VISUAL OUTCOMES IN PATIENTS WITH DIABETIC MACULAR EDEMA TREATED WITH DEXAMETHASONE IMPLANT IN ROUTINE CLINICAL PRACTICE

Mojca Urbančič[1], Ivana Gardašević Topčić[2] and Katja Matović[1]

[1]Eye Hospital, University Medical Centre Ljubljana, Ljubljana, Slovenia;
[2]Department of Ophthalmology, Novo mesto General Hospital, Novo mesto, Slovenia

SUMMARY – The aim was to evaluate visual outcomes of the real-life usage of dexamethasone (DEX) implants in diabetic macular edema (DME) patients and evaluate the possible additional visual acuity (VA) gain with combined treatment. We retrospectively reviewed medical records of DME patients treated with DEX implants. The mean best-corrected visual acuity (BCVA) and mean central retinal thickness (CRT) at baseline and one year were compared. BCVA improved from 58.4±14.9 letters at baseline to 62.4±14.5 letters at one-year evaluation (p=0.002). The mean change in BCVA was 5.2±11.1 letters. CRT decreased from 485.7±146.3 μm at baseline to 391.5±129.0 μm at one year (p<0.001). The mean change in CRT was -89.6±143.3 μm. Patients received a mean of 2.0±0.7 DEX implants. Study eyes were also divided into a group receiving DEX implant monotherapy and a group receiving DEX implant and vascular endothelial growth factor inhibitor (anti-VEGF) therapy. Changes in BCVA and CRT and the number of DEX implant injections were compared between the two groups. No difference in VA gain was found between the eyes receiving monotherapy and the eyes receiving combined treatment. In conclusion, DEX implant therapy was effective in gaining vision in DME patients. No additional VA gain was achieved with combined treatment.

Key words: *Diabetic macular edema; Dexamethasone implant; Routine clinical practice*

Introduction

Diabetic macular edema (DME) is a common complication of diabetes. It may affect up to 7% of patients with diabetes[1,2], and has a significant negative impact on the patient's quality of life[3,4]. The likelihood of diabetic retinopathy development is strongly related to the duration of diabetes. However, DME can develop at any stage of diabetic retinopathy. The prevalence of DME ranges from 3% among patients with diabetes within 10 years to 20% in those with 20 or more years of the disease[1]. In population-based studies, the prevalence of DME among patients with type 1 diabetes was between 4.2% and 7.9%. In patients with type 2 diabetes, it was between 1.4% and 12.8%[2]. Data available on DME incidence in different types of diabetes are limited and difficult to compare[2]. In Slovenia, the prevalence of patients treated for diabetes was 6.0% in 2018[5]. The prevalence of DME in Slovenia has not yet been systematically studied.

Corticosteroids have been shown to be effective in the treatment of DME by blocking the production of vascular endothelial growth factor (VEGF) and other inflammatory cytokines, by inhibiting leukostasis, and by enhancing the blood-retinal barrier[6]. Long-term corticosteroid use may also have a neuroprotective effect on the retina[7-9].

The results of several trials demonstrated the efficacy and safety of dexamethasone (DEX) implants (Ozurdex®; Allergan, Inc., Irvine, CA, USA) in improving visual acuity (VA) and reducing central retinal thickness

(CRT) in patients with DME[10-15]. According to recent guidelines for the management of DME[16], corticosteroids are mostly a second-line treatment.

Patients treated with DEX implants achieve similar rates of VA improvement with fewer injections than patients receiving anti-VEGF therapy, but there is a higher risk of intraocular pressure (IOP) increase and cataract formation in these patients[17]. Many clinicians combine various treatment modalities to achieve better treatment results or to reduce the burden of repeated injections in patients with DME[18].

Treatment in routine clinical practice differs from that in clinical trials, and there are many factors that may potentially influence the final outcome of treatment in real-life conditions. Patients are usually more heterogeneous, and the inclusion or exclusion criteria for the treatment might be less strictly followed in individual cases. Physicians' decisions may not always be optimal. A heavy burden of frequent visits may result in suboptimal, usually longer treatment intervals.

The primary objective of this retrospective study was to evaluate visual outcome in patients with DME treated with DEX implants in two ophthalmology centers in Slovenia. The secondary objective was to evaluate the possible additional VA gain with combined treatment (DEX implant and anti-VEGF therapy).

