Original Article

The efficacy of intravitreal dexamethasone implant as the first-line treatment for retinal vein occlusion-related macular edema in a real-life scenario

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Purpose: This study evaluated the effect of intravitreal dexamethasone implant (IDI; Ozurdex) injection for treating macular edema in patients with branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO). **Methods:** This prospective study included 40 eyes of 40 patients with nonischemic BRVO and 31 eyes of 31 patients with nonischemic CRVO who received IDI injection as the first-line treatment for macular edema. The best-corrected visual acuity (BCVA) value before and after the treatment; intraocular pressure; optic coherence tomography findings; and all ocular examination findings, including central foveal thickness (CFT) measurement and fluorescein angiography findings, were evaluated for each patient. **Results:** After the IDI injection, BCVA value increased ($P < 0.001$) and CFT value decreased ($P < 0.001$) in both groups. The recurrence rates of CFT elevation after the first and the second Ozurdex injections were 65.0% and 65.3%, respectively, in patients with BRVO and 70.9% and 68.1%, respectively, in patients with CRVO. A statistically significant correlation was observed between preinjection CFT value and postinjection recurrence of CFT elevation ($P = 0.017$). **Conclusion:** Treatment with the IDI injections resulted in significant short-term improvement in CFT and BCVA values in patients with clinically significant RVO-related macular edema. Moreover, we observed that high preinjection CFT value was associated with a risk of postinjection recurrence of CFT elevation.

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Retinal vein occlusion (RVO) is the second-most common retinal vascular disease after diabetic retinopathy.[1] Macular edema is the most common cause of reduced vision after RVO and is characterized by increased intraluminal pressure, vascular endothelial damage, and impaired blood–retina barrier that results in leakage.[2] Furthermore, secretion of proinflammatory mediators by the damaged tissue exacerbates the pathogenesis of macular edema.[3,4]

Intraocular injections reduce macular edema and improve the vision of patients with RVO. Intravitreal antivascular endothelial growth factor (VEGF) (bevacizumab, ranibizumab, and aflibercept), intravitreal triamcinolone acetonide, and intravitreal dexamethasone implant (IDI; Ozurdex) injections are effective for treating RVO-related macular edema.[5-9]

Corticosteroids have anti-inflammatory, antiangiogenic, and antivascular permeability characteristics. Several studies have shown that intravitreal steroid injections are effective for treating both branch RVO (BRVO)- and central RVO (CRVO)-related macular edema.[10-12] However, these injections exert a short-term effect and result in complications such as steroid-related increase in intraocular pressure (IOP) or cataract.[12]

The present study investigated the efficacy of recurrence rate of central foveal thickness (CFT) elevation after, alteration of best-corrected visual acuity (BCVA) after IDI injections, and complications associated with IDI injection in patients with treatment-naive BRVO- and CRVO-related macular edema in clinical practice.

Methods

This prospective study included 40 patients with BRVO and 31 patients with CRVO. All study procedures were conducted in accordance with the Declaration of Helsinki and informed consents were obtained from all the patients after obtaining approval from the local Ethics Committee (E-17-1484). All the patients were the Turkish Caucasians.

Complete ophthalmological examinations including biomicroscopy of the anterior segment and posterior segment using a postdilation + 90-diopter lens and a three-mirror contact lens were performed for the patients with diagnosed BRVO or CRVO, who were followed up at the retina department of a tertiary eye care center for treatment.

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This study included treatment-naive patients with CRVO- or BRVO-related macular edema who had a visual acuity of +0.3 logarithm of the minimum angle of resolution (logMAR) or worse and baseline CFT value of >300 μm, which was determined by performing spectral-domain optical coherence tomography (SD-OCT). The Turkish social security system suggests that IDI injection should be used as the first-line treatment for RVO-related macular edema and permits the use of a maximum of two doses of IDI within 1 year in patients with RVO. The patients were followed up every month after the first and the second IDI injections and planned on a PRN (as needed) protocol. After the second IDI injection, patients showing recurrence were treated with anti-VEGF agents (as needed) due to the dose restrictions in our country. Thus, the eyes of the patients who received two doses of the IDI injection as the first-line treatment for RVO-related macular edema were included in this study.

