Artigo Original

Safety of dexamethasone intravitreal implant injections for treatment of macular edema related to retinal vein occlusion

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RESUMO

Objetivos: Avaliar a segurança do implante intra-vítreo de dexametasona no tratamento de edema macular (EM) secundário a oclusões venosas retinianas.

Material e Métodos: Estudo retrospetivo dos doentes com EM secundário a oclusão venosa central (OVCR) ou de ramo (OVR) tratados com implante intra-vítreo de dexametasona (Ozurdex, Allergan Inc, Irvine, CA) entre Janeiro de 2011 e Agosto de 2015. A análise de segurança englobou os seguintes parâmetros: progressão de catarata, pressão intra-ocular (PIO), necessidade de hipotensores e/ou cirurgia de glaucoma.

Resultados: Vinte-e-quatro olhos (24 doentes) foram incluídos no estudo, 58% mulheres. A idade média foi de 66.5 anos (49 – 95 anos). Foram tratadas 13 OVR e 11 OVCR. 75% dos doentes realizaram tratamento prévio (laser, injeções ou vitrectomia). Em 6 doentes (25%) foi utilizado o implante como primeiro tratamento. 20 doentes (83%) eram fáquicos no início do estudo, tendo-se verificado progressão da catarata em apenas dois, os quais não necessitaram de cirurgia. Após colocação do implante documentou-se PIO>21mmHg em sete doentes (29.1%), a qual foi controlada com hipotensores. A elevação média da PIO de 3.53 mmHg não foi estatisticamente significativa face ao *baseline*. Na comparação de OVR e OVCR não foram detetadas diferenças na progressão de catarata, necessidade de facoemulsificação, elevação da PIO e necessidade de hipotensores.

Conclusões: O implante intra-vítreo de dexametasona é uma arma terapêutica para o tratamento do EM secundário a oclusões venosas. Nesta série a progressão de catarata foi negligenciável, apesar de 83% dos doentes serem fáquicos, e a elevação tensional (em 30% dos doentes) foi controlada com hipotensores.

Palavras chave

Oclusão venosa retiniana, edema macular, corticosteroides, injeções intra-vítreas, tomografia de coerência ótica.

ABSTRACT

Purpose: To assess the safety of the dexamethasone implant in the treatment of macular edema (ME) secondary to retinal vein occlusions.

Material and Methods: Retrospective study of patients with ME secondary to central retinal vein occlusion (CRVO) or branch retinal vein occlusion (BRVO) treated with dexamethasone implant (Ozurdex, Allergan Inc, Irvine, CA) from January 2011 through August 2015. Safety

assessment included analysis of cataract progression, intra-ocular pressure (IOP) changes, antihypertensive eye drops requirement and/or glaucoma surgery.
Results: Twenty-four eyes (24 patients) were included in the study, 58% female. Mean age was 66.5 years (49 – 95 years). Thirteen BRVO and 11 CRVO were treated in this series. 75% had history of previous treatment (laser, intravitreal injections or vitrectomy). In six patients (25%) the implant was used as first-line therapy. Twenty patients (83.0%) were phakic in the beginning of the study. Cataract progression was observed in two patients, though none required cataract surgery. Ocular hypertension (IOP>21mmHg) was documented in seven patients (29.1%) following treatment and control was reached with antihypertensive eye drops. A mean 3.53 mmHg elevation of IOP wasn't statistically significant. The subgroup analysis of BRVO and CRVO did not detect differences in the following parameters: cataract progression, cataract surgery, IOP elevation and hypotensive drug requirement.
Conclusions: The dexamethasone implant is an important therapeutic tool for ME secondary to retinal vein occlusions. In this series, cataract progression was negligible, though 83% of our patients were phakic. The IOP elevation, observed in 30% of patients, was readily managed with antihypertensive drops.

Key-words
Sixth nerve palsy, paresis, surgery, muscle transposition, botulinum toxin.

INTRODUCTION

Retinal vein occlusion (RVO) is a vascular disease of the retina that is an important cause of vision loss worldwide, being second to diabetic retinopathy only. It may involve the central retinal vein or branch retinal veins[1,2]. Branch retinal vein occlusion (BRVO), which usually implicates a single vein, is the most common type (prevalence of 0.6%–1.1%). Central retinal vein occlusion (CRVO) occurs less frequently (prevalence of 0.1%–0.4%)[3] and it may be ischemic (in up to 25% of cases), which puts the patient at a higher risk of ocular neovascularization and, consequently, visual impairment[4]. In addition, up to a third of nonischemic CRVO may become ischemic within 3 years[5].

