

Safety and Efficacy of Intravitreal Dexamethasone Implant on Macular Edema Due to Retinal Vascular Diseases

Intravitreal Deksametazon İmplantın Retinal Vasküler Hastalıklara Bağlı Maküla Ödeminde Etkinliği ve

Güvenliği

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Abstract

Background: Diabetic retinopathy and retinal vein occlusion are the most common retinal vascular diseases. This study investigates the efficacy and safety of a single dose intravitreal dexamethasone implant injection on macular edema due to retinal vascular diseases.

Materials and Methods: The medical records of 30 (13 with branch retinal vein occlusion-BRVO, 7 with central retinal vein occlusion-CRVO and 10 with diabetic macular edema-DME) patients with macular edema secondary to retinal vascular diseases and at least 6 months follow-up, were evaluated retrospectively. Best corrected visual acuity (BCVA), central macular thickness (CMT), intraocular pressure (IOP) and cataract progression were performed at first week, 1st, 2nd, 3rd and 6th months.

Results: The groups were similar in terms of demographic characteristics ($p>0.05$). In BRVO, there were no statistically significant improvement in BCVA from baseline at all visits ($p>0.05$). There were statistically significant difference at CMT reduction at 1st, 2nd and 3rd months from baseline ($p<0.05$). In CRVO, statistically significant improvement in BCVA was observed at 1st and 2nd months ($p<0.05$). CMT reductions from baseline were statistically significant different at all visits in CRVO group ($p<0.05$). In DME group, BCVA was significantly higher at 2nd and 3rd months from baseline ($p<0.05$) and CMT reductions at 1st, 2nd, 3rd and 6th months were statistically significant ($p<0.05$). The mean IOP values were significantly higher at 1st and 2nd months in all patients. IOP increases were transient and treated with topical antiglaucomatous medicine. The 6-month incidence of cataract in phakic study eyes was 17% and cataracts were extracted at 6th month.

Conclusion: Intravitreal injection of dexamethasone implant is an effective and safe method and provides increased BCVA, decreased CMT in patients with macular edema due to retinal vein occlusions and DME. Transient IOP increase and cataract progression at the end of 6th month are expected side effects.

Keywords: Dexamethasone intravitreal implant, Retinal vein occlusion, Diabetic retinopathy, Macular edema

Öz

Amaç: Diyabetik retinopati ve retinal ven tıkanıklığı en sık görülen retinal vasküler hastalıklardır. Bu çalışmada retinal vasküler hastalıklara bağlı makula ödemi üzerine tek doz intravitreal deksametazon implant enjeksiyonunun etkinliği ve güvenliği araştırılmıştır.

Materyal ve metod: Retinal vasküler hastalıklara bağlı makula ödemi olan ve en az 6 ay takip edilen 30 (13 retinal ven dal tıkanıklığı-BRVO, 7 santral retinal ven tıkanıklığı-CRVO ve 10 diyabetik makula ödemi-DME) hastanın tıbbi kayıtları retrospektif olarak değerlendirildi. En iyi düzeltilmiş görme keskinliği (BCVA), santral makula kalınlığı (CMT), göz içi basıncı (GİB) ve katarakt ilerlemesi birinci hafta, 1., 2., 3. ve 6. aylarda ölçüldü.

Bulgular: Gruplar demografik özellikler açısından benzerdi ($p>0.05$). BRVO'da, tüm vizitlerde BCVA'da başlangıç değerine göre istatistiksel olarak anlamlı bir iyileşme görülmedi ($p>0.05$). Başlangıç değerine göre 1., 2. ve 3. aylarda CMT azalmasında istatistiksel olarak anlamlı fark vardı ($p<0.05$). CRVO'da, 1. ve 2. aylarda BCVA'da istatistiksel olarak anlamlı iyileşme gözlemlendi ($p<0.05$). Başlangıç değerine göre CMT azalmaları, CRVO grubunda tüm vizitlerde istatistiksel olarak anlamlı farklılık gösterdi ($p<0.05$). DME grubunda, BCVA, 2. ve 3. aylarda başlangıç değerine göre anlamlı şekilde daha yüksekti ($p<0.05$) ve 1., 2., 3. ve 6. aylardaki CMT azalmaları istatistiksel olarak anlamlıydı ($p<0.05$). Ortalama GİB değerleri, tüm hastalarda 1. ve 2. aylarda anlamlı şekilde daha yüksekti. GİB artışları geçiciydi ve topikal antiglokomatöz ilaçlarla tedavi edildi. Fakik çalışma gözlerinde 6 aylık katarakt insidansı %17 idi ve 6. ayda opere edildi.

