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Research Article

Repeated Intravitreal Dexamethasone Implant for Macular Edema and Serous Macular Detachment due to Naive Branch Retinal Vein Occlusion

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Received: September 14, 2018; **Published:** January 31, 2019

Abstract

Background: To evaluate the effect of intravitreal dexamethasone implant in eyes with treatment naive macular edema and serous macular detachment (SMD) due to branch retinal vein occlusion.

Methods: We retrospectively analysed 35 eyes of 35 patients who received repeated Ozurdex injection with treatment-naive macular edema related with branch retinal vein occlusion. Best corrected visual acuity (BCVA), central macular thickness (CMT), incidence of side effects were recorded.

Results: Of the 35 eyes, 10 (28%) had received 3 consecutive dexamethasone injections and 25 (72%) had received 2 consecutive dexamethasone injections. Mean follow-up time was 12.7 months. Mean time for reinjection was 4.2 months. 62.85% of eyes showed ≥ 3 lines of improvement from baseline BCVA. CMT decreased 589,8 μm to 251,17 μm after 2 consecutive injections and 567,1 μm to 266,9 μm after 3 consecutive injections. SMD regressed completely in all cases after the 2nd injection. No serious adverse effects were observed.

Conclusions: Repeated Ozurdex implantation in macular edema and SMD secondary to branch retinal vein occlusion is an effective method and has good anatomical and functional results in naive patients.

Keywords: *Branch Retinal Vein Occlusion; Dexamethasone; Serous Macular Detachment; Naive Branch Retinal Vein Occlusion*

Introduction

Retinal Vein Occlusion is the second most common retinal vascular disease after diabetic retinopathy. Macular edema due to retinal vein occlusion is a common sight-threatening complication of both branch retinal vein occlusion (BRVO) and central retinal vein occlusion (CRVO).

The pathogenesis of macular edema due to retinal vein occlusion is not fully understood, however it may result from variety of factors, such as inflammatory cytokines (e.g. interleukin-6, prostaglandins), hydrostatic effects due to increased venous pressure, dysregulation of endothelial tight junction proteins and increased vascular endothelial growth factor (VEGF) [1-3]. Anti-VEGF agents and corticosteroids target these pathogenic mechanisms. Corticosteroids affect many inflammatory processes and reduce macular edema; inhibiting the synthesis of VEGF, prostaglandins, and other cytokines, stabilizing endothelial tight junctions, reducing vascular permeability, supressing migration of inflammatory cells [4].

Intravitreal injection of triamcinolone acetonide is effective for treatment of macular edema but has several adverse events (cataract and elevated intraocular pressure) [5,6].

Dexamethasone is a potent, water-soluble corticosteroid that is injected through the pars plana by a single-use applicator (DEX implant; OZURDEX, Allergan, Inc., Irvine, CA). Ozurdex implant consists of a biodegradable copolymer matrix of lactic acid and glycolic acid and the drug-copolymer complex releases total dexamethasone over series of months after injection of the implant through pars plana into the vitreous cavity. It has been used in clinical practice for the treatment of macular edema associated with retinal vein occlusion, non-infectious posterior uveitis, diabetic retinopathy, retinitis pigmentosa and Irvine-Gass syndrome [7-10].

We retrospectively evaluated efficacy and safety of repeated intravitreal Ozurdex for the treatment of macular edema and serous macular detachment (SMD) due to retinal vein occlusion and administered an “as needed” basis.

Materials and Methods

We reviewed the patients with decreased visual acuity secondary to nonischemic BRVO with macular edema who received at least two intravitreal Ozurdex injections at the retina department of Okmeydanı Training and Research Hospital.

Inclusion criteria for our report were:

1. Age > 18 years.
2. Macular edema due to BRVO.
3. Best corrected visual acuity (BCVA) between 20/400 and 20/32 (Snellen equivalent) at baseline examination.
4. Central macular thickness (CMT) > 250 μm, as measured by spectral-domain optical coherence tomography (SD-OCT) at baseline examination.
5. More than 2 consecutive Ozurdex injections during the study period.

