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An Evaluation of the Efficacy of Intravitreal Dexamethasone Implant in Treatment-Naive and Treatment-Resistant Diabetic Macular Edema Patients: A Retrospective Research

İntravitreal Deksametazon İmplant Etkinliğinin Naif ve Tedaviye Dirençli Diyabetik Makular Ödem Hastalarında Değerlendirilmesi: Bir Retrospektif Çalışma

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ABSTRACT Objective: To evaluate the effectiveness of single-dose intravitreal dexamethasone implant in treatment-resistant and -naive diabetic macular edema patients. **Material and Methods:** Twenty-five eyes of 18 diabetic patients receiving intravitreal dexamethasone between January 2017 and March 2020 were included in the study. Changes in best corrected visual acuity (BCVA), intraocular pressure, and retinal and choroidal thickness were determined before, and 1, 4, and 6 months after treatment. **Results:** Eleven of the 25 eyes had not previously received any anti-vascular endothelial growth factor injection, while the other 14 eyes had received a mean 9.28±6.83 anti-vascular endothelial growth factor injections. Initial BCVA was 0.81±0.46 logMAR, compared to 0.65±0.44 logMAR at 1 month, 0.66±0.45 logMAR at 4, and 0.78±0.44 logMAR at 6. While a significant difference was observed between initial and 1st month BCVA (p=0.005) a statistically significant difference was not observed between initial and 6th month BCVA values (p>0.05). Mean retinal thickness was 490.56±186.56 µm at baseline, 301.24±139.63 µm at 1 month, 304.84±129.97 µm at 4 month and 378.44±212.33 µm at 6 month. Retinal thickness decreased significantly at 1, 4, and 6 months compared to baseline (p<0.05). Initial mean subfoveal choroidal thickness was 300.32±32.78 µm, decreasing to 263.68±30.87 µm at 1 month, 258.44±31.5 µm at 4 month, and 268.20±40.10 µm at 6 month. The changes observed in choroidal thickness at 1, four and 6 months compared to baseline were statistically significant (p<0.05). A statistically significant difference in retinal thickness between patients with treatment resistant edema and patients with naive edema was only observed in the 1st month (p=0.001). **Conclusion:** Significant decreases in retinal and choroidal thickness were observed both in patients with diabetic macular edema refractory to anti-VEGF therapy and in treatment-naive diabetic macular edema patients administered dexamethasone, while visual acuity increased, particularly in the 1st and 4th months.

Keywords: Diabetic macular edema; intravitreal injection; dexamethasone implant; naive macular edema; refractory edema

ÖZET Amaç: Tedaviye dirençli ve naive diyabetik makular ödem hastalarında intravitreal tek doz deksametazon implant etkinliğini değerlendirmek. **Gereç ve Yöntemler:** Çalışmaya Ocak 2017-Mart 2020 tarihleri arasında intravitreal deksametazon uygulanan 18 diyabet hastasının 25 gözü dâhil edildi. Hastaların en iyi düzetilmiş görme keskinliği (EDGK), göz içi basınç ölçümü, retina ve koroidal kalınlık değişimleri tedavi öncesi ve tedavi sonrası 1, 4 ve 6. ayda değerlendirildi. **Bulgular:** Yirmi beş gözün 11'ine daha önce hiç antivasküler endotelyal büyüme faktörü enjeksiyonu yapılmamış olup, diğer 14 göze ortalama 9,28±6,83 antivasküler endotelyal büyüme faktörü enjeksiyonu yapılmıştı. EDGK başlangıçta 0,81±0,46 logMAR, 1. ayda ortalama 0,65±0,44 logMAR, 4. ayda ortalama 0,66±0,45 logMAR, 6. ayda ortalama 0,78±0,44 logMAR idi. Başlangıç ve 1. ayda EDGK açısından istatistiksel anlamlı farklılık izlenirken (p=0,005), başlangıç ve 6. ay EDGK arasında istatistiksel anlamlı farklılık izlenmedi (p>0,05). Ortalama retinal kalınlık başlangıçta 490,56±186,56 µm, 1. ayda 301,24±139,63 µm, 4. ayda 304,84±129,97 µm ve 6. ayda ise 378,44±212,33 µm idi. Retinal kalınlıkta başlangıç değerlerine göre diğer aylar arasında istatistiksel anlamlı azalma mevcuttu (p<0,05). Ortalama subfoveal koroidal kalınlık başlangıçta 300,32±32,78 µm, 1. ayda ortalama 263,68±30,87 µm, 4. ayda 258,44±31,5 µm ve 6. ayda ortalama 268,20±40,10 µm idi. Koroidal kalınlık değişimi açısından başlangıca göre 1, 4 ve 6. aydaki ölçümlerle anlamlı farklılık bulundu (p<0,05). Tedaviye dirençli ödemi olan hastalarla naif ödemi olan hastalar arasında sadece retinal kalınlık açısından tedavinin 1. ayında istatistiksel anlamlı farklılık izlendi (p=0,001). **Sonuç:** Çalışmamızda intravitreal deksametazon uygulanan hem anti-VEGF tedaviye direnç gösteren hem de naif diyabetik makular ödem hastalarında retinal kalınlık ve koroidal kalınlıkta anlamlı azalma gözlenirken, görme keskinliği özellikle 1 ve 4. aylarda artış göstermiştir