Macular edema (ME) is a common cause of vision loss in both BRVO and CRVO. The pathogenesis of ME in RVO is yet to be completely understood. In all likelihood, it is the consequence of a multifactorial process that includes the hypoxia resulting from the RVO itself, the hydrostatic effect from increased venous pressure, the dysregulation of endothelial tight junction proteins[6], the presence of inflammatory cytokines (e.g., prostaglandins and interleukin-6), and increased levels of vascular permeability factors, such as vascular endothelial growth factor (VEGF)[7], which contributes to blood-retinal barrier breakdown.

Several therapeutic options have been investigated for the treatment of ME associated with RVO. These include laser photocoagulation, anti-VEGF therapy -ranibizumab, bevacizumab and aflibercept - as well as corticosteroids - triamcinolone acetonide and dexamethasone implant.

The BRVO and CRVO clinical trials recommended laser in the macular region for ME in BRVO with best corrected visual acuity (BCVA) <20/40 and peripheral laser in both BRVO and CRVO cases with severe ischemia[8,9]. In CRVO patients, however, macular laser is no longer advocated as it provides no functional benefits[9].

Intravitreal anti-VEGF injections have severely altered the way clinicians treat retinal disease. Ranibizumab (Lucentis, Genentech, Inc., South San Francisco, CA) has showed efficacy in the treatment of ME secondary to RVO[10-12]. Similarly, aflibercept (Eylea, Regeneron Pharmaceuticals, Inc., Tarrytown, NY) has been validated for the treatment of ME in CRVO[13,14] and, more recently, in BRVO[15]. Bevacizumab (Avastin, Genentech, Inc.) has been used off-label to treat ME secondary to both, BRVO and CRVO[16-18].

Corticosteroids have anti-inflammatory proprieties. These drugs are thought to decrease edema by stabilizing vascular permeability, downregulating inflammatory mediators, and indirectly inhibiting the actions of VEGF[19]. Despite the clear advantages of injecting corticosteroids directly into the vitreous cavity, reports have arisen discussing its adverse effects. In addition to the complications related to an intravitreal injection[20,21], a corticosteroid injection has been linked to cataract formation and progression, higher incidence of cataract surgery and intra-ocular pressure (IOP) elevation. In some cases, the IOP change is insufficiently controlled with antihypertensive drops and, thus, requires laser therapy, or even surgery[20-22].

Triamcinolone acetonide is a lipophilic corticosteroid that has been shown to produce functional and anatomical benefits when injected into the vitreous of eyes with RVO. However, elevated IOP, formation and progression of cataract have been documented as adverse side-effects. The Standard Care versus Corticosteroid for REtinal Vein Occlusion (SCORE) study concluded that 1mg triamcinolone acetonide intravitreal injection was superior to observation for treating vision loss associated with ME secondary to perfused BRVO[22]. Furthermore, side effects were dose dependent, occurring more frequently with the 4mg injection.

Dexamethasone, on the other hand, is a potent, water-soluble corticosteroid. The dexamethasone intravitreal implant (DEX implant; OZURDEX, Allergan, Inc., Irvine, CA) is composed of a biodegradable copolymer of lactic acid and glycolic acid containing micronized dexamethasone (700 µg). The release of the drug is gradual and spread over months after insertion[23].

Haller *et al* reported the conclusions of the Global Evaluation of implaNtable dExamethasone in retinal Vein occlusion with macular edemA (GENEVA) trial: the implant can both reduce the risk of vision loss and actually promote visual improvement in eyes with ME secondary to BRVO or CRVO[21]. Moreover, single treatment with DEX implant had a favorable safety profile over 12 months. Repeated injections had a similar safety profile, with the exception of more frequent cataract progression[24].

Retrospective studies built on the safety studies by reporting the functional and anatomical improvement of repeated DEX implants[25]. However, the authors comment on the fact that anatomical improvements in CRT don't always result in BCVA improvements, probably because of ischemia and irreversible tissue damage caused by a long duration of edema before treatment[25]. Therefore, reports documenting a better response of both BRVO and CRVO patients treated early after the emergence of symptoms seem reasonable[10,11,26].

Nowadays many patients are being treated with anti-VEGF injections as a first line treatment. Clinical studies have been published on the functional and anatomical results of using combination therapy (anti-VEGF and DEX implant): not only are improvements seen in BCVA and CRT, but also a reduced number of injections is required to achieve those results[25,27]. In fact, some groups suggest that combining the DEX implant with anti-VEGF therapy may provide better vision than monotherapy[28].