Material and Methods

Medical records of patients treated with DEX implants due to DME at the University Medical Centre Ljubljana and Novo mesto General Hospital between June 2016 and June 2018 were retrospectively reviewed. The following data were collected: age, history of previous treatment for DME, best-corrected visual acuity (BCVA) at baseline and after one year, CRT at baseline and after one year, morphological type of edema on optical coherence tomography (OCT) imaging, presence of epiretinal membrane, stage of diabetic retinopathy (DR), lens status, IOP, follow-up intervals, number of DEX implant injections in the first year of treatment, intervals between injections in the first year, and adverse events. The inclusion criteria were patients older than 18 years, diagnosis of DME, availability of complete ophthalmologic medical records, and follow-up period of at least 48 weeks. The exclusion criteria were incomplete ophthalmologic data, significant vitreomacular traction, and vitrectomized eyes. Since for

approximately one-third of patients, there were no data on the type, duration or therapy of diabetes, other systemic risk factors for DR and glycated hemoglobin (HbA1c) levels, these data were not evaluated in this study.

All patients signed informed consent forms. Since this was a retrospective study, the management of patients was not changed in any way for the purpose of the study. The patients were managed according to the routine clinical practice. All patients underwent complete ophthalmologic examination (VA testing, slit lamp and fundus examination, IOP measurement), OCT, fundus photography, and fluorescein angiography at the first visit to evaluate DME and stage of DR before making any treatment decisions. Complete ophthalmologic examination, fundus photography and OCT were performed at every follow-up visit. VA testing was performed using an ETDRS chart (4-meter 2000 series revised ETDRS chart (Precision Vision®, La Salle, USA)), and BCVA was recorded as the number of ETDRS letters. CRT (average retinal thickness in the central subfield) was measured automatically by an SD-OCT machine (Spectralis SD-OCT; Heidelberg Engineering GmbH, Heidelberg, Germany) and/or 3D-OCT 1000 (Topcon Corp., Tokyo, Japan). Treatment options were discussed with the patient. The physicians followed the EURETINA and Slovene national guidelines[16,19] for the management of DME, and a *pro-re-nata* (PRN) treatment regimen was followed for DEX implant monotherapy. However, decision on combined treatment was based on the physicians' evaluation of individual patients. There was no predefined protocol for combined treatment.

Changes in BCVA and CRT and the number of DEX implant injections received in one year were noted. Since follow-up intervals varied and were rarely less than 6 weeks, the evaluation at the time point nearest to the 52nd week was considered to be the evaluation at one year. The mean BCVA and mean CRT for all included eyes at baseline were compared with the mean BCVA and mean CRT at one year. The study eyes were also divided into a group receiving DEX implant monotherapy and a group receiving combined treatment (DEX implant and anti-VEGF therapy). Changes in BCVA and CRT and the number of DEX implant injections were compared between the two groups.

Descriptive statistics included the mean and standard deviation for numerical variables. A paired t-test

was used to compare the mean differences between the baseline and one-year follow-up visits. Since a paired t-test was used, no corrections of CRT values measured by different machines were performed. Two independent samples t-tests were used to compare the mean differences between the two groups of eyes. Statistical analyses were performed using SPSS version 21 (SPSS IBM, New York, USA). A p-value of 0.05 was considered statistically significant.

The study adhered to the tenets of the Declaration of Helsinki and was approved by the Slovenian National Medical Ethics Committee (National Medical Ethics Committee number 0120-604-2018).

Results

Medical records of 153 patients (199 eyes) who received the first DEX implant between June 2016 and June 2018 were reviewed. After checking the inclusion and exclusion criteria, 68 patients (88 eyes) were included in the study. The mean age of the patients was 67.7±10.5 years, 41 (60%) were men and 27 (40%) were women. The baseline characteristics of the 88 eyes are presented in Table 1.

