Original Article

The Efficacy of Single-Dose Intravitreal Dexamethasone Implant for Diabetic Macular Edema Refractory to Anti-VEGF Therapy: Real-Life Results

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Abstract

Objectives: To investigate the efficacy, safety, and side effect profiles of a single-dose intravitreal dexamethasone implant (IDI, Ozurdex) in patients with diabetic macular edema (DME) refractory to anti-vascular endothelial growth factor (VEGF) therapy.

Methods: This study included 101 eyes of 78 diabetic patients with DME that remained persistent despite administering at least six doses of anti-VEGF therapy. The patients were evaluated at baseline and were followed up monthly until the sixth month after the IDI injection. The primary outcomes were central foveal thickness (CFT) and best-corrected visual acuity (BCVA).

Results: The mean number of anti-VEGF injection administered to patients was 6.50±0.33. One month after the last injection, the response to treatment was evaluated. IDI injection was performed approximately 1.14±0.08 months after the last anti-VEGF injection. After the IDI injection, BCVA value increased (p<0.001) and CFT value decreased (p<0.001). The peak effect of the IDI was observed in the second month after the injection. CFT values increased and BCVA values decreased from the beginning of the fourth month after the IDI injection. The recurrence rate of CFT elevation in the sixth-month follow-up was 57.4%. Moreover, we observed that high pre-injection CFT values were correlated with a high post-injection recurrence rate of CFT elevation (p<0.001).

Conclusion: These findings suggest that the IDI injection significantly improves BCVA and CFT values in patients with DME refractory to anti-VEGF therapy. However, recurrence of CFT elevation may occur in >50% patients in the sixth month after the first injection.

Keywords: Diabetic macular edema, efficacy, intravitreal dexamethasone implant, Ozurdex, recurrence.

Introduction

Macular edema is the most common cause of diabetes-related visual loss (1). Blood–retinal barrier breakdown, vascular anomalies, oxidative stress, and inflammatory cascade play an important role in inducing extravasation and edema (2). In recent years, intravitreal injections have replaced laser photocoagulation of the macula for treating diabetic macular edema (DME). Vascular endothelial growth factor (VEGF) has emerged as a key target for treating DME. Intravitreal injections of anti-VEGF drugs are widely employed to reduce

disease progression and improve the visual outcomes of affected patients (3). However, patients who do not respond to anti-VEGF therapy continue to be an important problem despite the availability of other treatment modalities.

Steroids have anti-inflammatory, antiangiogenic, and antivascular permeability properties. Studies have reported significant clinical improvements in patients with DME who receive off-label intravitreal triamcinolone (4, 5). However, intravitreal triamcinolone treatment is associated with severe ocular side effects, including cataract and elevated intraocular pressure (IOP). Previous studies suggest that a biodegradable intravitreal dexamethasone implant (IDI) (Ozurdex, 0.7 mg; Allergan Inc., Irvine, CA, USA) improves visual acuity and macular thickness in patients showing age-related macular degeneration (6), retinal vein occlusion (7), and diabetic retinopathy-related macular edema (8). The IDI injection is associated with a better safety profile and results in better improvements in visual acuity and macular edema than the intravitreal triamcinolone injection. Therefore, the present study investigated the efficacy, safety, and side effect profiles of a single dose of IDI injection in patients with DME refractory to anti-VEGF therapy.

Methods

This retrospective study evaluated 101 eyes of 78 patients with decreased visual acuity because of the presence of persistent DME who received a single dose of IDI injection between January 2016 and 2018. DME was defined as the presence of clinically significant macular edema and was diagnosed based on criteria developed in the Early Treatment Diabetic Retinopathy Study (ETDRS). Persistent DME was defined as macular edema with a central foveal thickness (CFT) of ≥ 300 µm, as measured by performing spectral-domain optical coherence tomography (SD-OCT), despite the administration of at least six consecutive ranibizumab injections once a month with no or partial response (CFT reduction to <50 µm).