Exclusion criteria for our report were:

1. Previous anti-VEGF or any other treatments for BRVO.
2. Any previous surgery in the last 6 months in the study eye.
3. Any other ocular conditions that can influence visual acuity such as diabetic retinopathy, epiretinal membrane, media opacities, vitreomacular traction syndrome.
4. Ocular hypertension or glaucoma history.

In this retrospective study, informed consent was obtained in agreement with the Declaration of Helsinki for research involving human subjects. All necessary authorizations were obtained from the Institutional Review Board of Okmeydanı Research and Training Hospital, İstanbul, Turkey. Demographic data of the pooled patients, duration of BRVO were recorded. At baseline and follow-up, we examined all the patients including BCVA, tonometry, biomicroscopy, fundus examination, SD-OCT (The Cirrus HD-OCT, Carl Zeiss Meditec, Dublin, CA). We performed SD-OCT at baseline, first and every month after each injections. Decreased visual acuity, intraretinal and/or SMD with CMT > 250 μm documented by SD-OCT were decision criteria for retreatment. We measured the height of the SMD (the distance between the outer retinal and the pigment epithelial surface at the fovea) at every visit. Ischemic areas were detected by fundus fluorescein angiography with a Zeiss VISUCAM 500 fundus camera (Carl Zeiss Meditec AG, Jena, Germany). More than 10 disk areas of retinal capillary obliteration were considered as the primary criteria for ischemia.

All the patients were treated with Ozurdex implant in the operatory room under local anaesthesia. After the injections, patients were treated with topical moxifloxacin for 2 weeks. Every month BCVA, CMT, macular edema recurrence, cataract progression, alterations of intraocular pressure (IOP), the proportion of injections with at least 3 lines of BCVA improvement and the proportion of injections exhibiting ≥ 3 lines of BCVA worsening were recorded.

Statistical analyses were performed using Statistical Package for Social Sciences, version 17.0 (SPSS, Inc., Chicago, Ill, USA). Visual acuity values were converted to the LogMar scale for statistical analysis. Friedman tests were conducted to test whether there was a significant change in BCVA and CMT. The Wilcoxon test was performed to test the significance of pairwise difference using Bonferroni correction to adjust for multiple comparisons. P value of less than 0.05 was considered to be statistically significant.

Results

In total, 35 eyes of 35 patients with macular edema secondary to BRVO were enrolled in this retrospective cohort study. All of the eyes were treatment-naive and had at least a minimum 1 year follow-up period. Table 1 shows the demographic characteristics of the subjects. The mean age of patients was 59.2 ± 12.08 years. 54.3% of the patients were male. The mean follow-up period was 12.7 months (median, 12; range, 12-19). The mean duration of macular edema was 2.6 months before the treatment. The mean time for retreatment was 4.2 months and the mean injection number was 2,28 in the follow-up period. Of the 35 eyes, 10 (28%) had received 3 consecutive Ozurdex injections. At baseline, 30 (85.7%) patients were phakic. Only 7 (26.6%) of those were diagnosed as having a cataract progression and only one (3.3%) of them underwent a routine phacoemulsification surgery during the follow-up period. In total, 7 (20%) patients needed to be started on an anti-glaucomatous medication due to elevated intraocular pressure but none of them required a surgical intervention. No cases of retinal detachment, vitreous hemorrhage, or endophthalmitis had been observed in any of these patients.

