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Intravitreal dexamethasone implant results in the treatment of non-infectious uveitis

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ABSTRACT

OBJECTIVE: The objective of this study was to evaluate the efficacy of intravitreal dexamethasone implant in non-infectious uveitic macular edema.

METHODS: Between April 2013 and February 2017, 27 eyes of 21 patients were included in the study at Haydarpasa Numune Training and Research Hospital. The files of patients who underwent intravitreal dexamethasone implantation for non-infectious uveitic macular edema and followed up at least 6 months were retrospectively reviewed. The patients were evaluated in terms of best-corrected visual acuity (BCVA) and central macular thickness (CMT) before and at the 1st, 3rd, and 6th months after injection and the need for re-injection.

RESULTS: Twenty-seven eyes of 21 patients were included in the study. The mean age of the patients was 39.2±11.7 years. The mean monitoring time was 24.15±10.08 months. In patients who received single-dose intravitreal dexamethasone implant, the decrease in CMT measurements and improvement in BCVA measurements at 1, 3, and 6 months after injection compared to baseline was found to be statistically significant (p=0.001 for each). Recurrence was detected in 33.3% (n=9) of the cases during follow-up; in cases with recurrence, second implants were repeated after an average of 9.67±3.12 months. The third dexamethasone implantation was applied due to the second relapse of four cases from nine relapsing cases. Third implants were performed at an average of 12.50±4.79 months. During the follow-up period, the most common complications in our patients were cataract (37%) and increased intraocular pressure (40.7%).

CONCLUSION: Intravitreal dexamethasone implantation is an effective and reliable treatment option in non-infectious uveitic macular edema. There was no difference between the first dose and re-implantations in terms of efficacy and safety.

Keywords: Intravitreal dexamethasone implant; macular edema; non-infectious uveitis.

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Uveitis is one of the most important causes of vision loss in developed countries and responsible for 20% of legal blindness [1, 2]. The fact that it affects the young population and its frequent occurrence in our country increases its importance.

Macular edema seen in uveitis patients is the most common cause of vision loss in this disease. It is seen in approximately 65% of intermediate and panuveitis [3]. The most important underlying mechanism in uveitic macular edema is the disruption of the integrity of the

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inner-blood retinal barrier by inflammatory cytokines such as prostaglandins, leukotrienes, protein kinase C, interleukins, tumor necrosis factor, and VEGF, which occur secondary to the uveitic reaction [4].

Prolonged macular edema can lead to permanent morphological changes in the retina, leading to vision loss and blindness. Therefore, rapid treatment of macular edema is important. However, there are some difficulties in the treatment of non-infectious posterior uveitis. Systemic and topical drugs used are often insufficient for treatment and reaching the back tissues of the eye cannot be at the desired level due to the blood-retinal barrier. The target tissue is in a deep hard-to-reach area; There is both inflammation and vascular leak in its pathophysiology; the process is generally chronic, long-term treatment protocols are required to prevent vision loss [5].

Furthermore, even if ocular inflammation is effectively controlled, uveitic macular edema can persist for a long time [6, 7]. In a multi-centered study about the usage of steroids in uveitis, it was reported that active uveitis could be effectively controlled with systemic immunosuppressive therapy, but after 2 years, cystoid macular edema improved only in 52% of the patients and 60% of these patients needed additional local corticosteroid applications [8].

Ozurdex (Allergan Inc., Irvine, CA, USA), a slow-release dexamethasone implant, which is frequently preferred in ophthalmology practice in the treatment of non-infectious uveitis, has strong anti-inflammatory properties. Studies have proven its effectiveness and reliability in the treatment of macular edema [9, 10].

In our study, we aimed to evaluate the efficacy and reliability of slow-release intravitreal dexamethasone implant in the treatment of non-infectious uveitic macular edema.

MATERIALS AND METHODS

The files of patients who received single or multiple intravitreal dexamethasone implant for macular edema due to non-infectious uveitis between April 2013 and February 2017 at Health Sciences University Haydarpasa Numune Training and Research Hospital Eye Clinic and followed up for at least 6 months were retrospectively analyzed.