All study procedures were conducted in accordance with the Declaration of Helsinki, and the study was ethically approved by the Ethical Committee of Numune Education and Research Hospital. Before administering the IDI injections, all the patients were informed about the potential adverse effects of the treatment, and their consent was obtained. All the patients were Turkish Caucasians.

Demographic characteristics of the patients, duration of diabetes and macular edema, and previous DME treatments received by the patients were recorded. All the patients underwent a complete ophthalmological examination, including best-corrected visual acuity (BCVA; Snellen equivalents converted to logarithm of the minimum angle of resolution [LogMAR] units for analysis), IOP measurement with appla-

nation tonometry, slit-lamp biomicroscopy, dilated fundus examination by using a 90-D lens, and OCT, at baseline and in the first, second, third, fourth, fifth, and sixth months after the IDI injection. Fluorescein angiography was performed at baseline to evaluate neovascularization and macular/peripheral ischemia.

Patients with a history of glaucoma or steroid response; patients who previously underwent laser photocoagulation or steroid therapy; patients with neovascularization in the anterior or posterior segment; patients with other ocular diseases, such as retinal vein occlusion, uveitis, macular pucker, or vitreomacular traction; and patients with a history of ocular surgery (except for cataract) and trauma were excluded from this study.

A SD-OCT volume scan (20×20 with 49 horizontal sections, ART 15) including, en-face images and macular mapping image obtained with HRA2 (Heidelberg Retina Angiograph-Optical Coherence Tomography, Heidelberg Engineering, Heidelberg, Germany) of the macula was performed for each study eye. Retinal thickness (RT) in the Early Treatment Diabetic Retinopathy Study (ETDRS) subfields was analyzed by the RT map analysis protocol.

Before injecting the IDI (Ozurdex, 0.7 mg), the eyelids and ocular surface of the patients were treated with 5% povidone–iodine under sterile conditions in the operating room. The IDI was injected into the inferior temporal quadrant at 3.0–4.0 mm from the limbus. After the injection, each patient was prescribed 0.3% ofloxacin eye drops (Exocin; Allergan, Westport Co. Mayo, Ireland) four times a day for a week. Moreover, each patient was monitored for treatment-related adverse effects during the entire study period. IOP of ≥ 22 mmHg was considered to be high. Patients with an IOP value of ≥ 25 mmHg were prescribed timolol or combined brinzolamide and timolol.

Statistical Analysis

Statistical analyses were performed using SPSS version 18.0 for Windows (SPSS Inc., Chicago, IL). Variables were investigated using visual (histograms and probability plots) and analytical methods (Kolmogorov–Smirnov or Shapiro–Wilk test) to determine their normal distribution. Paired Student's t-test was used to compare measurements obtained at two different time points. Greenhouse–Geisser correction was used when the sphericity assumption was violated. The changes of BCVA, CFT, and IOP measurements by the time were investigated using repeated-measures of ANOVA test. A p-value of <0.05 was considered statistically significant.

Results

This retrospective case series evaluated 101 eyes of 78 patients with persistent DME who received the IDI injection.

Of the 78 patients, 43 (55.1%) were men and 35 (44.8%) were women, with a mean age of 61.38±7.25 years. Time elapsed since the diagnosis of diabetes mellitus (DM) and DME was 17.71±3.33 years and 16.67±2.20 months, respectively. Systemic evaluation detected hypertension in 41 (52.5%) patients, hyperlipidemia in 13 (16.6%) patients, and both hypertension and hyperlipidemia in 9 (11.5%) patients. Moreover, 63 (62.3%) eyes were phakic (Table 1).

The mean number of previous anti-VEGF injections before the IDI injection was 6.50±0.33. BCVA (LogMAR) and CFT (µm) values before administering the anti-VEGF injections were 0.87±0.43 (0.22–3.10) and 483.65±145.23 (265–716), respectively. One month after the last injection, the response to treatment was evaluated. The mean BCVA (LogMAR) and CFT (µm) values in the first month after the last anti-VEGF injection were 0.81±0.41 (0.22–3.10) and 454.41±138.91 (301–659), respectively. Although no statistically significant difference was observed between the BCVA values before and after the anti-VEGF therapy (p=0.421), a significant difference was observed between the CFT values before and after the anti-VEGF therapy (p=0.022).