Age (years)	59.2 ± 12.08
Gender (male [%])	19 [54.3%]
Follow-up period (months[range])	12.7 [12 - 19]
Mean injection number	2.28
Phakic eyes (prior to treatment)	30 [85.7%]
Cataract progression only	7 [26.6%]
Phacoemusification surgery only	1 [3.3%]
Anti-glacomatous theraphy	7 [20%]
Serous macular detachment (number of eyes[%])	22 [62.8%]

Table 1: *Demographic Characteristics of the patients (n = 35).*

The mean BCVA in two consecutive injections group was 1.03 ± 0.53 Logmar at baseline and improved over time. However, as shown in figure 1, only the first injection was associated with a gain in visual acuity ($p< 0.01$ for the comparison of baseline and 1st injection). BCVA remained stable after the 1st injection and there was no statistically significant difference in BCVA between 1st and 2nd injections (post hoc analysis revealed that the p value was 0,351 for the comparison of 1st and 2nd injections). When we consider the patients (n=10) who had received 3 consecutive injections, a similar trend was noticeable, as depicted in figure 2. Only the 1st injection was associated with visual improvement ($p < 0.001$), since the BCVA was found to have been stable after 2nd and 3rd injections ($p = 0.088$, $p = 0.596$, respectively; after Bonferroni correction, p value must be considered < 0.008).

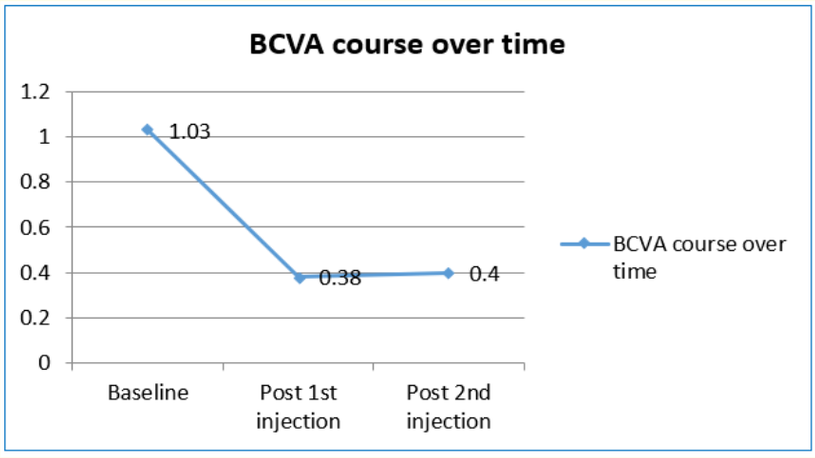

Figure 1: *Mean LogMar BCVA at baseline and after 2 months of each injection of dexamethasone (2 consecutive injections).*

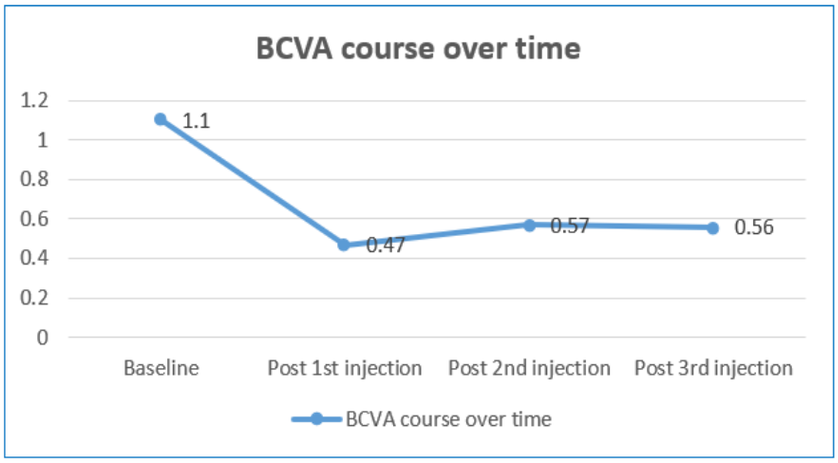

Figure 2: *Mean LogMar BCVA at baseline and after 2 months of each injection of dexamethasone (3 consecutive injections).*

The mean CMT was 589.8 ± 149.8 µm before treatment and had decreased significantly over time. In post-hoc analysis there was a statistically significant difference in CMT between baseline and each of the post-injection time points of the follow-up, as shown in figure 3 (all $p < 0.001$). When we consider the patients (n = 10) who had received 3 consecutive Ozurdex injections, a slightly discrete trend was noticeable, as illustrated in figure 4. Only the 1st injection was associated with CMT improvement ($p < 0.001$). The CMT was found to be slightly lower after 2nd and stable after 3rd injections but not statistically significant ($p = 0.022$, $p = 0.759$, respectively; after Bonferroni correction, p value must be considered < 0.008).