Primary outcome measures of the study were CFT as an anatomical indicator and BCVA as a functional indicator. IOP was measured by performing applanation tonometry. Moreover, recurrence of CFT elevation, time for the recurrence of CFT elevation, and IDI injection-related complications were recorded. Evaluation of the second IDI injection in patients showing recurrence was performed similar to the first injection.

Patients with other retinal vascular diseases, particularly diabetic retinopathy, age-related macular degeneration, uveitis, macular pucker or vitreomacular traction, and neovascularization in the anterior or posterior segment were excluded from the study. Moreover, patients who had previously undergone treatment for macular edema (with steroids, anti-VEGF injections, or laser) and patients with a history of glaucoma or steroid response, ocular surgery (except cataract), and trauma were excluded from the study.

Patients diagnosed with CRVO or BRVO underwent color fundus photography, fluorescein angiography, and SD-OCT.

An 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-OCT, Heidelberg Engineering, Heidelberg, Germany) of the macula was performed for each study eye. Retinal thickness (RT) in the Early Treatment Diabetic Retinopathy Study subfields was analyzed by the RT map analysis protocol.

In each patient, IDI (Ozurdex, 0.7 mg; Allergan, Inc., Irvine, CA, USA) was injected through the pars plana into the vitreous cavity using a customized, single-use 22-gauge applicator. All the injections were administered under sterile conditions in an operating room. After the injection, each patient was prescribed 0.3% ofloxacin eye drops four times a day for 1 week. The patients were monitored for adverse effects during the entire study period. An IOP value of ≥22 mmHg was considered to be high. Patients with an IOP value of ≥25 mmHg were prescribed timolol or combined brinzolamide and timolol therapy.

Statistical analysis

Statistical analyses were performed using SPSS version 18.0 for Windows (SPSS, Inc., Chicago, IL, USA). 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 for adjusting measurements for multiple comparisons, and repeated measures ANOVA test was used for measurements obtained for a single group. $P < 0.05$ was considered statistically significant.

Results

This study included 40 eyes of 40 patients with nonischemic BRVO and 31 eyes of 31 patients with nonischemic CRVO. Demographic data of the patients are shown in Table 1. No significant difference was observed between the two groups with respect to age and gender ($P = 0.480$ and $P = 0.387$, respectively).

The mean BCVA (logMAR) values of the BRVO and CRVO groups at baseline and in subsequent months are shown in Tables 2 and 3. The difference between the baseline and postinjection follow-up BCVA values was statistically significant ($P < 0.001$). BCVA values at each control visit improved significantly compared with the baseline BCVA values ($P < 0.001$). Moreover, BCVA values obtained in the 4th month showed a significant impairment compared with those obtained in the 3rd month ($P = 0.002$). The mean CFT (μm) values of the BRVO and CRVO groups at baseline and in subsequent months are shown in Tables 2 and 3. A statistically significant improvement was observed between the baseline and postinjection follow-up CFT values ($P < 0.001$). Moreover, CFT values obtained in the 4th month showed a significant impairment compared with those obtained in the 3rd month ($P < 0.001$). Recurrence of CFT elevation was observed in 26 (65.0%) eyes in the BRVO group and 22 (70.9%) eyes in the CRVO group at 4 months after the first IDI injection. These cases were treated using a second IDI injection.

The mean BCVA (logMAR) values of the BRVO and CRVO groups after the second IDI injection are shown in Tables 2 and 3. The difference between the baseline and postinjection follow-up BCVA values was statistically significant ($P < 0.001$). BCVA values of each control visit improved significantly compared with the baseline BCVA values ($P < 0.001$). Moreover, BCVA values obtained in the 4th month showed a significant impairment compared with those obtained in the 3rd month ($P = 0.011$). The mean CFT (μm) values of the BRVO and CRVO groups after the second IDI injection are shown in Tables 2 and 3. The improvement between the baseline and postinjection follow-up CFT values was statistically significant ($P < 0.001$). Moreover, CFT values obtained in the 4th month showed a significant impairment compared with those obtained in the 3rd month ($P < 0.001$). Recurrence of CFT elevation was observed in 17 (65.3%) eyes in the BRVO group and 15 (68.1%) eyes in the CRVO group at 4 months after the second IDI injection. These cases were treated using anti-VEGF injections.