The mean BCVA improved from 58.4±14.9 letters at baseline to 62.4±14.5 letters at the one-year evaluation (p=0.002). The mean change in BCVA was 5.2±11.1 letters. Approximately half of the eyes had a BCVA improvement of 5 or more letters (49%), improvement of 10 or more letters was observed in 29% of the eyes, and improvement of 15 or more letters was observed in 16% of the eyes. On the other hand, 8% of the eyes had 10 or more letters of vision loss, and 4% of the eyes experienced 15 or more letters of vision loss. The mean CRT decreased from 485.7±146.3 μm at baseline to 391.5±129.0 μm at one year (p<0.001). The mean change in CRT was -89.6±143.3 μm.

The follow-up intervals ranged from 4 to 16 weeks (mean 9.0±3.9 weeks). Based on these intervals, the evaluation at one year was the time point nearest to the 52nd week and ranged from 48 to 56 weeks. The patients received 1 to 4 DEX implants within the first year (mean 2.0±0.7), and the intervals between repeated injections varied from 15 to 56 weeks (mean interval 26.4±9.4). Twenty-five (25%) eyes received 1 injection, 45 (51%) eyes received 2 injections, 19 (22%) eyes received 3 injections, and 2 (2%) eyes received 4 injections within the first year.

Table 1. Baseline characteristics of all eyes with DME (N=88 eyes)

Type of DME based on OCT	Diffuse: 20 (23%) eyes Cystoid: 49 (56%) eyes Serous detachment: 19 (22%) eyes
Presence of epiretinal membrane	22 (25%) eyes
Stage of DR	Mild to moderate NPDR: 26 (29%) eyes Severe NPDR: 34 (39%) eyes PDR: 28 (32%) eyes
Lens status	Pseudophakic: 56 (64%) eyes Phakic: 32 (36%) eyes
Baseline IOP	15.9±2.5 mm Hg
Baseline BCVA	58.4±14.9 letters
Baseline CRT	485.7±146.3 μm
Previous treatment	Yes: 56 (64%) eyes No: 32 (36%) eyes

DME = diabetic macular edema; OCT = optical coherence tomography; DR = diabetic retinopathy; NPDR = non-proliferative diabetic retinopathy; PDR = proliferative diabetic retinopathy; IOP = intraocular pressure; BCVA = best-corrected visual acuity; CRT = central retinal thickness

Table 2. Treatments for DME prior to first DEX implant injection (previously treated eyes; n=56 eyes)

Prior treatment	Number of eyes (%)
Anti-VEGF	19 (34%)
Macular laser	6 (10.7%)
Triamcinolone	1 (1.8%)
Anti-VEGF + macular laser	24 (42.9%)
Anti-VEGF + triamcinolone	3 (5.3%)
Triamcinolone + macular laser	1 (1.8%)
Anti-VEGF + triamcinolone + macular laser	2 (3.6%)

DME = diabetic macular edema; DEX = dexamethasone; anti-VEGF = vascular endothelial growth factor inhibitor

Thirty-two (36%) eyes included in the study were treatment naïve (without any previous treatment for DME), while 56 (64%) eyes had been previously treated for DME. Prior treatments for the 56 previously treated eyes are summarized in Table 2. The length of previous treatment varied but was at least 6 months. Some patients had undergone laser treatment several years before and were without treatment for a longer period of time before receiving intravitreal therapy.

Table 3. BCVA and CRT at baseline and 1 year and number of DEX implant injections for all eyes with DME, for eyes receiving DEX implant monotherapy, and for eyes receiving combined treatment

	All eyes (N=88)	DEX monotherapy (n=51 eyes)	DEX + anti-VEGF combined treatment (n=37 eyes)	p (comparison of two treatment groups)
Baseline BCVA (letters)	58.4±14.9	58.2±15.1	59.3±15.0	0.75
BCVA at 1 year (letters)	62.4±14.5	62.3±13.6	63.1±15.6	0.95
Baseline CRT (μm)	485.7±146.3	482.1±135.0	488.8±164.0	0.78
CRT at 1 year (μm)	391.5±129.0	388.9±113.8	391.1±149.2	0.83
Number of DEX injections	2.0±0.7	2.1±0.7	1.9±0.8	0.35

DEX = dexamethasone; anti-VEGF = vascular endothelial growth factor inhibitor; BCVA = best-corrected visual acuity; CRT = central retinal thickness

There were no statistically significant differences in the mean baseline BCVA (p=0.15) or the mean baseline CRT (p=0.62) between treatment-naïve eyes and previously treated eyes. However, a larger proportion of previously treated eyes received additional anti-VEGF therapy during the follow-up period compared with treatment-naïve eyes, i.e. 33/56 (59%) eyes *versus* 4/32 (12%) eyes.