The authors aim to analyze the safety profile of the DEX implant in patients with BRVO and CRVO both in treatment naïve patients as well as in previously treated eyes.

MATERIAL AND METHODS

We conducted a retrospective study of patients with BRVO and CRVO treated with one or more DEX implants from January 2011 through August 2015 at a tertiary center, São João Hospital Center, Porto – Portugal. This study respected the principles of the Helsinki declaration.

Medical records were reviewed and the patients that met the following inclusion criteria were selected: diagnosis of RVO (BRVO or CRVO) with secondary ME; central foveal thickness (CFT) >250 µm on spectral domain optical coherence tomography (SD-OCT); received at least one DEX implant and had follow-up data for a minimum duration of 3 months (12±2 weeks) after the first injection. Patients were excluded if the area of capillary nonperfusion on the fluorescein angiography was bigger than five disks, had optic disk, retina, iris or angle neovascularization, or had any signs of ocular infection.

Data was collected from patient charts on medical history prior to DEX implant injection and on ocular data from several visits: visit 1 – baseline; first injection visit or subsequent DEX implant injection visits; visit 2+ – post-injection follow-up visits (2-26 weeks after each DEX implant injection or until the next DEX implant injection). Any ocular procedures performed following DEX implant injection (eg: laser photocoagulation, cataract surgery, injection of anti-VEGF or triamcinolone acetonide) were noted.

The DEX implant was administered in accordance with the manufacturer's instructions using the 22-gauge applicator device provided. (More information available at http://www.allergan.com/assets/pdf/ozurdex_pi.pdf).

Safety assessment

In order to assess the safety of the procedure, the authors monitored changes in IOP, use of IOP-lowering medications, incidence of glaucoma and glaucoma surgery requirement during the 6-month period following the DEX implant injection. Steroid response was defined with IOP elevations of >5 mmHg from baseline.

Furthermore, the development as well as the progression of cataract and cataract surgery were reported.

Other adverse events such as endophthalmitis, traumatic lens injury, retinal tear or retinal detachment were investigated.

Efficacy assessment

Efficacy was assessed by calculating the peak median change in BCVA on follow-up visits between 4 and 26 weeks following treatment. Central retinal thickness was

evaluated with Heidelberg SPECTRALIS® SD-OCT (Heidelberg Engineering Inc, Heidelberg, Germany) which was obtained at baseline and on follow-up visits, 2–26 weeks after the DEX implant injection.

Statistical analysis was performed using SPSS (IBM SPSS Version 21, IBM, New York, NY, USA). A nonparametric test (Wilcoxon signed-rank test) was used for paired comparisons (BCVA and CRT). The Student paired t-test was used to evaluate the changes in IOP throughout follow-up. A Mann Whitney U test was used to compare the BRVO and CRVO groups; and previously treated versus treatment naïve patients. A value of $p<0.05$ was considered statistically significant.

RESULTS

Baseline demographics

Twenty-four eyes from 24 patients were included in our study, 14 being female (58%). Mean age was 66.5 years (range: 49 – 95 years). 41.7% of patients were under treatment for arterial hypertension, 12,5% for dyslipidemia and only 8.3% were type 2 diabetic.

54.2% of patients had BRVO and 45.8% CRVO. Patients were diagnosed with CRVO or BRVO 1 to 16 months prior to the DEX implant. Interval between diagnosis and first treatment (eg: anti-VEGF or triamcinolone injection) was 1 to 9 months.

Twenty patients (83.0%) were phakic prior to the DEX implant injection. Five patients (20.8%) were on antihypertensive drops prior to enrollment in the study. Baseline clinical characteristics are presented in Table 1.

Median BCVA at the first visit was 20/225 (range: 20/2000 to 20/32). Median CRT was 552 µm (range: 340 – 986).

Prior treatments and ocular procedures

75% of patients had been previously treated for RVO related ME. Anti-VEGF intravitreal injections were the most frequent treatment choice (66.7%). Laser was used to treat 58.3% of patients prior to the DEX implant. Only 25% of patients were previously treated with intravitreal triamcinolone acetonide injection. 55.3% had combination therapy, most frequently laser and anti-VEGF injections (37.5%). 3 patients (12.5%) were vitrectomized for vitreous hemorrhage.

Six patients (25%) had the DEX implant as first therapy.

Comparison, at baseline, of patients that had previous treatment for ME and treatment-naïve patients did not differ regarding BCVA, CRT and IOP.