Table 1: Demographic data of groups

	BRVO (*n*=40)	CRVO (*n*=31)	*P**
Age (years), mean±SD	62.22±10.00	64.35±10.52	0.387
Sex (male/female), *n*	16/24	15/16	0.480

**P*: Independent samples *t*-test for age, Chi-square test for sex. BRVO: Branch retinal vein occlusion, CRVO: Central retinal vein occlusion, SD: Standard deviation

Table 2: Mean values from baseline to following up in best-corrected visual acuity, central foveal thickness, and intraocular pressure after first and second intravitreal dexamethasone implant injection in branch retinal vein occlusion group

	BCVA (LogMAR)	CFT (μm)	IOP (mmHg)
First IDI injection			
Baseline	1.11±0.61 (0.22-3.10)	570.65±172.01 (295-1171)	14.89±0.77
1st month	0.77±0.64 (0.05-2.10)	301.90±133.41 (141-825)	17.71±0.85
2nd month	0.79±0.63 (0.05-2.10)	303.13±134.68 (141-825)	16.66±0.76
3rd month	0.87±0.66 (0.15-3.10)	323.56±140.01 (150-888)	15.02±0.77
4th month	0.96±0.70 (0.22-3.10)	424.90±161.13 (178-915)	15.15±0.73
Second IDI injection			
1st month	0.87±0.44 (0.20-2.10)	310.50±141.67 (199-425)	18.21±0.85
2nd month	0.89±0.46 (0.22-2.10)	311.19±144.58 (141-825)	16.96±0.74
3rd month	0.90±0.48 (0.22-3.10)	315.10±138.24 (144-846)	15.25±0.72
4th month	0.97±0.50 (0.30-3.10)	363.56±140.01 (150-888)	15.23±0.67

BCVA: Best- corrected visual acuity, CFT: Central foveal thickness, IDI: Intravitreal dexamethasone implant, IOP: Intraocular pressure, LogMAR: Logarithm of minimum angle of resolution

Table 3: Mean values from baseline to following up in best corrected visual acuity, central foveal thickness, and intraocular pressure after first and second intravitreal dexamethasone implant injection in central retinal vein occlusion group

	BCVA (LogMAR)	CFT (μm)	IOP (mmHg)
First IDI injection			
Baseline	1.67±0.70 (0.52-3.10)	723.70±204.39 (412-1384)	14.67±0.61
1st month	1.13±0.58 (0.0-2.10)	335.77±125.70 (181-650)	16.89±0.78
2nd month	1.11±0.57 (0.0-2.10)	338.25±126.17 (181-656)	15.76±0.65
3rd month	1.15±0.55 (0.05-2.10)	355.04±135.44 (187-701)	14.98±0.69
4th month	1.30±0.66 (0.15-3.10)	445.28±152.67 (196-852)	15.03±0.68
Second IDI injection			
1st month	1.21±0.65 (0.50-3.10)	343.14±131.20 (203-692)	17.71±0.80
2nd month	1.23±0.63 (0.50-3.10)	342.43±134.12 (211-698)	16.10±0.70
3rd month	1.27±0.65 (0.52-3.10)	351.90±140.00 (211-755)	15.41±0.66
4th month	1.51±0.71 (0.70-3.10)	424.25±166.42 (246-1101)	15.34±0.63

BCVA: Best-corrected visual acuity, CFT: Central foveal thickness, IDI: Intravitreal dexamethasone implant, IOP: Intraocular pressure, LogMAR: Logarithm of minimum angle of resolution

IOP was measured in the 1st week after the first and the second IDI injections in both the BRVO and CRVO groups. In the BRVO group, the mean IOP value in the 1st week after the first and the second IDI injections was 19.11 ± 0.87 and 20.21 ± 0.93 mmHg, respectively. Topical anti-glaucomatous therapy was required for seven eyes (17.5%) with an IOP value of ≥25 mmHg. Topical timolol therapy and combined brinzolamide and timolol therapy were administered in 3 (7.5%) and 4 (10.0%) eyes, respectively, with an IOP value of ≥25 mmHg. In the CRVO group, the mean IOP value in the 1st week after the first and the second IDI injections was 18.98 ± 0.91 and 19.46 ± 0.95 mmHg, respectively. Topical anti-glaucomatous therapy was required for 5 (16.1%) eyes with an IOP value of ≥25 mmHg. Topical timolol therapy and combined brinzolamide and timolol therapy were administered in 2 (6.4%) and 3 (9.6%) eyes, respectively, with an IOP value of ≥25 mmHg. None of the patients required surgical intervention for glaucoma. The mean IOP value in the BRVO and CRVO groups was the highest in the 1st and 2nd months after the IDI injection. Moreover, no difference was observed between IOP values obtained in the 3rd and 4th months and baseline IOP values after the first and the second IDI injections ($P > 0.05$).