In patients persistent to anti-VEGF therapy, IDI injection was performed approximately 1.14±0.08 months after the last anti-VEGF injection. The mean BCVA (LogMAR) values before the IDI injection (baseline) and in the first, second, third, fourth, fifth, and sixth months after the IDI injection are shown in Table 2. The baseline and post-injection BCVA values were significantly different (p<0.001). The mean BCVA values of the patients at each visit were significant compared with the baseline BCVA value (pairwise comparison, p<0.001). Moreover, BCVA values obtained in the fourth and fifth months showed a significant impairment compared with BCVA the values obtained in the third month (p=0.001 and p<0.001, respectively).

The mean CFT (µm) values before the IDI injection (baseline) and in the follow-up visits after the IDI injection are shown in Table 2. The baseline and post-injection CFT values were significantly different (p<0.001). CFT values obtained in the fourth month were significantly higher than the CFT values obtained in the third month (p<0.001). Moreover, CFT values obtained in the fifth and sixth months were significantly higher than the CFT values obtained in the fourth month (p=0.001 and p=0.001, respectively; Table 2). Recurrence of CFT elevation was observed in 58 (57.4%) eyes in the sixth month after the IDI injection.

The mean IOP (mmHg) values before the IDI injection (baseline) and in the follow-up visits after the IDI injection

Table 1. Demographics and clinical features of patients with refractory diabetic macular edema (DME) before intravitreal dexamethasone implant (IDI) injection

Eyes/patients (n)	101/78
Male/female (n)	43/35
Age (years, mean±SD)	61.38±7.25
Diagnosis of diabetes mellitus (years, mean±SD)	17.71±3.33
Duration of DME (months, mean±SD)	16.67±2.20
Mean number of previous anti-VEGF injection (n, mean±SD)	6.50±0.33
Phakic/pseudophakic eyes (n)	63/38
Systemic disease (n)	
Hypertension	41
Hyperlipidemia	13
Hypertension + Hyperlipidemia	9

n: Number; SD: Standard deviation.

Table 2. Mean values of best-corrected visual acuity (BCVA), central foveal thickness (CFT), and intraocular pressure (IOP) before and after IDI injection

Months	BCVA (LogMAR)	P^a	CFT (µm)	P^a	IOP (mmHg)	P^a
Baseline	0.81±0.41 (0.22-3.10)	n/a	454.41±138.91 (301-659)	n/a	15.51±0.81	n/a
1st	0.46±0.38 (0.10-1.80)	<0.001	297.62±82.34 (222-364)	<0.001	18.68±0.87	<0.001
2nd	0.44±0.41 (0.10-1.80)	0.529	291.10±85.06 (227-370)	0.478	18.12±0.76	0.329
3rd	0.47±0.48 (0.10-2.10)	0.426	292.14±84.41 (228-381)	0.701	17.23±0.71	0.001
4th	0.53±0.52 (0.10-2.10)	0.001	311.56±96.91 (227-413)	<0.001	16.61±0.77	0.079
5th	0.57±0.60 (0.22-3.10)	0.003	322.39±105.40 (238-433)	0.001	16.67±0.78	0.249
6th	0.59±0.69 (0.22-3.10)	0.437	323.70±111.24 (240-459)	0.525	16.66±0.70	0.440
P^b	<0.001		<0.001		<0.001	

n/a: Not applicable; P^a values reflect the statistical analysis between measurements made in that month and in the previous month (pairwise comparison); P^b: Repeated measures of ANOVA.