Safety

Cataract progression

Mean follow-up time in our series was 727 days (range: 69 – 1606 days). 83% of our patients were phakic at the beginning of the study. No patient developed cataract during follow up. In two patients, however, cataract progression was observed. One of the patients was treated with DEX implant twice but no further progression was documented following the second implant. None of the patients required cataract surgery.

IOP monitoring

Five patients (20.8%) were medicated with antihypertensive drops before the DEX implant. All patients had controlled IOP (<21 mmHg) prior to treatment.

IOP measurement at the first follow up visit (day 30) was 17.1 mmHg (mean), not significantly different (p=0.422) from baseline. By day 60, a mean IOP elevation of 3.53 mmHg was not statistically significant (p=0.069). At day 180, IOP was similar to baseline 16.83 mmHg (mean). IOP changes throughout follow up are illustrated in Figure 1.

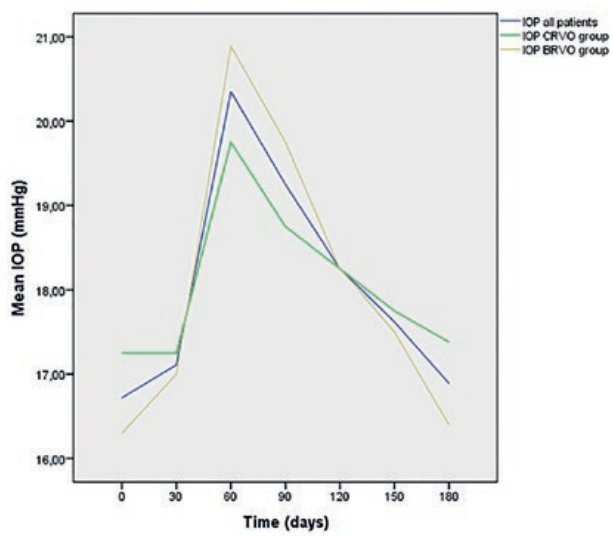

Fig. 1 | Mean IOP changes over a 6-month follow up period for all patients and for the BRVO and CRVO groups. Mean IOP changes are not significant both between groups, and between baseline and follow up visits. IOP intra-ocular pressure, BRVO branch retinal vein occlusion, CRVO central vein occlusion.

A total of seven patients (29.1%) required antihypertensive eye drops due to IOP elevation (IOP>21 mmHg). A steroid response (IOP change ≥ 5mmHg) was documented in five patients (20.8%). Four patients required a second antihypertensive drop and the remaining three

Table 1 | Clinical Characteristics of Patients with Retinal Vein Occlusion.

Case	Age (years)/ Sex	Diagnosis/ Study eye	Systemic Disease(s)	Previous treatment	Lens status	Glaucoma/ OHT
1	56/ F	BRVO / OD	AHT	Anti-VEGF, TA	Phakic	No
2	95/ F	BRVO / OD	Dyslipidemia	Anti-VEGF, TA, LASER	Pseudophakic	No
3	60/ F	CRVO / OD	None	Anti-VEGF, TA	Phakic	Yes
4	59/ F	CRVO / OS	AHT	None	Phakic	Yes
5	50/ M	CRVO / OD	None	PPV	Phakic	No
6	76/ M	BRVO / OD	AHT, DM, dyslipidemia	Anti-VEGF, LASER	Pseudophakic	No
7	49/ M	BRVO / OS	None	Anti-VEGF, LASER	Phakic	No
8	53/ F	BRVO / OS	None	Anti-VEGF, LASER	Phakic	No
9	57/ M	BRVO / OS	AHT	None	Phakic	No
10	59/ M	BRVO / OS	None	PPV	Pseudophakic	Yes
11	61/ F	CRVO / OS	AHT	TA	Phakic	Yes
12	58/ M	CRVO / OS	AHT	None	Phakic	No
13	67/ M	CRVO / OD	None	None	Phakic	No
14	84/ F	CRVO / OS	None	PPV	Pseudophakic	No
15	73/ M	CRVO / OD	AHT, dyslipidemia	Anti-VEGF, LASER	Phakic	Yes
16	74/ F	BRVO / OD	None	Anti-VEGF, TA	Phakic	No
17	73/ F	BRVO / OD	None	Anti-VEGF, LASER	Phakic	No
18	70/ F	BRVO / OD	None	Anti-VEGF, LASER	Phakic	No
19	68/ F	BRVO / OD	AHT	Anti-VEGF, LASER	Phakic	No
20	80/ M	CRVO / OD	AHT	None	Phakic	No
21	73/ F	BRVO / OS	AHT, DM	Anti-VEGF, LASER	Phakic	No
22	66/ M	CRVO / OD	None	None	Phakic	No
23	64/ F	CRVO / OD	None	Anti-VEGF, LASER	Phakic	No
24	70/ F	BRVO / OD	None	Anti-VEGF, TA, LASER	Phakic	No

F - female, M - male, BRVO - branch retinal vein occlusion, CRVO - central retinal vein occlusion, OD - right eye, OS - left eye, AHT - arterial hypertension, DM - diabetes mellitus, VEGF - vascular endothelial growth factor, PPV - pars plana vitrectomy, TA - triamcinolone acetonide.

patients reached IOP control with the introduction of ocular hypotensive therapy.

