Intravitreal Dexamethasone Implant Treatment in Patients With Diabetic Macular Edema Resistant to Anti-VEGF Treatment

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ABSTRACT

Purpose: To evaluate the efficacy and safety of intravitreal dexamethasone implant (IDI) (OZURDEX) in the patients with diabetic macular edema (DME) resistant to anti-VEGF treatment.

Study Design: This retrospective study included 93 eyes of 93 patients who underwent IDI injection and changes in best corrected visual acuity (BCVA), central macular thickness (CMT), intraocular pressure (IOP) as well as presence of DME and ocular side effects were investigated.

Results: Ninety three eyes of 93 patients (45 male, 48 female; the mean age was 67.32±10.68 years) were included. At least five monthly intravitreal ranibizumab (Lucentis) injections were administered before IDI and patients were considered to have resistant DME. A significant improvement was observed in BCVA while a significant decrease in CMT at all time points when compared to baseline ($p<0.05$). The maximum effect of IDI was seen on month 3, which was decreased gradually decreased after month 3. The mean IOP value was increased from 15.2±2.85 mmHg to 16.13±2.83 on month 6. The IOP elevation was controlled with topical anti-glaucomatous medication. Of the eyes included, 31 were phakic while 62 were pseudophakic and no cataract formation was detected in the patients during follow-up.

Conclusion: In this study, it was shown that IDI provided significant improvement in BCVA, DME and CMT. The effect was highest on month 3; however, the efficacy was maintained on month 6 in some patients. Although IDI treatment was found effective and safe in patients with anti-VEGF resistant DME, there is a need for studies with longer follow-up.

Keywords: Intravitreal dexamethasone implant, Ddiabetic macular edema, Anti-VEGF therapy.

INRODUCTION

Diabetic macular edema (DME) is macular thickening secondary to diabetic retinopathy (DR), which is commonly seen during non-proliferative stage of DR but may also occur at any stage of the disease. It is leading cause of central vision loss in DR.[1, 2] Focal or grid laser photocoagulation has been considered as standard treatment strategy in patients with DME until today. Currently, anti-VEGF agents or corticosteroids are recommended in the treatment of DME while vitrectomy is reserved to the patients with vitreomacular traction accompanying to DME.[3-5]

The effects of anti-VEGF agents such aflibercept, ranibizumab and bevacizumab on DME have been investigated in several clinical trials. The RESOLVE, RISE/RIDE and READ-2 trials, it was shown that ranibizumab is a good option in the treatment of DME.[4,6-8] In the BOLT study, bevacizumab was found superior to laser photocoagulation alone in patients with clinically relevant DME with central involvement.[9] In randomized, clinical trials, VIVID and VISTA, aflibercept was compared with laser photocoagulation and found to be superior to laser therapy regarding efficacy and safety.[10]

The anti-VEGF treatment in DME leads both increased costs due to need for frequent injections (every 4 or 8 weeks) in responsive patients and increased risk, albeit slight, for ocular complications such as endophthalmitis

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as well as cardiovascular and cerebrovascular event.[11, 12] Some authors report that chronic VEGF inhibition may have neurotoxic effects on retina.[13] When the role of inflammation was elucidated in the progression of DR, corticosteroid treatment has become a current issue. The corticosteroids block arachidonic acid release from cell membrane and reduce prostaglandin synthesis. In addition, they inhibit leukocyte migration and release of pro-inflammatory mediators such as TNF-α and VEGF. In a study comparing intravitreal triamcinolone acetate (IVTA) and intravitreal ranibizumab, it was found that ranibizumab was superior to IVTA, particularly in phakic eyes, due to adverse effects of IVTA.[14]

Intravitreal dexamethasone implant (IDI; Ozurdex, Allergan Inc., Irvine, CA, USA) is a biodegradable implant with sustained release and has been introduced into ophthalmology practice. Although some authors suggest that clinical effects of dexamethasone are limited to 4 months in majority of the eyes, it can be detected in retina and vitreous up to 6 months and maximum concentration is achieved on month 2.[15-17] In previous studies, it was shown that IDI can be an alternative treatment option in patients with DME poorly responsive to repeated intravitreal anti-VEGF injections or those with refractory DME.[18-24] In addition, there is a study suggesting IDI as a first-line treatment in DME.[25] Cataract and ocular hypertension (OHT) are common adverse effects of corticosteroids. It has been reported that elevated intraocular pressure (IOP) is better tolerated with dexamethasone implant and controlled with topical treatment when compared to currently available intravitreal corticosteroids (triamcinolone acetonide, fluocinolon acetonide).[26]

The IDI can provide additional benefit due to its effects on multiple signal transduction pathways in patients with DME refractory to anti-VEGF treatment. Here, wee aimed to evaluate the efficacy and safety of IDI in the patients with DME refractory to anti-VEGF treatment.