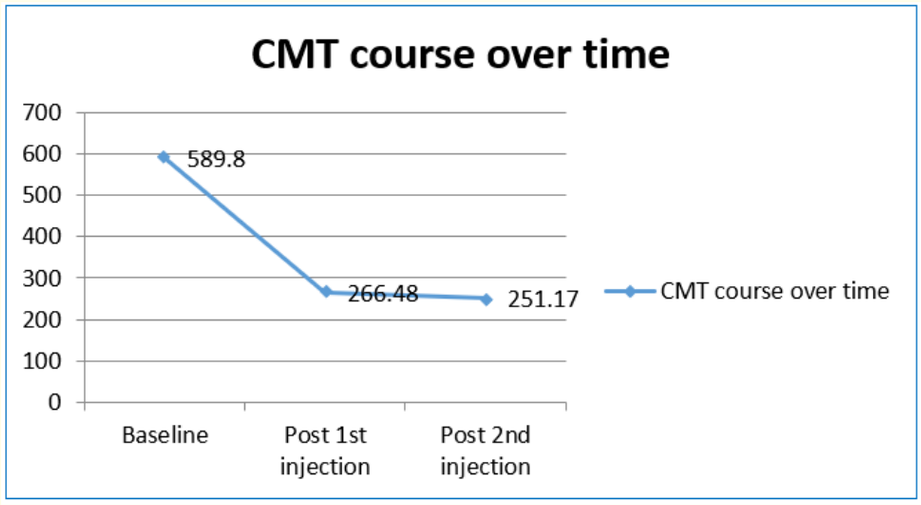

Figure 3: *Mean central macular thickness (µm) at baseline and after 2 months of each injection of dexamethasone (2 consecutive injections).*

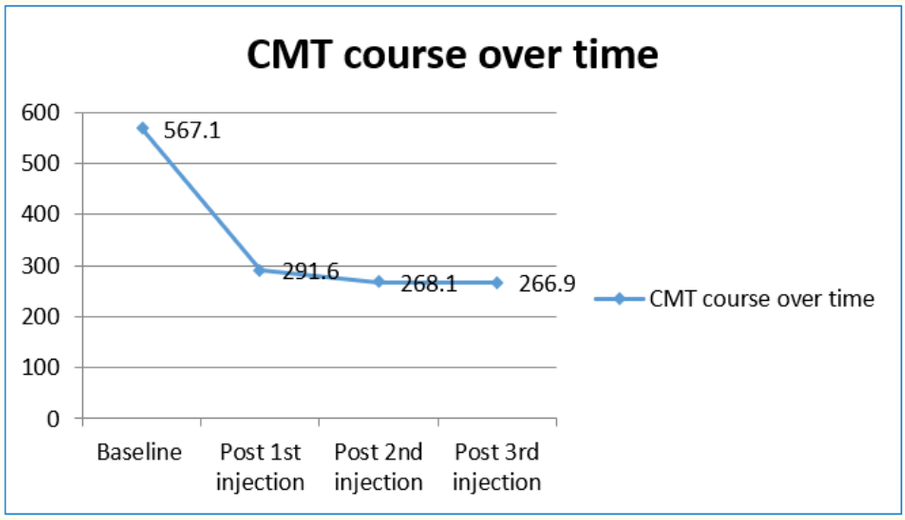

Figure 4: *Mean central macular thickness (µm) at baseline and after 2 months of each injection of dexamethasone (3 consecutive injections).*

62.8% (22 eyes) of the patients had SMD according to the results of the initial examination and it resolved completely in all cases after 2 months of 1st injection. SMD relapsed in 14.2% (5 eyes) of the patients at the 4th month visit and it regressed completely in all cases after the 2nd injection. The mean SMD height was 84.3 ± 52.4 µm at baseline and found 47.2 ± 25.3 µm at the 4th month visit. There was no subretinal fluid observed in any of the patients at the final visit (Figure 5).