Medical records of the patients that had a hypertensive response were reviewed. One patient had a previous transitory hypertensive response to triamcinolone, three patients were treated with bevacizumab (1, 3 and 4 injections, respectively) without an IOP change and a patient had previously been vitrectomized. Two patients were treatment naïve.

None of the patients required laser treatment or surgery to control IOP.

Adverse effects

In our series we did not observe the following adverse effects: endophthalmitis, traumatic lens injury, retinal tear or retinal detachment.

Efficacy

Visual acuity outcome

The biggest improvement of median BVCA was observed by day 60. Although vision improved from 20/225 at baseline, to 20/125, this improvement was not statistically significant ($p>0.05$).

Central retinal thickness

A significant reduction in CRT was observed from baseline and throughout follow-up. The most pronounced and significant difference was reported at day 60 following the DEX implant, when median CRT was 304 μm (p=0.002).

Subgroup analysis

CRVO versus BRVO

As far as procedure safety is concerned cataract progression occurred in one patient in both groups. Furthermore, IOP changes were not significantly different between CRVO and BRVO at day 30, 60 and 180 (Figure 1).

We found that BRVO patients had a significant improvement in BCVA while CRVO patients did not (p=0.033). Where anatomic changes are concerned, both groups displayed a significant CRT improvement from baseline up until day 180 (p<0.05). The CRT response to treatment was similar for CRVO and BRVO patients.

Previously treated patients *versus* treatment naïve patients

Initial median BCVA and CRT was similar in both previously treated patients and treatment naïve patients. Mean IOP mas not statistically different at baseline in both groups. After treatment with the DEX implant no significant difference was observed between groups in median BCVA, median CRT and mean IOP. In previously treated patients, the median CRT improvement was significant following the DEX implant (p=0.004). A significant median CRT improvement was not observed in the treatment naïve group (p=180).

Vitrectomized patients *versus* non-vitrectomized patiens

Cataract progression was observed in one vitrectomized patient. The other two patients were pseudophakic.

No significant IOP changes were documented at day 30 (p=0.197), 60 (p=0.288) or 180 (p=0.225). However, one patient, who was previously on antihypertensive drops, required a second drug to achieve IOP<21 mmHg.

Throughout follow up, the median BCVA in vitrectomized and in non-vitrectomized patients was not statistically different (p>0.05). Likewise, the anatomical changes were similar between groups (p=1.000).

Subsequent treatments

Eight patients received no further treatment for ME. The reasons for that included ME resolution, absence of response to multiple treatments (CCT, anti-VEGF and laser) or the patient declined an alternative treatment.

In our series, patients were treated multiple times with DEX implants: it was ministered twice in four patients; two patients received a total of three DEX implants; and one patient was treated five times. IOP changes were similar for the first and subsequent DEX implants (p>0.05). Cataract progression was reported in one patient treated twice with DEX implant. No further progression was observed after the second implant. Median BCVA changes and CRT response was similar for subsequent treatments.

Anti-VEGF was suggested as an alternative treatment for seven patients and two patients required laser to treat ischemia.

DISCUSSION

This study evaluated the safety of the DEX implant for ME secondary to RVO in treatment-*naïve* patients and in previously treated patients.

The adverse effects commonly associated with CCT: development and progression of cataract; and IOP elevation were analyzed in the study group. At the beginning of our study 83% of patients were phakic. Following the DEX implant, progression of cataract was observed in two patients (8.3%). Previous studies have reported a similar percentage of cataract progression[29]. However, higher percentages have been documented for combination therapy, namely DEX implant and anti-VEGF therapy (bevacizumab and/or ranibizumab)[28]. Most of our patients had undergone previous treatment for RVO (e.g. anti-VEGF injections, laser and vitrectomy) but, only in a minor group cataract progression was verified.