Sonuç: Deksametazon implantının intravitreal enjeksiyonu etkili ve güvenli bir yöntemdir ve retinal ven tıkanıklıkları ve DME nedeniyle makula ödemi olan hastalarda BCVA'da artma, CMT'de azalma sağlar. 6. ayın sonunda geçici GİB artışı ve katarakt ilerlemesi beklenen yan etkilerdir.

Anahtar Kelimeler: Deksametazon intravitreal implant, Retinal ven tıkanıklığı, Diyabetik retinopati, Maküla ödemi

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Introduction

Diabetic retinopathy (DR) and retinal vein occlusion (RVO) are the first and second most common retinal vascular diseases, respectively (1). Regardless of the disease stage, the most common cause of vision loss is macular edema in both conditions. The pathophysiological mechanisms underlying the development of macular edema include internal blood-retinal barrier disruption and pathological elevations in proinflammatory agents that increase vascular permeability (2). Due to their anti-inflammatory, anti-angiogenic, and anti-permeability properties, corticosteroids are a powerful treatment option in many diseases. They act primarily by stabilizing the blood-retinal barrier, reducing exudation, and controlling inflammation (3). Macular edema associated with retinal vascular diseases is treated by intravitreal injection of anti-VEGF agents to neutralize increased levels of VEGF and corticosteroids for their anti-inflammatory effects. Numerous studies demonstrated that intravitreal dexamethasone implant effectively improved best corrected visual acuity (BCVA) and reduced diabetic macular edema (DME) in patients resistant to anti-VEGF treatment (4). Similarly, intravitreal dexamethasone implant is effective in patients with chronic noninfectious uveitis and RVO (5-7).

In this study, efficacy and safety of intravitreal dexamethasone implant in the treatment of DME and macular edema due to RVO was evaluated.

Materials and Methods

Data pertaining to 30 eyes of 30 patients who underwent intravitreal dexamethasone implant injection due to DME or RVO-related macular edema in the Gaziantep University Faculty of Medicine Ophthalmology Department between January 2013 and January 2014 were analyzed retrospectively. This study was conducted by the principles of Declaration of Helsinki. This study was approved by the Gaziantep University Clinical Research Ethics Committee (approval no: 24.03.2014/130, date: March 24, 2014).

Patients with branch retinal vein occlusion (BRVO) comprised Group 1, patients with central retinal vein occlusion (CRVO) comprised Group 2, and patients with DME comprised Group 3. Moreover, patients with DME were classified as having proliferative diabetic retinopathy (PDR) or nonproliferative diabetic retinopathy (NPDR) based on fundus examination and fundus fluorescein angiography (FFA).

Patients who underwent complicated cataract surgery or pars plana vitrectomy, had uncontrolled diabetes ($HbA1c >10\%$), received intravitreal anti-VEGF injection within the last 3 months, or had a history of glaucoma or uveitis were not included in the study.

BCVA was assessed prior to injection using a Snellen chart. A complete ophthalmological examination was done using biomicroscopy. Central corneal thickness was measured using ultrasonic pachymetry (Nidek RKT-7700). Goldmann applanation tonometer was used to measure intraocular pressure (IOP) and corrected IOP was recorded. Each patient was evaluated with FFA before the study. Optic coherence tomography (OCT) (Spectralis OCT, Heidelberg Engineering, Germany) was used to measure central macular thickness (CMT) and quantitative assessment was used to monitor progression of macular edema. Continuity of the IS/OS band and presence of subfoveal exudate were recorded.