The study was carried out under the 1964 Helsinki Declaration ethical standards following the approval of the Ethics Committee of Health Sciences University Haydarpasa Numune Training and Research Hospital (HNEAH-KAEK 2017/KK/14).

Highlight key points

- Intravitreal dexamethasone implant application is an extremely effective treatment method to avoid possible side effects of long-term systemic corticosteroid therapy in the treatment of macular edema due to non-infectious uveitis.
- CMT significantly decreases in the early period and a significant increase in visual acuity occurs in the early post-implantation period.
- Its effectiveness lasts for about 6 months and the frequency of application is less compared to other local applications that can be considered as an important advantage in terms of complications related to the application.
- There was no difference between the first dose and re-implantations in terms of efficacy and safety.

After the patients were informed in detail about the possible risks and side effects of intravitreal injection, their written consents were obtained with the available consent forms. Patients under the age of 18, pregnant or breastfeeding patients, patients with advanced glaucoma, those who previously received anti-VEGF treatment, and patients who developed uveitis due to infectious causes were not included in the study.

Best-corrected visual acuity (BCVA) was measured according to the Snellen chart of all patients before injection. BCVA was measured and recorded again at 1, 3, and 6 months after intravitreal injection. For statistical analysis, the logMAR value was calculated by taking the minus logarithm of the decimal representation of the visual acuity value taken according to the Snellen chart as defined by Westheimer.

Anterior segment structures were evaluated with slit-lamp biomicroscopy and dilated fundus examinations were performed with a 90D lens in all subjects. Intraocular pressures (IOPs) were measured by the same physician (NTD) between 09 and 10 in the morning with Goldman applanation tonometry in order not to be affected by the diurnal change.

Central macular thickness (CMT) measurements were made with RTVue-100 (Optovue Inc., Fremont, CA, USA) Fourier Domain Optical Coherence Tomography (OCT) system before intravitreal injection and 1st, 3rd, and 6th after injection. At each OCT scan, patients were instructed to look at the internal fixation light, and foveal centered images were provided. The signal strength of all OCT scans was ensured to be above 70% and segmentation errors were not accepted. Measurements were repeated until good quality was achieved.

Table 1. Evaluation of CMT and BCVA measurements after a single dose intravitreal dexamethasone implant

n=27	CMT		LogMAR	
	Mean±SD	Min–Max (Median)	Mean±SD	Min–Max (Median)
Baseline	523.67±100.10	334–834	0.82±0.47	0.3 –1.8
1st month	286.19±50.36	235–436	0.30±0.34	0–1
3rd month	264.63±58.10	181–487	0.26±0.25	0–1
6th month	296.07±113.12	185–745	0.31±0.23	0–1
P	‡***0.001****		‡***0.001****	
Baseline – 1st month	+**0.001****		+**0.001****	
Baseline – 3rd month	+**0.001****		+**0.001****	
Baseline – 6th month	+**0.001****		+**0.001****	
1st month – 3rd month	+**0.006****		+**0.398**	
1st month – 6th month	+**0.886**		+**0.470**	
3rd month – 6th month	+**0.040***		+**0.049***	

‡: Friedman Test; +: Wilcoxon Signed-Ranks Test; *: P<0.05; **: P<0.01; CMT: Central macular thickness; BCVA: Best-corrected visual acuity.

Ozurdex (Allergan, Inc., Irvine, CA) is a slow-release intravitreal dexamethasone implant. This implant contains 700 μg dexamethasone and is injected from the pars plana into the vitreous with a special 22G applicator. Intravitreal injections were applied under operating room conditions. 0.5% proparacaine (Alcaine, Alcon) was dropped to the patients before the procedure. The injections were 4 mm behind the limbus in phakic eyes and 3.5 mm in pseudophakic/aphakic eyes; it was administered from the lower temporal quadrant with a 22 G needle tip. After the injection, the perfusion of the optic nerve was evaluated by controlling the light perception. After injection, moxifloxacin (Vigamox, Alcon) was used 4 times a day for 1 week. Antiglaucomatous treatment was initiated in patients whose IOP was 20 mmHg and above after injection. The patients were evaluated in terms of BCVA, CMT before and at the 1st, 3rd, and 6th months after injection and the need for re-injection. Complications related to treatment were noted.