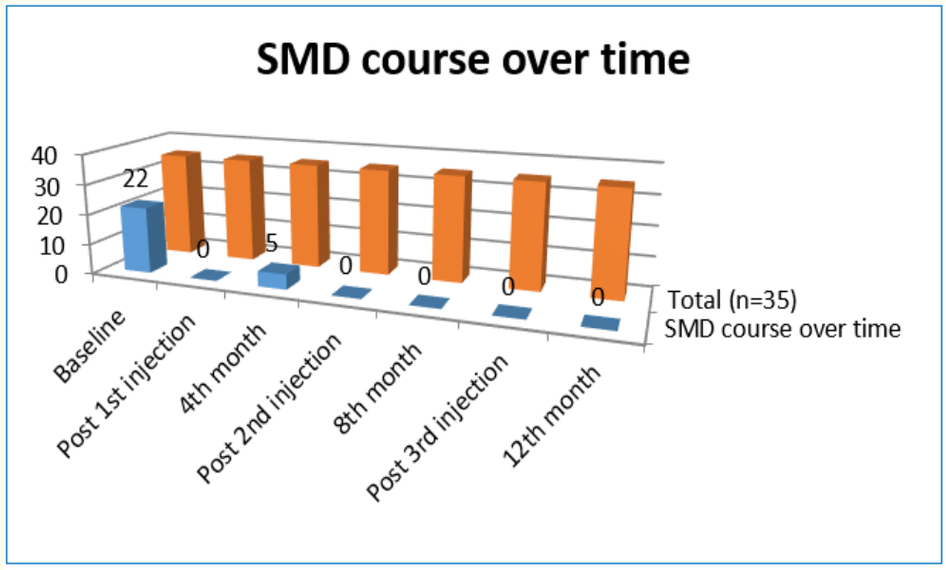

Figure 5: *Serous macular detachment (number of eyes) at all visits and after 2 months of each injection*

Discussion

We designed our study to evaluate the results of repeated Ozurdex implant for macular edema related to BRVO in naive patients. Based on this clinical study results, Ozurdex leads to the stabilization of visual acuity and sustains morphological improvements in the retreated population.

In the GENEVA study interval between two injections are 6 months but a pharmacokinetic and pharmacodynamic report showed peaking efficacy to be in the 1st to 2nd post-treatment month [11]. In the current series, recurrent macular edema due to retinal vein occlusion (RVO) after the first injection occurs nearly in 4 months. Early treatment has better visual gains and morphological results and optimum retreatment interval should be less than 6 months. The mean time between reinjection is 4.2 months in our study. We have found that 62.85% of eyes showed ≥ 3 lines of improvement from baseline BCVA, while there wasn't any ≥ 3 lines of worsening from baseline. These results are better than current studies, for example Coscas., *et al.* found 39% ≥ 3 lines of improvement from baseline BCVA and in Shasta study it was 48.1% [12,13]. Shasta study group reported subgroup analysis in naive patients with retinal vein occlusion and they found ≥ 3 lines of improvement in BCVA from baseline 53% in 3 consecutive injection groups and 59% in 2 consecutive injection groups. CRVO is a more visually disabling disorder but in our study all patients have naive branch retinal vein occlusion [14].