Intravitreal dexamethasone implant injection was administered under sterile conditions in the operating room. After establishing topical anesthesia, the intravitreal dexamethasone implant was injected through the superotemporal area using a 22-gauge single-use applicator. The patients were prescribed 0.5% moxifloxacin eye drops for 1 week.

Follow-up examinations were done at 1 day, 1 week, and 1, 2, 3, and 6 months after injection. BCVA, IOP, and CMT on OCT were measured at each visit. Logarithm of Minimal Angle of Resolution (LogMAR) scale was used for statistical analysis of visual acuity converted from Snellen decimals.

Patients with IOP > 21 mmHg during follow-up were treated with topical 2% dorzolamide HCl +0.5% timolol maleate eye drops. Treatment was discontinued when IOP fell below 21 mmHg in subsequent follow-up.

Statistical Analysis

SPSS for Windows version 22.0 package software was used for statistical analyses with statistical significance accepted as $p < 0.05$. The Kolmogorov-Smirnov test was used to test the conformity of continuous variables to normal distribution. For normally distributed variables, Student's t-test was used in comparisons of two groups and ANOVA was used in comparisons of more than two groups. In comparisons of repeated measurements, dependent samples t-test was used for normally distributed variables and Wilcoxon test was used for nonnormally distributed variables. Relationships between categorical variables were tested using chi-square analysis, and those between numerical variables were tested using Spearman's rank correlation coefficient.

Results

A total of 30 eyes of 30 patients were included in the study. The mean age of all patients was 56.3 ± 12.1 (29-80) years. Mean age was 60.4 ± 9.1 (40-72) in Group 1, 52.7 ± 15.6 (29-80) years in Group 2, and 53.6 ± 12.4 (32-66) in Group 3 ($p > 0.05$). There was no significant difference between the groups in sex distribution ($p > 0.05$). Among the diabetic patients, mean duration of DM

was 11.7 ± 5.5 (5-30) years and the mean HbA1c level was 7.5 ± 0.8 (6.2-8.5) mmol/L.

In Group 1, 10 of 13 patients (76.9%) had superior temporal vein occlusion and the other 3 (23.1%) had inferior temporal vein occlusion; 4 patients (30.8%) had ischemic type and 9 (69.2%) had non-ischemic type. Of the 7 patients in Group 2, 2 (28.6%) had ischemic and 5 (71.4%) had non-ischemic type. In Group 3, 5 of 10 patients (50%) had diffuse macular edema, and 5 (50%) had focal macular edema; 2 patients (20%) had mild NPDR and 8 (80%) had signs of PDR.

Before injection, 1 patient in Group 1 had previously undergone focal LPC and 2 patients had undergone intravitreal ranibizumab therapy; 2 patients in Group 2 had undergone focal LPC and 1 had intravitreal bevacizumab treatment; 8 patients with PDR in Group 3 had undergone panretinal LPC treatment and all patients had received 3 doses of intravitreal ranibizumab.

A significant reduction in CMT was detected in Group 1 at 1st, 2nd, and 3rd months; in Group 2 at 1st week, 2nd, 3rd, and 6th months; and in Group 3 at 1st, 2nd, 3rd, and 6th months ($p < 0.05$) (Table 1) (Figure 1). Analysis of the entire patient group showed

that BCVA was significantly improved at 1st, 2nd, and 3rd months compared with pre-injection values ($p < 0.05$) (Table 2). Although subgroup analysis showed no significant increase in visual acuity in Group 1 ($p < 0.05$), BCVA at 6th months was improved in 5 of 13 patients (38.5%), remained unchanged in 1 patient (7.7%), and decreased in 7 patients (53.8%). Of the 7 patients with reduced visual acuity, 4 patients had an increase in CMT compared to pre-injection level and 4 developed cataract. In Group 2, a significant increase in mean BCVA over baseline was observed at 1st and 2nd months ($p < 0.05$). At 6 months, BCVA was increased in 3 of 7 patients (43%), unchanged in 2 patients (28.5%), and decreased in 2 patients (28.5%). Of the 2 patients with decreased visual acuity, 1 had subfoveal exudate and the other showed no change in CMT. In Group 3, a significant increase in BCVA over baseline was observed at 2nd and 3rd months ($p < 0.05$). At 6th months, BCVA was increased in 7 of 10 patients (70%), unchanged in 1 patient (10%), and decreased in patients (20%). Of the 2 patients with reduced visual acuity, 1 developed cataract and the other showed an increase in CMT.