MATERIAL AND METHOD

This single-center, retrospective study included eyes underwent IDI injection between January, 2013 and July, 2015.

Data regarding best-corrected visual acuity (BCVA) as measured by Snellen charts, IOP, anterior and posterior segment examination and central macular thickness (CMT) as measured by optical coherence tomography (OCT, Topcon 3D OCT-2000 System) were extracted from patient files. In the study, all patients underwent fundus fluorescein angiography (FFA) to exclude neovascularization and macular or peripheral ischemia. The BCVA values were transformed into logMAR digits for statistical purposes.

The IDI (0.7 mg) was injected via intravitreal route using 22 G applicator through pars plana. All patients gave written informed consent before injection.

The study included patients (aged≥18 years) with macular edema secondary to non-proliferative DR who received at least 5 consecutive intravitreal ranibizumab (Lucentis) injections and had and CMT thickness ≥300 μm on OCT and follow-up of at least 6 months. The patients with macular edema due to reasons other than DR, those with additional retinopathy, those with history of ocular hypertension or glaucoma, patients with proliferative DR, those underwent focal, grid or panretinal laser photocoagulation, those with macular or peripheral ischemia on FFA and those with follow-up<6 months were excluded. All procedures were conducted in accordance to tenets of Helsinki Declaration.

The demographic characteristics, number and date of IDI injections, follow-up duration and BCVA, IOP and CMT values were recorded throughout study period.

The primary outcome measure was mean BCVA change during follow-up period when compared to baseline. Secondary outcome measures were mean CMT change, mean IOP change and adverse effects.

All statistical analyses were performed using IBM SPSS version 22.0 (IBM SPSS, Turkey). Normal distribution of data was assessed using Shapiro-Wilk test. Data were analyzed using descriptive statistics (mean, standard deviation, frequency. Paired sample t test was used to compare quantitative data with normal distribution while Wilcoxon sign rank test was used to compare data with skewed distribution. McNemar test was used compare qualitative data. A p value<0.05 was considered as statistically significant.

FINDINGS

The study included 93 eyes of 93 patients with DME (45 men, 48 women; mean age 67.32±10.68 years. Mean duration of diabetes mellitus was 11.39±4.15 years. There was DME refractory to ranibizumab (Lucentis). Table 1 presents primary characteristics of patients and eyes included.

Mean BCVA (logMAR) was 0.77±0.3 at baseline and 0.50±0.23 on month 6. Significant increases were observed in mean BCVA on months 1, 3, 4, and 6 when compared to baseline (p<0.05). Table 2 and Graphic 1 present the change of the mean

Table 1: *Demographic and clinical characteristics of the patients.*

	Min-Max	Mean± SD
Age	46-87	67,32±10,68
Number of previous anti-VGEFs,	4-10	6,13±1,26
Duration of diabetes mellitus (years)	5-25	11,39±4,15
HbA1c	6,2-9,8	7,53±0,83
	n	**%**
Gender		
Male	45	48,4
Female	48	51,6
Side		
Right	47	50,5
Left	46	49,5
Lens		
Phakic	31	33,3
Pseudophakic	62	66,7

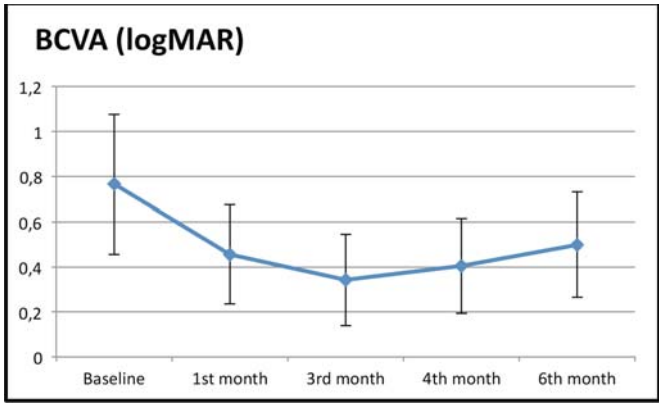
Min: minimum, Max: maximum, SD: standard deviation

BCVA values of the patients with time.

Mean CMT was 461.68±111.14 µm at baseline. Significant improvement was observed in CMT after IDI. Significant improvement was observed in mean CMT on months 1, 3, 4 and 6 when compared to baseline ($p<0.05$). The lowest mean CMT was detected on month 3 while there was an increase in mean CMT after month 3. Table 3 and Graphic 2 present CMT change during follow-up.