Statistical Analysis

NCSS (NumberCruncher Statistical System) 2007 (Kaysville, Utah, USA) program was used for statistical analysis. While evaluating the study data, in addition to descriptive statistical methods (mean, standard deviation, median, frequency, ratio, minimum, and maximum), the Mann–Whitney U-test was used to compare two groups of quantitative data that did not show normal distribution. The Friedman Test was used for the comparison of the follow-up of the parameters that did not show a normal distribution, and the Wilcoxon Signed-Ranks Test was used for the paired comparisons. Fisher's Exact test was used to compare qualitative data. The paired sample t-test was used for intragroup comparisons of parameters showing normal distribution, and the Wilcoxon Signed-Ranks Test was used for intragroup comparisons of parameters not showing normal distribution. Significance was evaluated at $p<0.01$ and $p<0.05$ levels.

RESULTS

The study included 27 eyes of 21 patients with a mean 39.2±11.7 (21–61) years. About 52.4% (n=11) were men and 47.6% (n=10) were female. When the patients were evaluated according to their diagnoses, the largest group was idiopathic uveitis (n=8). However, there were Behçet desiase (n=6), sarcoidosis (n=5), Vogt-Koyanagi-Harada syndrome (n=1), and sympathetic ophthalmia (n=1).

The change in CMT measurements before injection, at 1st, 3rd, and 6th month after injection in patients who received intravitreal dexamethasone implant was statistically significant (p=0.001). In pairwise comparisons; compared with pre-injection, the decrease in

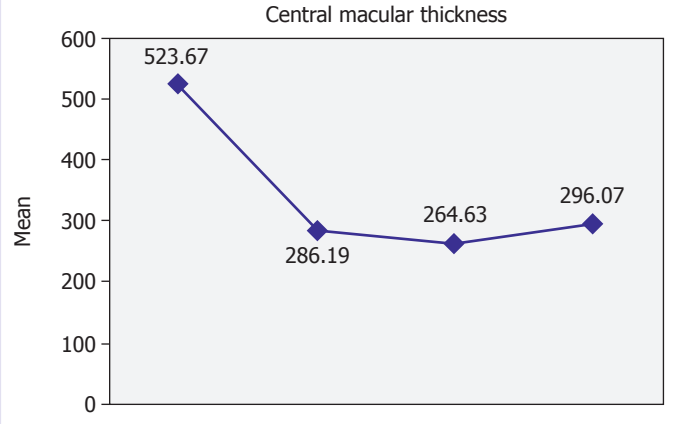

FIGURE 1. Distribution of central macular thickness measurements after single-dose intravitreal dexamethasone implant.

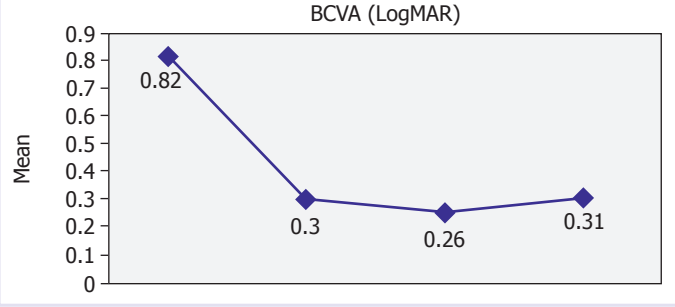

FIGURE 2. Distribution of BCVA (LogMAR) measurements after single-dose intravitreal dexamethasone implant.

BCVA: Best-corrected visual acuity.

CMT measurements at 1, 3, and 6 months after injection was found to be statistically significant (p=0.001 for each). While the decrease in CMT continued in the 3rd month compared to the 1st month after injection (p=0.006), a statistically significant increase was found in the CMT compared to the 3rd month in the 6th month. (p=0.04) (Table 1 and Fig. 1).

The change in mean BCVA measurements who received single-dose intravitreal dexamethasone implant before injection 1st, 3rd, and 6th month after injection was found to be statistically significant (p=0.001). According to the paired comparisons, improvement in mean BCVA measurements at 1 month, 3 months, and 6 months after injection compared to baseline was found to be statistically significant (p=0.001 for each). The decrease in mean BCVA at the 6th month after injection compared to the 3rd month was found to be statistically significant (p=0.049) (Table 1 and Fig. 2).