Anahtar Kelimeler: Diyabetik makula ödemi; intravitreal enjeksiyon; deksametazon implant; naif makula ödemi; refrakter ödem

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Diabetic macular edema (DME) is an important complication of retinopathy that occurs through complex mechanisms and impairs vision. DME can develop at any stage of the disease as a result of vascular leakage, and the incidence rises in line with the severity of diabetic retinopathy. It is seen in 3% of cases of mild and in 38% of cases of moderate nonproliferative retinopathy, and in as many as 71% of eyes with proliferative retinopathy.[1] Increased vascular endothelial growth factor (VEGF) and inflammatory markers (interleukin-6, interleukin-8, and prostaglandins) increase retinal vascular permeability, and play a role in the emergence of macular edema.[2,3] The therapeutic options in DME include laser photocoagulation, intravitreal anti-VEGF and intravitreal steroid and steroid implants, together with pars vitrectomy as a surgical treatment. Although laser therapy is the standard therapeutic method, anti-VEGF applications have in recent years been shown to be more advantageous than laser for increasing visual acuity and improving the disease manifestation.[4,5] Long-term VEGF suppression in DME management reduces macular edema and improves visual acuity.[6,7] However, this requires long-term and repeated intravitreal injections. A sufficient response may also not be achieved in some cases. The stress caused by intraocular injections, frequent presentations to hospital for treatment, and the possibility of serious complications such as endophthalmitis have encouraged the search for different options in terms of treatment and reducing the frequency of injections.

Chronic inflammation is regarded as playing a key role in the pathogenesis of DME. Histopathological studies have also suggested that abnormalities involving the choroid, such as obstruction of the choriocapillaris, aneurysms, arteriosclerosis, and choroidal neovascularization, in patients with diabetes may figure in the pathogenesis of diabetic retinopathy.[8-10] Various cytokines and growth factors also affect choroidal vascular structures and can contribute to the development of DME.

Due to their potent anti-inflammatory effects, corticosteroids reduce the development of macular edema by lowering capillary permeability, preventing fibrin accumulation, and delaying endothelial tight junction proteins.[11-13] With their anti-inflammatory, anti-VEGF, and anti-proliferative properties, corticosteroids can be employed as an alternative therapeutic option in cases resistant to anti-VEGF agents. Dexamethasone, a potent corticosteroid, has been approved for use in various ocular diseases, including DME, and particularly in treatment-resistant cases.[14] Intravitreal dexamethasone implant at 0.7 mg (Ozurdex Allergan Inc., Irvine, CA, USA) was introduced in 2009. This assumed the form of a copolymer of lactic acid and glycolic acid (Novadur Allergan Inc.). Analysis showed that cumulative biodegradation led to an equivalent accumulation in the vitreous chamber for as long as 180 days following a single injection.

This research was intended to determine the influence of intravitreal dexamethasone implant in treatment-resistant and -naive DME patients, and at the same time to evaluate changes in choroidal thicknesses.