The IOP values were <21 mmHg in all measurements before IDI administration. None of the patients had history of glaucoma or topical anti-glaucomatous agent use. Six patients with IOP≥25 mmHg and given topical anti-glaucomatous agent were detected on month 1. The highest IOP value was 30 mmHg (one patient) on month 1. During follow-up, highest IOP value was recorded on month 1. On month 4, IOP was measured as ≥25 mmHg in a patient given anti-glaucomatous agent previously and IOP was controlled by increasing number of anti-glaucomatous agents. There was no patient with IOP≥25 mmHg on month 6 but there were 2 patients on topical anti-glaucomatous treatment. Table 4 and Graphic 3 present mean IOP values and IOP changes during follow-up.

DME was detected at initial examination in all patients with significant decreases on month 1, 3, 4 and 6 ($p<0.05$). The lowest DME detection rate was recorded on month 3, which increased on subsequent months (Table 5).



Graphic 1: *Change of BCVA during the follow-up period.*

BCVA: best corrected visual acuity, **logMAR:** logarithm of the minimum angle of resolution

Table 2: *Mean BCVA values at different time points.*

	BCVA (logMAR)		p
	Mean±SD	Median	
Baseline	0.77±0.31	0.7	
Month 1	0.46±0.22	0.4	0.000*
Month 3	0.34±0.2	0.3	0.000*
Month 4	0.40±0.21	0.4	0.000*
Month 6	0.50±0.23	0.5	0.000*

Wilcoxon sign test *$p<0.05$

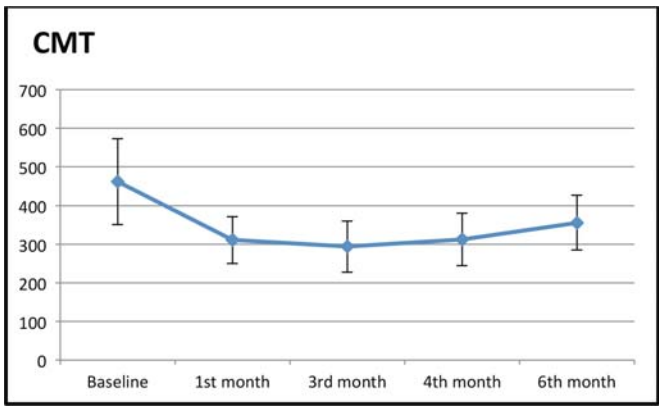
BCVA: best-corrected visual acuity. logMAR: logarithm of the minimum angle of resolution

Table 3: *Changes in CMT at different time points.*

	CMT (µm)		p
	Mean±SD	Median	
Baseline	461.68±111.14	435	
Month 1	310.58±60.60	302	0.000*
Month 3	293.63±66.12	284	0.000*
Month 4	312.25±67.73	300	0.000*
Month 6	355.57±70.83	350	0.000*

Wilcoxon sign test *$p<0.05$

CMT: central macular thickness



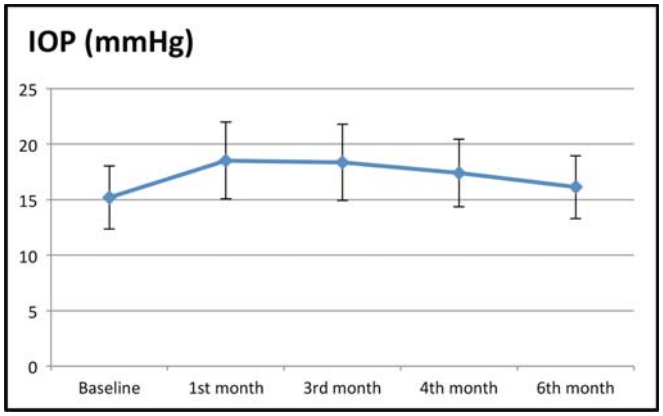
Graphic 2: *Change of the mean CMT values during the follow-up period.*

CMT: central macular thickness

Table 4: *Mean IOP values at different time points zamanlarda ölçülen ortalama GİB değerleri.*

	IOP (mmHg)	p
	Mean±SD	
Baseline	15.2±2.85	
Month 1	18.52±3.46	0.000*
Month 3	18.35±3.43	0.000*
Month 4	17.40±3.04	0.000*
Month 6	16.13±2.83	0.001*

Paired Samples t test **p<0.05*
IOP: intraocular pressure



Graphic 3: *Change of the mean IOP values during the follow-up period.*

IOP: intraocular pressure

On month 6, there was ≥2 order BCVA gain in 67 patients (72%) while ≥2 order reduction in 4 patients (4.3%) and BCVA remained stable in 22 patients (23.7%) when compared to baseline. On month 5, there was a decrease in CMT in 76 patients while an increase in 3 patients (3.2%) when compared to baseline and CMT remained stable in 22 patients (15.1%).