With regards to IOP, 29.1% of patients presented with IOP>21 mmHg following the DEX implant. 20.8% witnessed an IOP elevation of ≥5 mmHg, defined as a steroid response. These results were similar to those reported in previously published studies: 9% to 30.1% cases of ocular hypertension after DEX injection[29]. In our series, the 3.53 mmHg elevation of IOP, that occurred by day 60 following injection, did not reach statistical significance and the IOP was controlled with antihypertensive eye drops. None of the patients required glaucoma surgery. Evidence from clinical studies have shown that IOP elevation occurring after DEX implant injections is usually transient, as we showed in our series, and it is usually moderate in severity and may be managed with IOP-lowering medication[21,24].

In the subgroup of patients that received multiple DEX implants no further cataract progression was observed. Moreover, the IOP elevation followed the same pattern as with the first implant. The safety profile of the DEX

implant was also confirmed in patients previously treated with laser, CCT, anti-VEGF, vitrectomy or a combination of these. These results are in line with those by Singer *et al*[28]. A recent study that aimed to evaluate the safety of repeat injection of DEX implant reported a statistically significant increase in IOP after each of the first two DEX implant injections. However, the incidence of new patients with ocular hypertension decreased sequentially to 26%, 21 % and 17% following the first, second and third DEX implant injections, respectively[30]. Contrary to the results of Haller *et al*[24], cataract progression was not documented more frequently in patients who received more than one DEX implant, even though our series is small.

It has been suggested that sequential therapy with an anti-VEGF injection followed by a DEX implant results in faster gains in BCVA in BRVO patients than the DEX implant monotherapy[31]. Most of our patients, 75%, were previously treated with anti-VEGF, triamcinolone, laser or were previously vitrectomized. Although a significantly improved BCVA was not observed in this group, the CRT improvement was significant (p=004). This finding may be partially explained by an initially higher median CRT (although not significantly higher than the median CRT for the treatment naïve patients).

The most pronounced improvement in BCVA and CRT in our series was reported by day 60, which is in accordance with published results[24]. Our study group did not reach a significant improvement in BCVA. Longer mean duration of ME prior to the DEX implant, with consequent irreversible damage to the retina, might explain these results. The elderly population, the combination of comorbidities, the worse BCVA at baseline and the time from diagnosis to treatment makes our study population similar to the SHASTA study. Even though this study reported functional improvement, as well as anatomical[28], ours did not. To further support the hypothesis of the importance of the duration of ME, Dugel *et al* subanalyzed the treatment naïve patients in the SHASTA study and reported greater improvement in BCVA for RVO-associated ME with 4.9 months duration versus the average 24 months ME duration in the SHASTA study. It supports our findings of multiple DEX implants being a safe therapeutic option for ME secondary to RVO treatment[32].

Anatomic improvements in CRT were achieved at follow up visits after the DEX implant insertion. The biggest change in median CRT was observed at day sixty, 304 µm (p=0.002). Complete resolution of ME (CRT<250 µm) at two months was observed in six patients (25.0%). Our series corroborates results from previous clinical studies that state that the DEX implant, whether in monotherapy or in combination therapy, reduces CRT significantly[24]. The optimal treatment interval for DEX implant is yet to be determined. Although some authors have reported efficacy of the implant up until six months, most studies document a shorter lifespan[24,33].

The subgroup analysis revealed that the use of the DEX implant in BRVO and CRVO was safe but only anatomically effective. CRT response was significant for both BRVO and CRVO patients. BCVA improvements, however, reached statistical significance in the BRVO group only. Conflicting results have been published concerning the best treatment regimen for ME due to BRVO. While the COMRADE--B study concluded that ranibizumab was superior to the DEX implant in improving BCVA over a 6-month period[34], Reigner et al reported that corticosteroids, namely the DEX implant, improved CRT more than ranibizumab, while both drugs provided similar improvements in BCVA[35].

This study has the limitations inherent to nonrandomized, observational, chart review studies. The direct comparison with previous case series is also difficult due to variability in inclusion criteria and demographic characteristics. Future definition of algorithms and ideal timing of treatment of BRVO and CRVO should be investigated.

In summary, the results of this study demonstrate that the clinical use of two or more DEX implants, either alone or in combination with common adjunctive RVO treatments, is safe in the treatment of ME secondary to RVO. Although over 80% of our patients were phakic, cataract progression was negligible (8,3%). Moreover, IOP elevation wasn't statistically significant throughout follow up – IOP control was achieved with medical therapy. Reductions in CRT were seen after each subsequent DEX implant and no new adverse events occurred with the use of multiple implants. Contrary to previous reports visual acuity did not significantly improve with treatment, except in the BRVO group.