Table 1. Median central macular thickness (CMT) values (μm) before and at 1 day, 1 week, and 1, 2, 3, and 6 months after intravitreal dexamethasone implant injection

Group	Pre-injection	1 week	1 month	2 months	3 months	6 months
Group 1	408.0	320.0	263.0*	267.0*	345.0*	346.0
Group 2	769.0	606.0*	283.0*	252.0*	240.0*	560.0*
Group 3	603.5	529.5	379.5*	257.5*	293.5*	354.5*
All patients	649.0	457.0*	282.5*	257.5*	293.5*	375.0*

*Wilcoxon signed-rank test, $p < 0.05$

Table 2. Median best corrected visual acuity (BCVA) values (LogMAR) before and at 1 day, 1 week, and 1, 2, 3, and 6 months after intravitreal dexamethasone implant injection

Group	Pre-injection	1 week	1 month	2 months	3 months	6 months
Group 1	0.50	0.40	0.40	0.40	0.40	0.50
Group 2	0.70	0.70	0.50*	0.50*	0.70	1.0
Group 3	0.76	0.66	0.70	0.60*	0.60*	0.70
All patients	0.70	0.60	0.50*	0.45*	0.50*	0.70

*Wilcoxon signed-rank test, $p < 0.05$

No significant increase in mean IOP was detected at day 1 or 1 week post-injection, whereas an increase in IOP was detected in 2 eyes (6%) at 1st month, in 6 eyes (20%) at 2nd months, and in 2 eyes (6%) at 3rd months. All eyes in which IOP increase was detected were phakic. Mean IOP at 1st and 2nd months

was significantly higher compared with pre-injection values ($p < 0.05$). For patients with increased IOP, fixed combination topical timolol maleate and dorzolamide HCl eye drops twice a day were recommended. For all patients prescribed antiglaucoma drugs, treatment was discontinued when IOP

was measured below 21 mmHg in follow-up examination. The patients' mean IOP values and changes by month can be seen in Table 3.

Prior to injection, 13 eyes (43.3%) had clear lens, 12 (40%)

had mild cataracts, 3 (10%) had corticonuclear cataract, and 2 (6.6%) had posterior chamber intraocular lens. Six months after injection, 5 of the 28 phakic eyes (17%) had shown cataract progression and undergone cataract surgery.