Of the eyes included, 31 were phakic while 62 were pseudophakic and no cataract formation was detected in the patients during follow-up. No IDI-related local or systemic adverse effect was observed.

Table 5: *DME incidence at different time points.*

	DME		p
	+	-	
	n (%)	n (%)	
Baseline	93 (100)	0 (0%)	
Month 1	26 (28%)	67 (72%)	0.000*
Month 3	17 (18.3%)	76 (81.7%)	0.000*
Month 4	22 (23.7%)	71 (76.3%)	0.000*
Month 6	50 (53.8%)	43 (46.2%)	0.000*

Mc Nemar test **p<0.05*
DME: diabetic macular edema

DISCUSSION

This study was conducted to assess efficacy of IDI in patients with DME refractory to anti-VEGF therapy. The changes in BCVA and CMT were assessed during 6 months follow-up. The results showed significant improvements in BCVA on months 1, 3, 4 and 6 after IDI administration. In addition, significant reduction was also observed in CMT and DME on months 1, 3, 4 and 6. The maximum IDI effect was recorded on month 3, which was gradually decreased after month 3.

In the study, all patients received intravitreal ranibizumab (Lucentis) injections before IDI administration. Although intravitreal ranibizumab was found to be effective in DME treatment in RESOLVE, RISE/RIDE and READ-2 studies, there may be resistance against ranibizumab in some eyes with DME. In the DRCR.net study, it was estimated that persistent DME will be present in 40% in the post hoc analysis of eyes having persistent DME 24 months after initiation of intravitreal ranibizumab treatment.[27]

Haller et al. showed that BCVA and CMT were significantly improved in DME eyes treated with IDI (0.7 mg) every 3 months when compared to controls.[28] The proportion of eyes with at least 15 letters gain in BCVA was 17.44% on day 90 in IDI group. Authors showed the difference between IDI and control groups continued throughout study period. In a study on 1048 patients by MEAD Work Group, the patients were assigned into 3 groups including group 1 (0.7 mg IDI), group 2 (3.5 mg IDI) and group 3 (sham group). Based on interim results on year 3, CMT reduction was 111, 108 and 42 µm, respectively.[24]

In a study on patients with DME refractory to anti-VEGF injection and laser photocoagulation, Akıncıoğlu et al. showed that anatomic and functional improvement persisted until month 4; however, authors could not draw definitive conclusion whether CMT reduction on months 7, 8 and 9 was associated with first or second injection due to early administration of second IDI injection.[29] In our study, maximal IDI effect was recorded on month 3. As none of the patients received a second IDI injection, it was seen that there were patients with persisted effects of single injection up to 6 months.

Since phakic patients were also included to the study by Akıncıoğlu et al., BVCA improvement following IDI administration was found to be insignificant when whole study population was assessed; however, cataract formation

was observed as early as 3 months and BCVA gain was observed up to month 4 in pseudophakic group.[29] .In our study, no cataract development requiring surgery due to reduction in visual acuity was detected during 6-months follow-up although there was 31 phakic patients in the study. In addition, in the study by MEAD Work Group, it was emphasized that final visual outcomes were excellent by cataract surgery even if cataract developed after IDI administration.[24]

In the study by Callanan et al., it was shown that elevated IOP after IDI administration was generally controlled with topical anti-glaucomatous treatment and that IOP was spontaneously decreased 4 months after IDI administration.[30] In the same study, it was suggested that topical anti-glaucomatous agents were required in 39.2% of patients during study period.[30] In our study, topical anti-glaucomatous agents were required in smaller number of patients. In addition, topical anti-glaucomatous agents were withdrawn in some patients due to spontaneous recovery of IOP after month 4. Only 2 patients continued to use topical anti-glaucomatous agents on month 6. In the study by Callanan et al., patients received 3 IDI injections at baseline and on months 5 and 10 during 12-months follow-up.[30] The IOP can be elevated due to cumulative doses in patients with IOP related to steroid sensitivity. In our study, the lower rate of patients with IOP elevation may be due to single IDI administration with 6-months follow-up.

This study has some weaknesses including 6-months follow-up and retrospective design. The long-term studies may effects of IDI on cataract formation and long-term adverse effects. In addition, studies with longer follow-up may be designed to assess factors underlying varying duration of action in different patients..

CONCLUSION

In this study, it was shown that IDI provided significant improvement in BCVA, DME and CMT on months 1, 3, 4 and 6. Although there were patients with IDI effects up to 6 months, the effect was highest on month 3. There is a need for studies with longer follow-up to individual variations in duration of action.

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