MATERIAL AND METHODS

Twenty-five eyes of 18 patients diagnosed with DME and being followed-up in the Karadeniz Technical University Medical Faculty Retinal Unit, Turkey, between January 2017 and March 2020 were included in the study. The study adhered to the principles of the Declaration of Helsinki, and approval for the research was granted by the institutional ethics committee. The study was also approved by the Karadeniz Technical University, Faculty of Medicine Ethics Committee (Number: 2020/328, date: 21.12.2020). Informed consent was obtained from all individual participants included in the study. Treatment-naive patients with no previous history of intraocular injection and patients with DME refractory to at least 6 doses of anti-VEGF injection and with central foveal thicknesses >300 μm at optical coherence tomography (OCT) were included in the study. Patients with vasculopathies other than diabetic retinopathy capable of leading to macular edema (such as central vein occlusion, branch vein occlusion, and uveitis), with maculopathies (epiretinal membrane, macular degeneration, hereditary maculopathies, etc.), choroidal pathologies, glaucoma, with pathologies such as cataract and vitreous hemorrhage capable of affecting the measurement meth-

ods, undergoing panretinal or focal laser therapy in the previous 3 months, with myopia> -5D or hypermetropia >+5D, or with histories of vitreoretinal surgery were excluded. Complete ophthalmological examinations were performed on all participants. These included best-corrected visual acuity (BCVA), intraocular pressure (IOP) assessment using a Nidek NT-530 device, and full biomicroscopic and fundoscopic evaluation.

Consent forms were received from patients prior to dexamethasone implant injection. All injections were performed in an operating room environment. Topical proparacaine drops were applied, followed by 5% povidone iodine to the upper temporal regions 3.5-4.0 mm posterior to the limbus. Following the injection, a quinolone group antibiotic was prescribed for use four times daily for 7 days.

All patients underwent OCT (Optovue RTVue (RT 100, software version 6.3, Optovue, Fremont, CA, USA) examination. These OCT images were then employed to assess macular edema and to determine choroidal thickness values. Measurements were repeated after 1, 4, and 6 months. Choroidal imaging was conducted in cross-line scanning mode, with the scan protocol being set to a retina cross-line involving two orthogonal 6-mm lines consisting of 1024A scans. For the purpose of better visualization of the choroidal layer, the scan number was later adjusted to 80 by means of chorioretinal scanning mode on "manual tab" and by selecting "auto all" function on "auto tab". Choroidal thickness in this study was regarded as the vertical distance from the retinal pigment epithelium to the choroidoscleral interface. Central retinal thickness (CRT) and subfoveal choroidal thickness (SFCT) were calculated manually in subfoveal section by 2 separate researchers based on OCT images showing a visible and measureable choroid.

STATISTICAL ANALYSIS

Statistical Package for the Social Sciences (SPSS, Chicago, IL, USA) software version 20.0 was used for all analyses. BCVA was converted to LogMAR units for the analytical purposes. The Kolmogorov-Smirnov test was applied to evaluate normality of data distribution. The test Wilcoxon test was applied in the comparison of mean values between groups. Correlations between parameters were also investigated. p values <0.05 were regarded as statistically significant.

RESULTS

Twenty five eyes of 18 patients with a mean age of 72.52±9.33 years, 6 women (40%) and 12 men (60%), were included in the study. A history of accompanying non-diabetic hypertension was present in 15 patients. Seven eyes (28%) of 6 patients were phakic, and the other 18 (72%) were pseudophakic. Eleven (44%) of the 25 eyes had not previously received anti-VEGF injection, while a mean 9.28±6.83 anti-VEGF (bevacizumab, ranibizumab, or aflibercept) injections had been performed on the remaining 14 eyes (56%). Panretinal photocoagulation had been applied to 11 eyes (44%) and focal laser to 8 (32%), while laser had not been applied to 6 eyes (24%).

Mean BCVA values were 0.81±0.46 logMAR at baseline, 0.65±0.44 logMAR at 1 month, 0.66±0.45 logMAR at 4 months, and 0.78±0.44 logMAR at 6 months. The difference between baseline and 1st month BCVA was statistically significant (p=0.005). However, the difference between baseline and 6th month BCVA was not significant (p>0.05). Similarly, BCVA values differed significantly between months 1 and 6, and between months 4 and 6 (p=0.01 and p=0.02, respectively).