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REFERENCES

1. Mitchell P, Smith W, Chang A. Prevalence and associations of retinal vein occlusion in Australia. The Blue Mountains Eye Study. Archives of ophthalmology (Chicago, Ill : 1960). 1996;114(10):1243-7.
2. Yau JW, Lee P, Wong TY, Best J, Jenkins A. Retinal vein occlusion: an approach to diagnosis, systemic risk

factors and management. Internal medicine journal. 2008;38(12):904-10.
3. Klein R, Klein BE, Moss SE, Meuer SM. The epidemiology of retinal vein occlusion: the Beaver Dam Eye Study. Transactions of the American Ophthalmological Society. 2000;98:133-41; discussion 41-3.
4. Natural history and clinical management of central retinal vein occlusion. The Central Vein Occlusion Study Group. Archives of ophthalmology (Chicago, Ill : 1960). 1997;115(4):486-91.
5. McIntosh RL, Rogers SL, Lim L, Cheung N, Wang JJ, Mitchell P, et al. Natural history of central retinal vein occlusion: an evidence-based systematic review. Ophthalmology. 2010;117(6):1113-23.e15.
6. Antonetti DA, Barber AJ, Khin S, Lieth E, Tarbell JM, Gardner TW. Vascular permeability in experimental diabetes is associated with reduced endothelial occludin content: vascular endothelial growth factor decreases occludin in retinal endothelial cells. Penn State Retina Research Group. Diabetes. 1998;47(12):1953-9.
7. Campochiaro PA, Hafiz G, Shah SM, Nguyen QD, Ying H, Do DV, et al. Ranibizumab for macular edema due to retinal vein occlusions: implication of VEGF as a critical stimulator. Molecular therapy: the journal of the American Society of Gene Therapy. 2008;16(4):791-9.
8. Argon laser photocoagulation for macular edema in branch vein occlusion. The Branch Vein Occlusion Study Group. American journal of ophthalmology. 1984;98(3):271-82.
9. Evaluation of grid pattern photocoagulation for macular edema in central vein occlusion. The Central Vein Occlusion Study Group M report. Ophthalmology. 1995;102(10):1425-33.
10. Brown DM, Campochiaro PA, Bhisitkul RB, Ho AC, Gray S, Saroj N, 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(8):1594-602.
11. Campochiaro PA, Brown DM, Awh CC, Lee SY, Gray S, Saroj N, 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(10):2041-9.
12. Heier JS, Campochiaro PA, Yau L, Li Z, Saroj N, Rubio RG, et al. Ranibizumab for macular edema due to retinal vein occlusions: long-term follow-up in the HORIZON trial. Ophthalmology. 2012;119(4):802-9.
13. Brown DM, Heier JS, Clark WL, Boyer DS, Vitti R, Berliner AJ, et al. Intravitreal aflibercept injection for macular edema secondary to central retinal vein occlusion: 1-year results from the phase 3 COPERNICUS study. American journal of ophthalmology. 2013;155(3):429-37.e7.
14. Korobelnik JF, Holz FG, Roider J, Ogura Y, Simader C, Schmidt-Erfurth U, et al. Intravitreal Aflibercept Injection for Macular Edema Resulting from Central Retinal Vein Occlusion: One-Year Results of the Phase 3 GALILEO Study. Ophthalmology. 2014;121(1):202-8.
15. Campochiaro PA, Clark WL, Boyer DS, Heier JS, Brown DM, Vitti R, et al. Intravitreal aflibercept for macular edema following branch retinal vein occlusion: the 24-week results of the VIBRANT study. Ophthalmology. 2015;122(3):538-44.
16. Epstein DL, Algvere PV, von Wendt G, Seregard S, Kvanta A. Benefit from bevacizumab for macular edema in central retinal vein occlusion: twelve-month results of a prospective, randomized study. Ophthalmology. 2012;119(12):2587-91.
17. Epstein DL, Algvere PV, von Wendt G, Seregard S, Kvanta A. Bevacizumab for macular edema in central retinal vein occlusion: a prospective, randomized, double-masked clinical study. Ophthalmology. 2012;119(6):1184-9.
18. Kornhauser T, Schwartz R, Goldstein M, Neudorfer M, Loewenstein A, Barak A. Bevacizumab treatment of macular edema in CRVO and BRVO: long-term follow-up. (BERVOLT study: Bevacizumab for RVO long-term follow-up). Graefe's archive for clinical and experimental ophthalmology = Albrecht von Graefes Archiv fur klinische und experimentelle Ophthalmologie. 2015.