Twenty-eight (70.0%) patients in the BRVO group and 21 (67.7%) patients in the CRVO group were phakic. Cataract, which impairs visual acuity and requires surgical intervention, developed in 3 (10.7%) phakic eyes in the BRVO group and 3 (14.2%) phakic eyes in the CRVO group after the two IDI injections and was treated by performing phacoemulsification surgery.

During follow-up, none of the patients developed endophthalmitis and other ocular complications related to IDI injections.

When the cases were grouped as CFT <500 μm, 500–699 μm, and ≥700 μm before IDI injection, a significantly different recurrence of CFT elevation development was observed between the groups in the postinjection period ($P = 0.032$) [Table 4]. Furthermore, results of binary logistic regression analysis, which was performed to investigate the correlation between preinjection CFT value and postinjection recurrence of CFT

Table 4: Relationship between preinjection central foveal thickness and postinjection recurrence

CFT (μm)	Recurrence (*n*=48)	No recurrence (*n*=23)	*P**
<500 (*n*=17)	8	9	0.032
500-699 (*n*=32)	21	11	
≥700 (*n*=22)	19	3	

**P*: Chi-square test. CFT: Central foveal thickness

elevation, showed a significant association between high preinjection CFT value and postinjection recurrence of CFT elevation (binary logistic regression analysis, $P = 0.017$; not shown in the tables).

Discussion

RVO is a disease with an increased risk with age and that may have systemic vascular risk factors such as atherosclerosis, diabetes mellitus, or hypertension. Studies have reported that individuals aged 60–70 years commonly develop RVO.[1,13] In the present study, the mean age of the patients in the BRVO and CRVO groups was 62.22 ± 10.00 and 64.35 ± 10.52 years, respectively, which was consistent with that reported in the literature.

Studies have shown clinically significant improvement and increased vision after the administration of the IDI injection in patients with RVO.[9,10,14,15] In the present study, the IDI injection decreased CFT value and increased BCVA value in both the BRVO and CRVO groups. Moreover, a significant difference was observed between pre- and post-injection CFT and BCVA values ($P < 0.001$ and $P < 0.001$, respectively).

The Geneva Study is a pivotal study that showed the efficacy of the IDI injection for treating RVO. This study showed that corticosteroids exerted anti-inflammatory and anti-angiogenic effects, affected vascular permeability, and reduced macular edema and serous macular detachment.[16] The IDI injection results in visual improvement in the early period after the injection, which peaks by 6 weeks after the injection. However, a single IDI injection results in short-term improvement in vision that lasts for a maximum of 3–4 months, after which the BCVA value decreases. Although significant improvement was observed in the vision of the study patients in the early stage of the study, 65.0% patients with BRVO and 70.9% patients with CRVO showed recurrence of CFT elevation after the first IDI injection. Moreover, macular edema recurrence was observed after 4 months in the two groups, and patients showing recurrence received repeated IDI injections. However, the recurrence rates after the second IDI injection were 65.3% and 68.1% in the BRVO and CRVO groups, respectively, after 4 months, which were similar to that after the first injection. Similarly, Joshi *et al*. reported recurrence rates of 56% and 60% in patients with RVO after the first and the second Ozurdex injections, respectively.[17]

Chiquet *et al*. compared the efficacy of IDI and anti-VEGF therapies in patients with treatment-naive RVO-related macular edema.[18] The mean IDI injection was 1.6 ± 0.6, and anti-VEGF injection was 6 ± 1.5 at the end of the 1st year. Moreover, visual acuity in the 3rd month was significantly higher in the IDI group than in the anti-VEGF group; however, no difference was observed in recurrence rates, visual acuity, and CFT values between the two groups in the 6th month and thereafter. In similar studies, anti-VEGF therapy administered PRN monthly and IDI therapy administered PRN at 6-month intervals yielded functionally and anatomically comparable outcomes after a follow-up of 12 months. Therefore, more anti-VEGF injections according to IDI injections are required to maintain similar clinical activity after the 3rd month.[19,20]