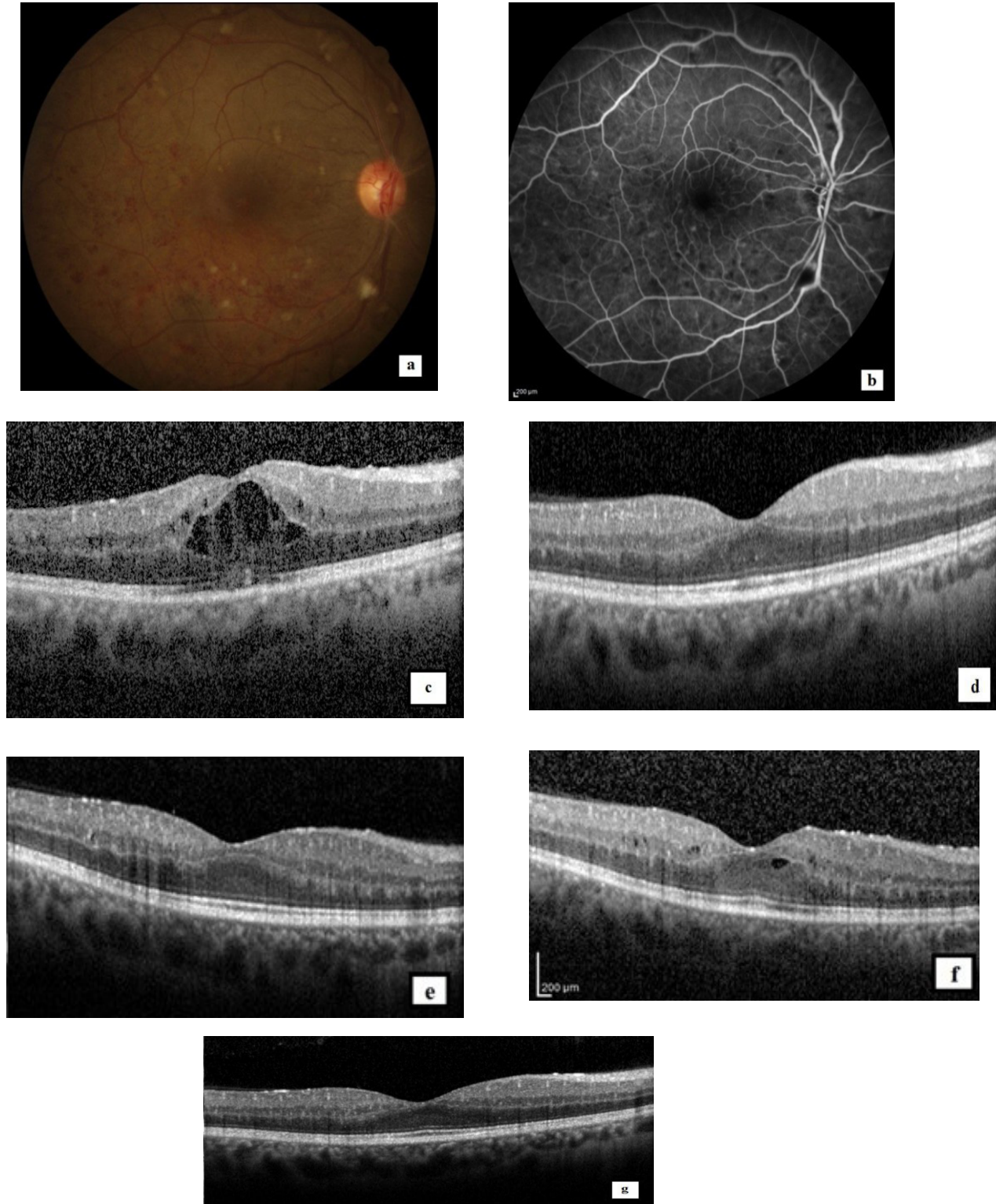


Figure 1. Eye with nonischemic central retinal vein occlusion (CRVO)

a) Pre-injection fundus image, b) Pre-injection fundus fluorescein angiography, c-g) Optical coherence tomography images before and at 1, 2, 3, and 6 months after injection

Table 3. Mean intraocular pressure (IOP) values (mmHg) before and at 1 day, 1 week, and 1, 2, 3, and 6 months after intravitreal dexamethasone implant injection

	Pre-injection	1 month	2 months	3 months	6 months
Group 1	15.9±2.3	17.9±3.9	19.6±4.1*	17.6±4.0	14.5±2.4
Group 2	13.7±2.1	15.2±4.1	16.7±5.7	13.2±1.6	14.8±2.8
Group 3	15.3±3.3	16.4±4.8*	20.1±6.5*	15.0±3.0	14.6±2.7
All patients	15.2±2.7	16.8±4.2*	19.1±5.3*	15.7±3.6	14.6±2.5

*Paired samples t test, p<0.05

Discussion

Corticosteroids have been shown to repair blood-retinal barrier damage by improving endothelial tight junctions and to reduce macular edema through the inhibition of VEGF and pro-inflammatory cytokines (8). Intravitreal triamcinolone has proven efficacy and safety (9).