19. Park SP, Ahn JK. Changes of aqueous vascular endothelial growth factor and interleukin-6 after intravitreal triamcinolone for branch retinal vein occlusion. Clinical & experimental ophthalmology. 2008;36(9):831-5.
20. Glanville J, Patterson J, McCool R, Ferreira A, Gairy K, Pearce I. Efficacy and safety of widely used treatments for macular oedema secondary to retinal vein occlusion: a systematic review. BMC ophthalmology. 2014;14:7.
21. Haller JA, Bandello F, Belfort R, Jr., Blumenkranz MS, Gillies M, Heier J, et al. Randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with macular edema due to retinal vein occlusion. Ophthalmology. 2010;117(6):1134-46.e3.
22. Ip MS, Scott IU, VanVeldhuisen PC, Oden NL, Blodi BA, Fisher M, 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. Archives of ophthalmology (Chicago, Ill : 1960). 2009;127(9):1101-14.
23. Bandello F, Parravano M, Cavallero E, Cascavilla ML, Triolo G, Querques L, et al. Prospective evaluation of morphological and functional changes after repeated intravitreal dexamethasone implant (Ozurdex(R)) for retinal vein occlusion. Ophthalmic research. 2015;53(4):207-16.
24. Haller JA, Bandello F, Belfort R, Jr., Blumenkranz MS, Gillies M, Heier J, 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(12):2453-60.
25. Capone A, Jr., Singer MA, Dodwell DG, Dreyer RF, Oh KT, Roth DB, et al. Efficacy and safety of two or more dexamethasone intravitreal implant injections for treatment of macular edema related to retinal vein occlusion (Shasta study). Retina (Philadelphia, Pa). 2014;34(2):342-51.
26. Yeh WS, Haller JA, Lanzetta P, Kuppermann BD, Wong TY, Mitchell P, et al. Effect of the duration of macular edema on clinical outcomes in retinal vein occlusion treated with dexamethasone intravitreal implant. Ophthalmology. 2012;119(6):1190-8.
27. Singer MA, Bell DJ, Woods P, Pollard J, Boord T, Herro A, et al. Effect of combination therapy with bevacizumab and dexamethasone intravitreal implant in patients with retinal vein occlusion. Retina (Philadelphia, Pa). 2012;32(7):1289-94.
28. Singer MA, Capone A, Jr., Dugel PU, Dreyer RF, Dodwell DG, Roth DB, et al. Two or more dexamethasone intravitreal implants as monotherapy or in combination therapy for macular edema in retinal vein occlusion: subgroup analysis of a retrospective chart review study. BMC ophthalmology. 2015;15:33.
29. Chiquet C, Dupuy C, Bron AM, Aptel F, Straub M, Isaico R, et al. Intravitreal dexamethasone implant versus anti-VEGF injection for treatment-naive patients with retinal vein occlusion and macular edema: a 12-month follow-up study. Graefe's archive for clinical and experimental ophthalmology = Albrecht von Graefes Archiv fur klinische und experimentelle Ophthalmologie. 2015.
30. Bakri SJ, Omar AF, Iezzi R, Kapoor KG. Evaluation of multiple dexamethasone intravitreal implants in patients with macular edema associated with retinal vein occlusion. Retina (Philadelphia, Pa). 2015.
31. Iu LP, Zhao P, Yeung IY, Fung NS, Lee JW. Sequential therapy with ranibizumab and dexamethasone intravitreal implant is better than dexamethasone monotherapy for macular oedema due to retinal vein occlusion. 2015;99(2):210-4.
32. Dugel PU, Capone A, Jr., Singer MA, Dreyer RF, Dodwell DG, Roth DB, et al. Two or more dexamethasone intravitreal implants in treatment-naive patients with macular edema due to retinal vein occlusion: subgroup analysis of a retrospective chart review study. BMC ophthalmology. 2015;15:118.
33. Regnier SA, Larsen M, Bezlyak V, Allen F. Comparative efficacy and safety of approved treatments for macular oedema secondary to branch retinal vein occlusion: a network meta-analysis. BMJ open. 2015;5(6):e007527.
34. Hattenbach L-O. Efficacy and Safety of 0.5 mg Ranibizumab compared with 0.7 mg dexamethasone intravitreal implant in patients with branch retinal vein occlusion over 6 months: The COMRADE-B study. Investigative Ophthalmology & Visual Science. 2014;55(13):1830-.
35. Yumusak E, Buyuktortop N, Ornek K. Early results of dexamethasone implant, ranibizumab, and triamcinolone in macular edema due to branch retinal vein occlusion. European journal of ophthalmology. 2015:0.

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