Mean IOP values were 13.76±3.53 mmHg at baseline, 16.68±4.55 mmHg at one month, 15.16±3.13 mmHg at four months, and 14.44±3.11 mmHg at 6 months. IOP increased statistically significantly between baseline and 1 month (p=0.001), but no significant difference was determined at 4 or 6 months (p>0.05). Mean CRT was 490.56±186.56 μm at baseline, 301.24±139.63 μm at 1 month, 304.84±129.97 μm at 4 months, and 378.44±212.33 μm at 6 months. Retinal thickness decreased significantly in a time dependent manner compared to initial measurements (p<0.05), but no significant change was observed after 1 month (p>0.05). Mean SFCT was 300.32±32.78 μm at baseline, 263.68±30.87 μm at 1 month, 258.44±31.5 μm at 4 months, and

268.20±40.10 µm at 6 months. Choroidal thicknesses decreased significantly between the months compared to baseline measurements ($p<0.05$), but no statistically significant change was determined between months 1, 4 and 3 ($p>0.05$). CRT, SFCT, IOP, and BCVA values before and after injection are shown in Table 1.

Retinal thickness was significantly correlated with visual acuity at baseline and all other time points ($r=0.665$, $p<0.05$). A statistically significant correlation was also determined between visual acuity and choroidal thickness ($r=0.514$, $p=0.009$). However, pre-treatment retinal thickness values exhibited no significant correlation with choroidal thickness ($r=0.35$, $p=0.086$), but a significant correlation was determined at months 1, 4, and 6 ($r=0.54$, $p=0.02$). IOP and choroidal thickness were significantly correlated at baseline and after 1 and 6 months of treatment ($r=0.47$, $p=0.02$), but not in the 1st month after treatment ($r=0.15$, $p=0.46$).

Comparison of patients with refractory DME who had previously undergone anti-VEGF injection and those undergoing injection for the 1st time revealed no significant difference in terms of visual acuity, IOP or SFCT in the 2 groups at any time point ($p>0.05$). Retinal thickness only differed significantly between the patients with treatment-resistant edema and the naive edema patients at month 1, while no significant difference was observed at baseline or at months 4 and 6 ($p>0.05$). A comparison of patient with treatment-resistant macular edema and naive macular edema patients is shown in Table 2.

IOP values rose to 28 mmHg in 2 patients (8%) in the 1st month after dexamethasone injection. This was brought under control with antiglaucoma medication (timolol-dorzolamide). Seven eyes were phakic prior to injection in this study, with cataract developing in the 6th month in 2 (28%) of these, while no cataract was observed in the remaining five. All the phakic patients were from the treatment-resistant macular edema group, while all the naive patients were pseudophakic.

DISCUSSION

Several previous studies have described anti-VEGF injections as potentially effective in the treatment of DME, although lack of response to anti-VEGF therapy may be seen in some patients.[4] In the Diabetic

TABLE 1: Central retinal thickness, subfoveal choroidal thickness, best corrected visual acuity, and intraocular pressure findings following intravitreal dexamethasone implant.

	Baseline (0)	1st month (1)	4th month (2)	6th month (3)	p value
CRT	490.56±186.56	301.24±139	304.84±129.97	378.44±212.33	0-1 p<0.05 0-2 p<0.05 0-3 p<0.05 1-2-3 p>0.05
SFCT	300.32±32.78	263.68±30.87	258.44±31	268.20±40.10	0-1 p<0.05 0-2 p<0.05 0-3 p<0.05 1-2-3 p>0.05
BCVA (logMAR)	0.81±0.46	0.65±0.44	0.66±0.45	0.78±0.44	0-1 p=0.005 0-2 p>0.05 0-3 p>0.05 1-2 p>0.05 1-3 p=0.01 2-3 p=0.02
IOP	13.76±3.53	16.68±4.55	15.16±3.13	14.44±3.11	0-1 p=0.001 0-2-3 p>0.05 1-3 p=0.03

CRT: Central retinal thickness; SFCT: Subfoveal choroidal thickness; BCVA: Best-corrected visual acuity; IOP: Intraocular pressure.