Our visual outcomes were similar as previously reported [15]. The overall mean decrease in CMT values after the 2 consecutive injections was 338 μm and 301 μm after 3 consecutive injections. According to the results of reports taken after 2 months of each injections; only the 1st injection was associated with visual improvement ($p < 0.001$), since the BCVA was found to have been stable after 2nd and 3rd injections. These results can be attributed to our injection timing; we performed the 2nd and the 3rd injections when macular edema occurred. In our study mean time of reinjections and mean duration of macular edema were lower compared to other studies (4.2 and 2.6 months, respectively) [12,13,15].

Corticosteroids regress macular edema by several different mechanisms such as reducing leukocyte adhesion and extravasation, triggering the retina pigment epithelium pump, restoring the function of blood-retinal barrier and downregulating the synthesis of VEGF [16]. Shon., *et al.* have studied the changes of aqueous cytokines after intravitreal triamcinolone versus bevacizumab for macular edema in BRVO and they showed that in the triamcinolone group, levels of IL-6, IL-17, IP-10, platelet derived growth factor (PDGF)-AA and VEGF were reduced significantly but in bevacizumab group, only VEGF was significantly reduced [17]. A study about the changes of aqueous cytokines after Ozurdex injection in RVO revealed a number of inflammatory cytokines that correlated with disease activity in patients with BRVO (MCP-1 and IL 17-E) and CRVO (MCP-1 and IL1-α) [18]. Intravitreal Anti-VEGF agents have short duration effect relatively, and they result in the need for a large number of injections.

There are limited numbers of studies showing the effects of anti-VEGF agents on SMD. Cinal., *et al.* studied the effect of intravitreal bevacizumab on 19 CRVO patients with SMD and found that SMD were resorbed in 16 patients with an average number of 5.9 injections [19].

Several authors showed that the inflammatory cytokines have an important role in the development of SMD and macular edema in diabetic patients. In a study consisting of diabetic patients, inflammatory cytokines were higher in macular edema with SMD than diffuse retinal thickening group but there was no correlation with VEGF levels between these two groups [20,21]. Similarly, Dacheva., *et al.* searched the effects of cytokines in CRVO patients and found that inflammatory cytokines such as IL-6 were correlated with the extension of SMD [22]. In our study SMD regressed in all eyes at the final visit.

The common side effects of Ozurdex injection are transient IOP increasing and cataract progression, but the IOP elevation is generally mild and transient, easy to control and generally doesn't call for glaucomatous surgery. Having mentioned that, cataract surgery is a simple, safe and standard procedure.

In the Geneva study 32.8% of study eyes in the retreated Ozurdex group had at least a 10-mmHg increase in IOP from baseline at some point in the 12-month study [23]. In the Shasta study, IOP (> 10 mmHg) occurred in 32.6% of patients; 29.1% used intraocular pressure-lowering medication to treat increases associated with Ozurdex implant and 1.7% of patients required surgery [13]. The rate of IOP increases was lower in our study; 7 of 35 eyes (20%) needed anti-glaucomatous medication. We excluded the patients that have glaucoma and ocular hypertension history. This could explain our smaller percentage of patients using anti-glaucomatous medication. We didn't need any glaucoma surgeries in this period.

30 eyes were phakic and 7 of them had cataract progression (26,6%) and only 1 needed cataract surgery (%3.3) in our report. In the GENEVA study, cataract progression occurred in approximately 30% of patients after 1 year with 2 Ozurdex injections, but cataract extraction was needed in only 1.3% of the eyes [23]. There are higher cataract progression rates leading to cataract surgery in literature, it could be better explained with longer follow-up time and more injections [15].

Conclusions

Although we have several limitations (uncontrolled, retrospective and a relatively small study population), repeated Ozurdex implantation in macular edema secondary to BRVO is an effective method and has good anatomical and functional results in naive patients. In order to achieve a greater visual gain, when macular edema is present, reinjection may be considered immediately. Reinjections should be performed in 4 - 5 months, with approximately 2 - 3 injections per year. In order to reduce glaucoma complication, the patients that have glaucoma history and ocular hypertension may not be injected.

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Volume 10 Issue 2 February 2019
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