Thirty-seven (42%) of 88 eyes received additional anti-VEGF therapy within the first year of treatment with DEX implant (the mean number of anti-VEGF injections was 3.9±1.5). We found no significant differences in BCVA and CRT changes at one year between the eyes treated only with DEX implant and the eyes receiving combined treatment (Table 3). There were 33 (64.7%) pseudophakic eyes receiving DEX implant monotherapy and 23 (62.1%) pseudophakic eyes receiving combined treatment.

There were no significant differences in the mean baseline BCVA (p=0.95) and the mean BCVA at one year (p=0.93) between phakic and pseudophakic eyes regardless of treatment. None of the observed eyes underwent cataract surgery within the observed period. An IOP increase greater than 30 mm Hg was observed in 4 (4.5%) eyes during the first year and was controlled by topical medications. No other adverse events were noted.

Discussion

Our study showed significant improvements in BCVA in the eyes treated with DEX implants. The mean BCVA change was 5.2±11.1 letters in one year. An improvement of 10 or more letters was observed in 29%, and improvement of 15 or more letters in 16% of the eyes. Changes in CRT were also significant, with a mean CRT change of -89.6±143.3 μm. The mean number of DEX injections within one year was 2.0±0.7.

In a 12-month study comparing DEX implants with ranibizumab, patients with DME were retreated with DEX implants every 5 months. The mean BCVA change from baseline over 12 months was 4.3 letters, and approximately 27% of patients showed more than 15-letter BCVA improvement. The mean CRT change from baseline was -173.9 μm[20]. The patients in this study received 3 DEX injections over the follow-up period and were evaluated 2 months after the third injection. Many studies have shown that the maximal effect of DEX implants is approximately 2 months after injection[11,21-23], so these patients were evaluated at an optimal time point. Although our patients on average received fewer DEX injections and were evaluated mainly at the time when the physician planned retreatment, a similar mean BCVA change was observed at one year. In a study performed by Shah *et al.*, patients treated with DEX implants received 2.7±0.5 injections over 7 months. The mean BCVA change at month 7 was 6 letters, 33% of patients gained 10 or more letters, and 15% gained 15 or more letters[24]. In the BEVORDEX study, patients received a mean of 2.7 DEX implant injections over a period of 12 months; more than 10 letters of VA gain was observed in 41% of eyes, and the mean CRT decreased by 187 μm[12]. We observed 10 or more letters of VA gain in 29% of eyes, but with fewer DEX implant injections. Compared with the REL-DEX study, where BCVA increased by a mean of 4.2 letters at one year, CRT decreased from 451 μm to 370 μm, and patients received a mean of 1.5 injections in

the first year[25], higher VA gains were achieved in our study, but with more injections.

The injection and reinjection criteria for DEX implants vary among different studies. Two crucial studies for DEX implant evaluation, the MEAD and PLACID studies, had fixed retreatment regimens[11,21]. On the other hand, the BEVORDEX study and most real-life studies used the PRN regimen[12,13,26-28]. Our patients were treated according to the PRN regimen, although the follow-up intervals were influenced by health care resources and other factors.

Laser treatment has been a standard of care for DME for many years. However, only 3% of patients showed VA improvement in more than 3 lines after laser treatment. The new standard of care is intravitreal therapy with anti-VEGF agents or steroids. Higher proportions of patients gaining 3 or more lines of VA can be achieved with intravitreal therapy[16]. In our retrospective study, 56 (64%) eyes were previously treated with laser treatment, triamcinolone and/or anti-VEGF agents, which suggests that most of these eyes had chronic, refractory DME.

A larger proportion of previously treated eyes (59%) than treatment-naïve eyes (12%) received additional anti-VEGF therapy in our study, which might suggest that there was a larger proportion of refractory DME in this group of eyes. In a retrospective study performed by Chhablani *et al.*, 43.7% of previously treated eyes and 33.3% of treatment-naïve eyes received additional treatment[27].