TABLE 2: A comparison of treatment-naïve and treatment-resistant macular edema patients.

	Baseline (0)	1st month (1)	4th month (2)	6th month (3)	p value
BCVA (logMAR)					p0=0.2
Group 1	0.69	0.48	0.50	0.68	p1=0.08
Group2	0.90	0.79	0.78	0.87	p2=0.1
					p3=0.3
IOP					p0=0.7
Group 1	14	17.45	16.45	15.18	p1=0.4
Group 2	13.57	16.07	14.14	13.86	p2=0.06
					p3=0.3
CRT					p0=0.1
Group 1	429.73	231.64	292.27	355.27	p1=0.01
Group 2	538.36	355.93	314.71	396.64	p2=0.7
					p3=0.6
SFCT					p0=0.1
Group 1	290.09	252.73	245.36	267.55	p1=0.1
Group 2	308.36	272.29	268.71	268.9	p2=0.2
					p3=0.9

BCVA: Best-corrected visual acuity; IOP: Intraocular pressure; CRT: Central retinal thickness; SFCT: Subfoveal choroidal thickness.

Retinopathy Clinical Research Network, central macular edema (OCT central subfield ≥250 μm) persisted at 2 year follow-up visits in approximately 40% of the eyes in the 2 ranibizumab groups.[15] In the present study, a single-dose intravitreal dexamethasone implant produced a decrease in retinal thickness and choroidal thickness at 1, 4, and 6 months compared to baseline in both anti-VEGF therapy-resistant patients and treatment-naive macular edema patients. Although anti-VEGF agents are currently employed as the first choice option in the treatment of DME, they can also be used in combination with intravitreal dexamethasone implants, and dexamethasone implants can also be employed as the therapy of choice, particularly in pseudophakic patients. Lo Giudice et al. reported obtaining a very short-term effect in treatment-naive patients, suggesting that the effect of dexamethasone might not be solely restricted to chronic and/or recalcitrant DME.[16] Özsaygılı et al. compared the effectiveness of intravitreal dexamethasone and aflibercept administration in treatment-naive DME patients. Those authors concluded that dexamethasone implant and aflibercept were both safe and efficacious in such patients with inflammatory phenotypes. They also described the fact that few injections were required in their dexamethasone implant group as a particular advantage.[17]

Inconsistent results have been reported by studies examining choroidal thickness changes in diabetic patients. Some have reported a decrease in choroidal thickness in diabetic patients compared to the normal population, while others have reported an increase correlated with the severity of retinopathy. Kim et al. reported that mean SFCT increased significantly in line with worsening severity, from mild to moderate to severe non-proliferative diabetic retinopathy (NPDR) to proliferative diabetic retinopathy (PDR). They also showed a greater choroidal thickness in patients with severe NPDR or PDR compared to a healthy controlgroup.[18] Similarly, Ohara et al. reported significantly higher choroidal thickness values in severe NPDR and PDR compared to mild to moderate NPDR. Choroidal thickness values in patients with diabetic retinopathy varied depending on the severity of the condition and the treatment administered.[19] Rewbury et al. reported that SFCT increased in line with the severity of diabetic retinopathy, although no significant relationship was observed with the presence of DME.[20] In contrast to these studies, Regatieri et al. reported a thinner choroid in patients with DME than in non-diabetic patients.[21] Lains et al. observed a decrease in macular choroidal thickness in the proliferative stages of diabetic retinopathy using swept-source OCT.[22]