Anatomic recurrence (increase in CSMT of 50 mm or more identified using SD-OCT imaging) or functional recurrence (decrease in BCVA 1 line or more) was detected in 33.3% (n=9) of the cases during follow-up; in cases with recurrence, intravitreal dexamethasone implants were repeated after an average of 9.67±3.12 months.

The change in CMT measurements before injection, at 1st, 3rd, and 6th month after injection in patients with recurrence was found to be statistically significant (p=0.001). In paired comparisons, there was an increase in the 6th month after injection compared to the 3rd month, while the difference was not statistically significant (p=0.859) (Table 2). The change in BCVA measurements before injection, at 1 month, 3 months, and 6 months after injection in patients with recurrence was statistically significant (p=0.001). In paired comparisons, the improvement in BCVA was statistically significant at 1 month after injections from baseline (p=0.012), at 3 months after injections from baseline (p=0.012), and at baseline and 6 months after injections (p=0.017). Changes at other follow-ups were not statistically significant (Table 2).

Additional intravitreal dexamethasone implants were required in four of nine cases with recurrence. Third implants were performed in an average of 12.50±4.79 months. The distribution of CMT and BCVA measurements in cases with recurrence for the 2nd time is shown in Table 3.

When the change in CMT and BCVA values in the first month after injection in relapse cases compared to the baseline was examined, no statistically significant difference was observed in the first and second implant applications in terms of efficiency (Table 4).

The follow-up period of the cases ranged from 6 to 45 months, with an average of 24.15±10.08 months. A cataract at different levels was developed in 37% of the cases (n=10) during the follow-up period, and cataract surgery was performed in 11.1% (n=3). In 40.7% (n=11) of the cases, IOP was measured above 21 mmHg after injection and all of them could be controlled with anti-glaucomatous drugs. In 88.9% of the cases, there was a history of additional immunosuppressor or immunomodulatory drug usage. About 36.1% of the patients were taking 150 mg/day azathioprine, 13.9% of them 12.5 mg/week methotrexate, 13.9% of them 200 mg/day cyclosporine, and 88.8% of them 5–10 mg/day methylprednisolone.

Table 2. Evaluation of CMT and BCVA (LogMAR) measurements in patients who received a second intravitreal dexamethasone implant

n=9	CMT (µm)		BCVA (LogMAR)	
	Mean±SD	Min–Max (Median)	Mean±SD	Min–Max (Median)
Baseline	477.11±120.03	383–745	0.47±0.18	0.4 –1
1st month	284.78±39.56	234–350	0.11±0.14	0.15 –0.7
3rd month	255.67±42.04	205–331	0.07±0.08	0–0.4
6th month	257.67±33.22	196–292	0.13±0.16	0–0.15
P	‡***0.001****		‡***0.001****	
Baseline-1st month	+**0.008****		+**0.012***	
Baseline-3rd month	+**0.008****		+**0.012***	
Baseline-6th month	+**0.008****		+**0.017***	
1st month-3rd month	+**0.008****		+**0.102**	
1st month-6th month	+**0.028***		+**1.000**	
3rd month-6th month	+**0.859**		+**0.131**	

‡: Friedman Test; +: Wilcoxon Signed-Ranks Test; *: P<0.05; **: P<0.01; CMT: Central macular thickness; BCVA: Best-corrected visual acuity.

Table 3. Evaluation of CMT and BCVA (LogMAR) measurements in patients with a second relapse and a third dexamethasone implant

n=4	CMT (µm)		BCVA (LogMAR)	
	Mean±SD	Min–Max (Median)	Mean±SD	Min–Max (Median)
Baseline	535.25±106.42	438–686	0.305±0.186	0.15 –0.52
1st month	271.25±73.27	231–381	0.075±0.087	0–0.15
3rd month	254.50±26.79	225–290	0.075±0.087	0–0.15
6th month	268.00±30.29	248–312	0.075±0.096	0–0.2

CMT: Central macular thickness; BCVA: Best-corrected visual acuity; SD: Standard deviation; Min: Minimum; Max: Maximum.