The dexamethasone intravitreal implant (Ozurdex; Allergan, Inc., Irvine, CA) is a slow-release form that was approved by the US Food and Drug Administration (FDA) in 2009 for use in the treatment of macular edema due to RVO. It is also used in the treatment of DME and uveitic macular edema. According to the results of pharmacokinetic and pharmacodynamic studies, dexamethasone reaches its highest concentration in the vitreous and retina in 60 days and continues to be released up to 6 months after injection (10).

All patients in our study showed a significant increase in median BCVA (LogMAR) at 1st, 2nd, and 3rd months compared with pre-injection values. After 6 months, BCVA was increased in 15 (50%), unchanged in 4 (13%), and decreased in 11 (37%) of the 30 patients. Compared to pre-injection values, visual acuity improved by 2 lines or more in 26.6% of the patients at 1st week, 40% at 1st month, 46.7% at 2nd months, 50% at 3rd months, and 43.4% of the patients at 6th months.

No significant increases in visual acuity compared to pre-injection values were detected in the BRVO group at any of the follow-up visits. BCVA at 6th months was increased in 5 of 13 patients (38%), unchanged in 1 patient (8%), and decreased in 7 patients (54%). In the GENEVA pilot study, BCVA was improved in 46% of patients at 6th months (11). We attribute the lack of significant visual improvement in the BRVO group in our study to progressive cataract that required surgery in 4 eyes (30%) and ischemic-type BRVO in 4 eyes (30%). The CRVO group showed a significant increase in BCVA over pre-injection values at 1st and 2nd months. After 6th months of follow-up, BCVA had improved in 3 (42%) of 7 patients but remained unchanged in 2 patients (29%) and declined in 2 patients (29%).

In the DME group, BCVA at 2nd and 3rd months was significantly improved compared with pre-injection values. At 6th months,

BCVA was increased in 7 (70%) of 10 patients, unchanged in 1 patient (10%), and decreased in 2 patients (20%). The better outcomes in the DME group compared with the other groups may be due to prior treatment with three doses of ranibizumab in the DME eyes and the additive effect of ranibizumab. Similar to our study, a significant increase in BCVA compared with pre-injection values was detected at 2nd months in 16 patients who received dexamethasone implant for DME that did not respond to 3 consecutive monthly intravitreal injections of 1.25 mg anti-VEGF (12).

Among all patients, the median CMT value pre-injection was 649.0 µm, while mean post-injection CMT was 457.0 µm at 1st week, 282.5 µm at 1st month, 257.5 µm at 2nd months, 293.5 µm at 3 months, and 375.0 µm at 6 months. CMT was significantly lower than pre-injection values at all follow-up time points.

Mean CMT in the DME group was 594.0±163.5 µm before injection, and a significant decrease was detected at post-injection 1st, 2nd, 3rd, and 6th months. In our study, follow-up examinations were not conducted between 3rd and 6th months and an increase in mean CMT was detected at 6th months. There are studies in the literature reporting that CMT values increased at 4th months after injection (13-16). In a study comparing the efficacy of intravitreal bevacizumab and intravitreal dexamethasone implant in DME, a significantly greater decrease in CMT at 12th months was observed in the dexamethasone implant group compared to the bevacizumab group. Mean number of injections was 2.7 in the dexamethasone group and 8.6 in the bevacizumab group (17). Based on this information, it was concluded that intravitreal dexamethasone implant reduced the number of injections in the treatment of DME. Inconsistent with this study, a meta-analysis showed that patients who received dexamethasone implant required fewer injections in comparison to those received anti-VEGF treatment (18).

In our study, improved BCVA was seen in 20% of the patients in the BRVO and CRVO groups at 1st week and continued at the same rate at 6th months. A multicenter study evaluated the onset and duration of BCVA gain of ≥15 letters after Ozurdex® injection in patients with CRVO- or BRVO-related macular edema. At first week, 10.3% of the patients treated with dexamethasone

implant showed BCVA gains of ≥ 15 letters and 27.2% had gains of ≥ 10 letters. The interval between first and last observation of ≥ 15 letters BCVA gain was 70 days (19). Yap et al. reported a significant visual acuity change at 30 days compared to baseline (20). Consistent with the literature, we found that the dexamethasone implant took effect after 1 week. Although the DME group in our study showed no significant increase in the BCVA or decrease in CMT at first week, Pacella et al. (13) reported a reduction in CMT on post-injection day 3.

