaro PA, Heier JS, FeinerL, et al. Ranibizumab for macular edema following branch retinal vein occlusion: Six-month primary end point results of a phase III study. Ophthalmology 2010;117:1102-12.

13. Brown DM, Campochiaro PA, Bhisitkul RB, et al. Sustained benefits from ranibizumab for macular edema following branch retinal vein occlusion: 12-month outcomes of a phase III study. Ophthalmology 2011;118:1594-602.
14. Brown DM, Campochiaro PA, Singh RP, et al. Ranibizumab for macular edema following central retinal vein occlusion: Six-month primary end point results of a phase III study. Ophthalmology 2010;117:1124-33.
15. Campochiaro PA, Brown DM, Awh CC, et al. Sustained benefits from ranibizumab for macular edema following central retinal vein occlusion: Twelve-month outcomes of a phase III study. Ophthalmology 2011;118:2041-9.
16. Scott IU, Ip MS, Van Veldhuisen PC, et al. A randomized trial comparing the efficacy and safety of intravitreal triamcinolone with standard care to treat vision loss associated with macular edema secondary to branch retinal vein occlusion: The Standard Care vs Corticosteroid for Retinal Vein Occlusion (SCORE) study report 6. Arch Ophthalmol 2009;127:1115-28.
17. Ip MS, Scott IU, VanVeldhuisen PC, et al. A randomized trial comparing the efficacy and safety of intravitreal triamcinolone with observation to treat vision loss associated with macular edema secondary to central retinal vein occlusion: The Standard Care vs Corticosteroid for Retinal Vein Occlusion (SCORE) study report 5. Arch Ophthalmol 2009;127:1101-14.
18. Haller JA, Bandello F, Belfort R Jr, et al. Randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with macular edema due to retinal vein occlusion. Ophthalmology 2010;117:1134-46.
19. Haller JA, Bandello F, Belfort R Jr, et al. Dexamethasone intravitreal implant in patients with macular edema related to branch or central retinal vein occlusion twelve-month study results. Ophthalmology 2011;118:2453-60.
20. Holladay JT. Proper method for calculating average visual acuity. J Refract Surg 1997;13:388-91.

Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sciencedomain.org/review-history.php?iid=523&id=23&aid=4829