DISCUSSION

Macular edema due to the disruption of the blood-retinal barrier is the most important cause of vision loss in non-infectious uveitis patients [11, 12]. Corticosteroids have been used for many years in the treatment of uveitic macular edema and are still the first-line treatment of non-infectious uveitis despite new generation anti-inflammatory treatments [13, 14]. Corticosteroids can be used topically, systemically, and peribulbar in the treatment of non-infectious uveitic macular edema. However, long-term systemic therapy cannot be tolerated by patients due to its possible side effects. For this reason, interest in the use of intravitreal implants, which avoids systemic side effects and minimizes ocular side effects by reducing the frequency of treatment, is increasing day by day in this patient group [15].

In our study, single-dose dexamethasone implantation in addition to systemic treatment in non-infectious uveitic macular edema was found successful in 66.7% of the patients during a mean follow-up period of 24.15±10.08 months. It was observed that the improvement in visual acuity and CMT continued in the first 6 months of follow-up and recurrence occurred in an average of 9.67±3.12 months.

In the present study, with a single dose of dexamethasone implant, an average of 237 µm thinning in the 1st month was detected in the CMT, and it was shown to be

Table 4. Evaluation of CMT and BCVA (LogMAR) changes after the first and sec-ond implant application in patients with recurrence

n=9	First injection	Second injection	p
CMT (µm)			
Baseline			
Mean±SD	514.11±84.64	477.11±120.03	
Min/Max	407/656	383/745	
1st month			
Mean±SD	277.89±48.18	284.78±39.56	
Min/Max	235/402	234/350	
Baseline-1st month			
Mean±SD	-236.22±90.92	-192.33±103.15	**0.236**
Min/Max	-391/-145	-395/-59	
BCVA LogMAR			
Baseline			
Mean±SD	0.49±0.14	0.47±0.18	
Min/Max	0.3/0.7	0.15/0.7	
1st month			
Mean±SD	0.11±0.13	0.11±0.13	
Min/Max	0/0.15	0/0.4	
Baseline-1st month			
Mean±SD	-0.43±0.13	-0.36±0.13	**0.395**
Min/Max	-0.6/-0.25	-0.55/-0.15	

Wilcoxon Signed-Ranks Test; CMT: Central macular thickness; BCVA: Best-corrected visual acuity; SD: Standard deviation; Min: Minimum; Max: Maximum.

an effective treatment in uveitic macular edema. Similarly, in the literature, Zarranz-Ventura et al. [16] found an average of 194 µm thinning, Yalcinbayir et al. [17] 186 µm thinning and Cao et al. [18] 200 µm thinning at the end of the 1st month with single-dose dexamethasone implant application.

Compared to the baseline, in our patients who underwent single-dose intravitreal dexamethasone implant, the improvement in CMT and BCVA measurements at the 1st, 3rd, and 6th months after injection was found to be statistically significant. With these results, it was demonstrated that the effectiveness of the treatment continued for 6 months, both with an increase in visual acuity and a decrease in macular thickness anatomically.

In a published study, pre-injection BCVA (logMar) measurements decreased from 1.14 to 0.6 in the 1st month after injection after dexamethasone implant applied to 17 eyes of 12 patients with macular edema due to Behcet posterior uveitis, which showed a significant improvement [19]. Similarly, Hasanreisoglu et al. [20], after applying dexamethasone implant to 62 eyes with uveitic cystoid macular edema, recorded a significant increase in visual acuity, which was 0.55 logMar BCVA at the beginning and 0.38 in the 1st month after injection. On the other hand, Nobre-Cardoso et al. [21], in their study on patients with non-infectious uveitic macular edema, found a significant increase in visual acuity in a group of 28 patients and found a significant improvement in the mean BCVA after a single dose of dexamethasone implant, changing from 0.64 logMAR to 0.41 logMAR. Tomkins-Netzer et al. [22] achieved a significant increase in visual acuity after a single dose of dexamethasone implant, changing BCVA from 0.47 logMar to 0.27 logMAR in the 1st month after injection.

In the present study, in which we included 27 eyes of 21 patients, the mean BCVA value has changed from 0.82 logMar to 0.30 logMar in the 1st month after single-dose dexamethasone implant injection that means a significant improvement was achieved in the early period.