In our study, there was an IOP increase of 5 mmHg or more in 2 eyes (6%) at 1 month, 6 eyes (20%) at 2 months, and 2 eyes (6%) at 3 months, and the increase was significant at 1 and 2 months compared to pre-injection values. At 2 months, IOP was increased 10 mmHg or more in 2 eyes (6.6%). IOP elevation was not associated with neovascular glaucoma in any of the patients, and the increase was attributed to the dexamethasone implant. Neves et al. (21) reported that increase of IOP was transient and manageable with topical treatment. Similarly, in our study, all patients with increased IOP responded to treatment with topical antiglaucoma medication, and none required laser or surgical procedures to reduce IOP. These results indicate that at 60 days, when the intravitreal dexamethasone concentration reaches its maximum level, IOP shows a significant increase, but this increase is transient and responds to medical treatment. Inconsistent with other studies the development of new cataract or worsening of pre-existing cataract is a common complication associated with dexamethasone implant injection (22). In our study, five (17%) of 28 phakic eyes exhibited cataract progression during the follow-up period and underwent phacoemulsification. Of the 28 phakic eyes, mild cataract was present in 12 eyes and corticonuclear cataract in 3 eyes before dexamethasone implant. Mayer et al. (23) reported the presence of mild cataract in 10 of the 11 phakic eyes in their BRVO group, while the other eye had a clear lens. At 1 year, the mean number of injections was 1.9 and 8 eyes (72%) had undergone cataract surgery. Based on these results, the authors concluded that the presence of cataract before injection is an important factor in patient selection.

At the end of our study, 16 patients with CMT ≥ 350 μ m at 6 months received a second dexamethasone implant injection. As this study was retrospective and there were no follow-up examinations between 3 and 6 months, determining re-injection time was problematic. Although there were 12 patients with CMT ≥ 350 μ m at 3 months, postponing reinjection until 6 months as in the pilot study is acceptable considering that the intravitreal dexamethasone implant is effective at low doses for up to 6 months. In fact, CMT continued to decrease in 4 (33%) of 12 patients who had CMT >350 μ m at 3 months and fell below 350 μ m in 2 patients (16.6%), who did not undergo re-injection. Mayer et al. (23) reported that the mean re-injection time was 17.5 ± 4.2 weeks in the BRVO group, and 17.6 ± 4.2 weeks in the CRVO group. In our study, a second dexamethasone implant was needed in 6 of the 13 eyes (46%) in the BRVO group, 5 of the 7

eyes (71%) in the CRVO group, and 5 of the 10 eyes (50%) with DME. The relatively greater need for re-treatment in the CRVO group may be attributable to the larger area of blocked venous drainage and subsequently greater VEGF increase.

Our study is not without limitations. Firstly, the follow-up time is short, but we aimed to investigate the efficacy and safety in a short time period. Secondly, a limited number of patients were included who received no previous anti-VEGF treatment before enrollment in the study. Thirdly, there was no control group as we solely investigated the results of a single dose dexamethasone implant injection.

Conclusion

In conclusion, the intravitreal dexamethasone implant is a safe and effective method for the treatment of DME and RVO-related macular edema. Dexamethasone implant injection leads to reduced CMT and improved BCVA. Intravitreal, slow-release dexamethasone induces treatable and transient IOP elevation that emerges in the second month, and that promotes cataract progression at 6 months.

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Literature Review: E.Ö.

Desig E.C., E.Ö.

Data acquisition: E.Ö.

Analysis and interpretation: E.C., E.Ö.

Writing manuscript: E.Ö.

Critical revision of manuscript: E.Ö.

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