Studies have reported a decrease in choroidal thickness following platelet rich plasma in diabetic patients, after intravitreal anti-VEGF injection, and following intravitreal dexamethasone implant.[23-25] Yiu et al. reported a decrease in central choroidal thickness values after 6 months following anti-VEGF therapy administered for DME. However, they also suggested that this might not be linked to functional or anatomical outcomes in patients with DME.[26] Aksoy et al. reported that diabetic patients had a greater choroidal thickness compared to members of a control group, decreasing from 288 µm to193 µm in the 3rd month following dexamethasone application in patients with refractory DME ($p<0.001$).[27] In Kim et al.'s study, choroidal thickness decreased from 288.91 µm to 266.85 µm in the 3rd month ($p=0.01$) after intravitreal dexamethasone implant in patients with refractory DME, subsequently rising to 278.63 µm in the 6th month ($p=0.137$).[28] In the present research, and consistent with several previous studies, SFCT was initially measured at 300.32±32.78 µm, decreasing to 263.68 µm at 1 month, and to a mean 258.44 µm at 4 months. In Aksoy et al.'s study, mean retinal thickness decreased from 532 µm to 267 µm three months after intravitreal dexamethasone application in patients with refractory DME.[27] In the present study, retinal thickness decreased from 490 µm before injection to 304 µm at 4 months.

Initial visual acuity in the present study was 0.81 logMAR. This subsequently increased at 1 and 4 months, before decreasing again to 0.78 logMAR at 6 months. Aksoy et al. reported that BCVA rose from 0.19 Snellen to 0.5 Snellen in patients with refractory macular edema in the 3rd month following dexamethasone administration.[27] Gillies et al. compared the efficacy of intravitreal bevacizumab and dexamethasone in DME and reported similar rates of acuity improvement with dexamethasone implant compared with bevacizumab for DME, as well as superior anatomical outcomes and fewer injections being required.[29]

The effectiveness of intravitreal dexamethasone implant in the previous literature peaks between 1 and 3 months, subsequently tending to decrease between 4 and 6 months.[30] Özsaygılı et al. reported an optimal therapeutic outcome in terms of visual acuity and CRT in the 3rd month in their dexamethasone group, and also observed that the effectiveness of treatment declined toward the 6th month.[17] Zhioua et al. reported that the implant efficacy decreased gradually from the 4th month to the 6th, in line with the increase in CRT.[31] Similarly in the present study, the effect of dexamethasone implant on changes in BCVA, retinal thickness and choroidal thickness was greater at one and 4 months, persisting up to the 6th month.

The 2 most frequent and important complications that may develop after intravitreal dexamethasone implant in DME are cataract and increased IOP.[31-33] The cataract development rate in the present study was 28%, while the rate for glaucoma was 8%. Totan et al. reported IOP elevation at a rate of 13.3% in patients with chronic DME. Good control was achieved in those eyes with topical anti-glaucoma monotherapy.[32] Zhioua et al. reported that IOP elevation developed at a rate of 15% following intravitreal dexamethasone implant in patients with refractory DME. This elevation in IOP was brought under control by medical treatment and was transitory in nature, resolving after 4 months. At the same time, significant cataract developed in one patient (9%).[31] IOP elevation observed in 2 patients in the present study was treated and brought under control with topical antiglaucoma therapy.

The limitations of the present study include its retrospective design, the low number of cases, the short 6 month follow-up period, and the fact that no control group was established. Another limitation was the use of manual segmentation during computed tomography measurement. The choroid-sclera margin will become unclear in patients with excessive intraretinal or subretinal fluid, which may result in measurement errors compared to cases with milder edema.[26] As reported by Yiu et al., a floor effect may result in additional thinning not occurring in eyes with a thinner choroid at baseline.[26] These factors may account for the discrepancies in choroidal thickness measurements in the literature.

CONCLUSION

Significant decreases in retinal thickness and choroidal thickness were observed following intravitreal dexamethasone implant in cases of refractory macular edema and in treatment-naive DME patients. Visual acuity increased, particularly in the 1st and 4th months.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Dilek Uzlu, Hidayet Erdöl, Mehmet Kola;* ***Design:*** *Dilek Uzlu, Murat Günay, Nurettin Akyol;* ***Control/Supervision:*** *Dilek Uzlu;* ***Data Collection and/or Processing:*** *Dilek Uzlu, Nurcan Günay;* ***Analysis and/or Interpretation:*** *Dilek Uzlu, Hidayet Erdöl;* ***Literature Review:*** *Nurcan Gürsoy, Dilek Uzlu;* ***Writing the Article:*** *Dilek Uzlu;* ***Critical Review:*** *Dilek Uzlu, Hidayet Erdöl.*

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