While macular edema could be controlled with a single dose of intravitreal dexamethasone implant in 66.7% of 27 cases included in our study, we observed recurrent macular edema in 33.3% of the patients. In cases with recurrence, the second dose of intravitreal dexamethasone implant was applied at the earliest in the 5th month and was repeated after an average of 9.67±3.12 months. In four of nine cases with recurrence, a third implant was required. Third injections were done at a mean of 12.50±4.79 months. The mean disease-free survival time was 35.83±1.99 months. In a multicenter retrospective study by Zarranz-Ventura et al. [16], it was reported that 40.7% of the patients followed up for at least 12 months had a second intravitreal dexamethasone implant and re-injection that were performed in an average of 6.6±1.9 months. It was also reported that 11.2% of these patients needed more than three injections and the third injections were made in an average of 11th month, similar to our study.

In our study, we found that the improvement in BCVA measurements and the significant decrease in CMT measurements at the 1st, 3rd, and 6th months after re-injection compared to the previous values was statistically significant. The effectiveness we achieved in the 1st month after re-injection continued at the same level in the 3rd and 6th months.

In a study by Tomkins-Netzer et al. [22] involving 38 eyes of 27 patients, they had to implant dexamethasone in 24 eyes for a 2nd time. They found that BCVA and CMT changes were similar to the first implantation. The third dexamethasone implant was performed in a smaller group and similar results were obtained. As a result, when the efficiency of the first implantation and re-implantation was compared, no statistically significant difference was found.

Besides, we had the chance to obtain the efficiency that we observed in the first implantation in patients who underwent re-implantation. When we compared the first dose and re-injections in nine patients with the first relapse in terms of effectiveness, no statistically significant difference was observed in terms of reduction in macular thickness and increase in visual acuity in the 1st month, similar to other studies in the literature.

Although many side effects related to systemic steroid use can be prevented with intravitreal dexamethasone implant treatment, we may encounter local ocular complications such as cataracts, glaucoma, endophthalmitis, and retinal detachment. Turkcu et al. [23] reported that the most common complications in the follow-up of patients with uveitis were glaucoma and cataracts. Although IOP was measured above 21 mmHg in 40.7% of our subjects after implant application, all of them could be controlled with medical treatment. Dorzolamide+timolol combination was the first choice agent in these patients, and brimonidine tartrate was added as the second antiglaucomatous agent in only two patients. Similarly, after the implant injection antiglaucomatous drug treatment was initiated in 23% of the cases in the HURON study, [11] 13% in the study by Kuppermann et al., [24] and 36.2% in the study by Nobre-Cardoso et al. [21] Although an increase in IOP was detected in about half of our patients, severe vision loss and refractory glaucoma did not develop, clearly demonstrating that implant treatment is safe.

During the follow-up period, different degrees of cataract developed in 37% of our cases, and cataract surgery was performed in 11%. When we investigated similar publications in the literature, the rate of cataract development was reported as 13.2% in the HURON study, and 2.6% of the cases underwent cataract surgery [11]. Nobre-Cardoso et al. [21] examined 41 eyes of 31 patients in their study, and three patients underwent cataract surgery during the follow-up period. In the study conducted by Arcinue et al. [25], in which 11 patients were examined, it was reported that cataracts developed as high as 50% of the patients. Since uveitis patients are frequently exposed to intensive topical and systemic steroid therapy, it affects the rate of cataract development. Inflammation caused by uveitis alone is a sufficient cause of cataract development. Besides, cataract rates will increase with repeated implantations.

The limiting factors of our study are the inability to make a comparison according to the diagnoses of the patients due to the small number of patients, and the low number of patients who underwent re-injection.

Ethics Committee Approval: The Haydarpasa Numune Training and Research Hospital Clinical Research Ethics Committee granted approval for this study (date: 13.02.2017, number: HNEAH-KAEK 2017/KK/14).

Conflict of Interest: No conflict of interest was declared by the authors.

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Authorship Contributions: Concept – ETV; Design – NTD, ETV; Supervision – ETV, NMY; Materials – NTD, NMY; Data collection and/or processing – ESE, NTD; Analysis and/or interpretation – NTD, FD; Literature review – FD; Writing – NTD; Critical review – AK, NMY, ETV.

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