The Turkish social security system permits the use of a maximum of two doses of IDI injection within 1 year in patients with RVO. However, in studies performed in other countries, there is no restriction on the number of doses of IDI injection used for treating RVO-related macular edema.[21-24] Therefore, in the present study, we used anti-VEGF injections in patients who showed recurrence after the second IDI injection. Recurrence of macular edema is still an important problem. New strategies for Ozurdex injection, such as administration of several injections per year or regular administration of the injection at specific intervals, will help in overcoming this problem. Quergues *et al*. reported that administration of Ozurdex injection at intervals shorter than 6 months provided prolonged clinical benefits in patients with macular edema.[25] Coscas *et al*. reported good efficacy and safety profiles of repeated IDI injections.[26] Studies have also shown that properly implanted Ozurdex according to the PRN protocol yields high efficacy, and the number of injections per year has increased.[24,27]

Increase in VEGF levels plays a primary role in inducing neovascularization, vascular leakage, and macular edema in patients with diabetic retinopathy and retinal vascular occlusions. However, VEGF is not the only cytokine that whose levels increase in patients with these pathologies. Cytokines such as MCP-1, intercellular adhesion molecule-1, and interleukin-6 also play a role in the pathogenesis of these diseases.[28,29] Specific therapeutic agents targeting a single molecule (e.g., anti-VEGF agents) exert a partial effect on specific pathways involved in the pathogenesis of these diseases. Development of resistance to these agents and frequent recurrence after treatment in some patients may be because of the involvement of different cytokines in the etiopathogenesis of these diseases. The normal vitreous level of VEGF in one-third patients with CRVO is one of the factors that affect the alternatives of the treatment and the response to the therapy.[30]

We investigated the effect of CFT value before the IDI injection on recurrence after the injection in the present study. We observed a statistically significant association between preinjection CFT value and postinjection recurrence ($P = 0.032$). Yoo *et al*. observed a positive correlation between baseline central RT value and macular edema recurrence in 63 patients receiving intravitreal bevacizumab injection for treating BRVO-related macular edema.[31] In contrast, Yasuda *et al*.[32] observed a strong correlation between a pretreatment low CFT value and post-treatment macular edema recurrence in patients with BRVO receiving intravitreal bevacizumab injection; however, this correlation was not statistically significant (odds ratio, 0.98; 95% confidence interval, 0.96–1.00, $P = 0.063$). We determined the correlation between preinjection CFT value and postinjection macular edema recurrence by performing binary regression analysis ($P = 0.017$) and found that high preinjection CFT value was associated with increased

postinjection macular edema recurrence. This is the first study to investigate the relationship between preinjection CFT value and postinjection macular edema recurrence in patients with RVO following IDI administration.

IOP value increased in both groups after the IDI injection. Studies have reported that the requirement of topical medication for managing IOP elevation varies between 6% and 27%.[9,17,33] In the present study, 17.5% patients in the BRVO group and 16.1% patients in the CRVO group required topical antiglaucomatous treatment. Moreover, none of the patients required filtration surgery and/or systemic treatment.

The risk of cataract formation is high in patients receiving multiple IDI injections.[34] However, cataract may form because of long-term steroid secretion after a single injection. In the present study, cataract surgery was required in 12.2% (6/49) phakic patients during the follow-up for 18 months. These six patients were those who received two intravitreal Ozurdex injections because of recurrence. Ozkaya *et al*. reported a cataract surgery rate of 4.4% after a single IDI injection.[35] In a wide-series study by Eter *et al*. involving 573 patients, the cataract surgery rate was 6.1% after a mean of 1.17 IDI injections.[36]

Our study has some limitations. First, this study included a small sample size. Second, the study patients were followed up for a short duration. Therefore, the results of the present study should be considered as preliminary outcomes. Furthermore, this clinical study investigated the effect of preinjection CFT value on postinjection recurrence in RVO patients treated with IDI.

Conclusion

Our results indicate that the IDI injections were well tolerated and resulted in short-term clinical improvement in patients with BRVO- and CRVO-related macular edema. However, different strategies such as frequent injection or regular administration protocols should be developed because of the short-term efficacy and high recurrence rates of CFT elevation associated with this treatment. We believe that IDI injections should be administered on a PRN basis (as needed) in patients with RVO-related macular edema. However, different approaches should be considered, especially in patients with high preinjection CFT values, to eliminate the high risk of postinjection recurrence.

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Conflicts of interest

There are no conflicts of interest.

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