are shown in Table 2. Moreover, IOP value was measured in the first week after the IDI injection, and the mean IOP value was found to be 19.08±0.84 mmHg. After the first week, topical antiglaucoma therapy required in 17 (16.8%) eyes with an IOP of ≥25 mmHg. Of these 17 eyes, topical timolol therapy required in five (4.9%) eyes, and combined brinzolamide and timolol therapy required in twelve (11.8%) eyes. Analysis of IOP alterations showed an increase in IOP values in the first and second months after the IDI injection compared with the baseline IOP values (p<0.001 and p=0.006, respectively). Although IOP values obtained in the third month were significantly lower than the IOP values obtained in the second month (p=0.001), no difference was observed between IOP values obtained in the fourth month and the afterwards (Table 2). Topical antiglaucoma medication (combined brinzolamide and timolol) required in five (4.9%) eyes in the sixth month. None of the patients required surgical intervention for glaucoma.

Cataract, which impairs visual acuity and requires surgical intervention, developed in six out of 63 (9.5%) phakic eyes after the IDI injection and was treated by performing phacoemulsification surgery. During follow-up, none of the patients developed endophthalmitis and other ocular complications related to IDI injection.

Classification of the patients according to CFT (μm) values, i.e., CFT value of <400 μm (n=46 eyes) and ≥400 μm (n=55 eyes) before the IDI injection showed a statistically significant difference among the patients with respect to the recurrence of CFT elevation (Table 3, p=0.013). Results of binary logistic regression analysis showed a significant correlation between high pre-injection CFT values and post-injection recurrence of CFT elevation (not shown in the Table, p<0.001).

Discussion

The present study investigated the effectiveness and safety of a single dose of IDI injection in patients with anti-VEGF therapy-resistant DME. Administration of the IDI injection significantly improved BCVA and CFT values. The peak effi-

Table 3. Relationship between pre-injection central foveal thickness (CFT) and post-injection recurrence

	Recurrence (n=58)	No recurrence (n=43)	p
CFT, μm			
<400 (n=46)	17	29	0.013
≥400 (n=55)	41	14	

P: Chi-square test.

cacy in BCVA and CFT values was observed in the second month after the IDI injection. The effectiveness of the IDI decreased in the fourth month after the injection. Recurrence of CFT elevation was observed in 58 (57.4%) eyes in the sixth month after the injection.

The mean reduction in CFT values after a single-dose of the IDI injection in patients with DME refractory to anti-VEGF therapy was 163 μm (from 454 to 291 μm, 32.9%). Kim et al. (9) showed a mean improvement of 210 μm (from 526 to 316 μm, 39.9%) and Dutra Medeiros et al. (10) showed a mean improvement of 202 μm (from 543 to 341 μm, 37.2%) in CFT values. Various studies have investigated the effectiveness of the IDI injection in patients with refractory DME. Zucchiatti et al. reported that the peak efficacy in BCVA and CFT values was observed in the third month after treatment with a single dose of IDI injection and that these values returned to the baseline values in the sixth month after the injection (11). A study by Pacelle et al. involving 20 eyes reported that the effectiveness of the IDI injection was observed on the third day after the injection and was maintained until the third month after the injection (12). These findings suggest that the IDI exerts a maximum effect in the second and third months after its injection and that this effect is maintained until the sixth month after the injection; however, this effect starts decreasing from the third month after the injection (13–15). In the present study, minimum CFT values were obtained in the second month after the IDI injection. The effect of the IDI injection on CFT values seemed to be preserved in the third month after the injection, and no significant difference was observed between CFT values obtained in the second and third months after the injection. Although CFT values increased in the sixth month after the IDI injection, indicating a decrease in the effectiveness of the IDI, the CFT values obtained in the sixth month after the injection were significantly lower than the baseline CFT values.

The IDI exerts its effect on the retina in different ways. Studies indicate that corticosteroids exert an anti-inflammatory effect by inhibiting phospholipase and exert an antiangiogenic effect by stabilizing the blood–retina barrier (16). The IDI reduces ICAM-1 expression by inhibiting its transcription, inhibits VEGF and leukostasis, and exerts an anti-apoptotic effect (17, 18). Although VEGF is a very important mediator of the etiopathogenesis of DME, other inflammatory cytokines also play an important role in this process. Therefore, an intervention that affects other pathways in addition to the VEGF pathway is required.

Despite the effectiveness of corticosteroids in the treatment of DME, unlike BRVO and CRVO, IDI is not the first choice for DME treatment. Therefore, no or low response to anti-VEGF therapy should be legally determined before

administering the IDI injection. The success of the IDI treatment in patients who are refractory to anti-VEGF therapy cannot be precisely compared with its success in treatment-naive patients with DME. At present, the use of the IDI is limited to patients with refractory DME. High recurrence rates of CFT elevation after the IDI injection observed in the present study are not surprising because the target population included only patients with refractory DME who showed no or limited response to anti-VEGF therapy. Therefore, the use of the IDI injection as the first treatment choice in patients with DME who have not received any previous treatment may yield different outcomes.

Recurrence of DME is still an important problem. New strategies for administering the Ozurdex injection, such as administration of several injections per year, regular administration of the injection at specific intervals, or personalized treatment, may help in overcoming this problem. Sarao et al. (19) reported that a pro-re-nata protocol with the Ozurdex injection is more effective than a single injection for maintaining functional and anatomical benefits.

The presence of fluid because of persistent DME or repeated anti-VEGF injections may result in an irreversible cellular loss in the retina. Therefore, no functional improvement may be observed despite achieving anatomical integrity in retina. Kim et al. (9) reported two or more lines of improvement in visual acuity in only 26% of the patients despite observing a significant anatomical improvement in the sixth-month after the IDI injection. Repeated anti-VEGF injections trigger atrophy in the retina (20). Thus, Ozurdex injection may allow fewer injections per year in patients with diabetic macular edema. However, the IDI injection is associated with some significant side effects because of long-term steroid use. In the present study, IOP elevation was observed in 17 (16.8%) eyes in the first week after the IDI injection, which remained high in five (4.9%) eyes until the sixth month after the injection. IOP elevation in all the affected patients was controlled using antiglaucoma medication. Moreover, topical antiglaucoma medication required in five (4.9%) eyes in the sixth month after the injection. While Kim et al. (9), Unsal et al. (21), and Kaldirim et al. (22) reported IOP elevation in 8.6%, 17.3%, and 11.4% patients after a single dose of IDI injection, Dutra Medeiros et al. did not report a significant IOP elevation in 58 patients after a single dose of IDI injection (10). MEAD study reported IOP elevation in 38.1% eyes receiving anti-VEGF therapy and IDI injection for a mean of 4.1 times during 3 years (23). These results suggest that the risk of IOP elevation increases because of the cumulative effect of repeated injections. In the present study, surgery for cataract progression required in six (9.5%) phakic patients. Yucel et al. (13) reported that surgery for treating cataract required in 13.0% patients who received a single dose of IDI

injection, which was similar to that observed in the present study. Cicinelli et al. (24) reported a cataract progression rate of 11.1% after a mean of 1.9±1.1 IDI injections for one year, and the MEAD study reported a cataract progression rate of 70.3% after a mean of 4.1 IDI injections for three years (23).

The present study showed a significant correlation between high pre-injection CFT values and high post-injection risk of the recurrence of CFT elevation. Therefore, it can be suggested that early intervention with the IDI injection could provide better outcomes in patients with low pre-injection CFT values.

The present study has several limitations. First, this study included a relatively small sample size that cannot be adapted to the general population. Second, systemic regulation of DM was not performed and blood HbA1C levels were not measured. Third, this study evaluated the effects of only a single dose of IDI injection.

In summary, the IDI injection is an effective and safe option for treating patients with DME refractory to anti-VEGF therapy. The IDI injection is associated with some advantages, i.e., it exerts a long-standing effect, it simultaneously exerts both antiangiogenic and anti-inflammatory effects, its side effects can be controlled, and it requires fewer numbers of injections than anti-VEGF therapy. However, recurrence of CFT elevation was observed in >50% of the patients in the sixth month after the first injection.

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