We found no significant differences in visual outcome between the eyes treated only with DEX implants and the eyes receiving combined treatment. The authors of a recent large review of published trials comparing anti-VEGF monotherapy with anti-VEGF therapy combined with steroids found no meaningful difference in the change in BCVA or in change in CRT at one year and conclude that there is no additional benefit in combining anti-VEGF therapy with steroids[29]. Trials that compared anti-VEGF monotherapy with DEX implant monotherapy showed similar VA gains in both treatment groups[12,20,24]. To summarize the results from previous studies, similar VA gains can be achieved by using anti-VEGF monotherapy, steroid monotherapy, or a combination of both. Our results are in concordance with those of previous studies. Combining DEX implant injections with anti-VEGF therapy resulted in no additional benefit.

No significant effect of cataract progression in the one-year follow-up period was observed in our study, which was probably due to slow cataract progression. It has been shown in the MEAD study that the majority of surgeries due to cataract formation were performed between 18 and 30 months[11]. However, 24% of eyes underwent cataract surgery within the first year in the IRGREL-DEX study[30].

An IOP increase ≥30 mm Hg was observed in four (4.5%) eyes during the first year and was controlled by topical medications in our study. A transient increase in IOP of ≥25 mm Hg was observed in 10% of eyes in the RELDEX study[25]. IOP increases of ≥35 mm Hg were observed in 4% of patients in the PLACID study[21].

The main limitations of our study were its retrospective nature with limited data and no matching and randomization for eyes receiving DEX monotherapy or combined treatment. The patient baseline characteristics varied greatly; some patients were treatment naïve, and some had already been treated with other treatment modalities. Data on the duration of diabetes, type of diabetes, diabetes control, and duration of DME were not known in all patients and could not be evaluated. Moreover, many physicians were involved in the management of the patients. The physicians did not always strictly follow the criteria for retreatment. In individual cases, the decision on treatment modality or retreatment was at the physician's discretion. The follow-up intervals were influenced by the total number of patients needing treatment and available health care resources. The evaluation after one year could not be performed exactly at the same time point in all patients. However, our study reflects the routine clinical practice management of patients with DME, and it is the first study evaluating visual outcomes in patients with DME treated with DEX implants in Slovenia.

In conclusion, DEX implant injections were effective in gaining vision in eyes with DME. The visual outcomes in routine clinical practice in Slovenia were comparable to previously published real-life outcomes. There was no additional VA gain in combining DEX implant injections with anti-VEGF therapy.

Acknowledgment

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Sažetak

ISHOD VIDNE OŠTRINE U BOLESNIKA S DIJABETIČKIM MAKULARNIM EDEMOM
LIJEČENIM IMPLANTATOM DEKSAMETAZONA U RUTINSKOJ KLINIČKOJ PRAKSI

M. Urbančič, I. Gardašević Topčić i K. Matović

Cilj je bio procijeniti ishod vidne oštrine (VA) uz primjenu implantata deksametazona (DEX) u stvarnom životu kod bolesnika s dijabetičkim makularnim edemom (DME) te moguće dodatno poboljšanje VA uz kombinirano liječenje. Proveden je retrospektivni pregled medicinske dokumentacije bolesnika liječenih implantatom DEX zbog DME. Uspoređivane su srednje vrijednosti najbolje korigirane vidne oštrine (BCVA) i srednje vrijednosti centralne debljine mrežnice (CRT) na početku i nakon godinu dana. BCVA se poboljšala s 58,4±14,9 slova u početnoj procjeni na 62,4±14,5 slova pri procjeni nakon godinu dana (p=0,002). Srednja promjena BCVA iznosila je 5,2±11,1 slova. CRT se smanjio s 485,7±146,3 μm na početnoj razini na 391,5±129,0 μm nakon godinu dana (p<0,001). Srednja promjena CRT bila je -89,6±143,3 μm. Bolesnici su primili u prosjeku 2,0±0,7 implantata DEX. Oči su podijeljene u skupinu koja je primala monoterapiju implantatom DEX i skupinu koja je primala kombinaciju implantata DEX i blokatora vaskularnog endotelnog faktora rasta (anti-VEGF). Promjene u BCVA i CRT te broj injekcija implantata DEX uspoređene su između dviju skupina. Nije utvrđena razlika u poboljšanju VA između dviju skupina. Zaključeno je da je implantat DEX bio učinkovit u poboljšanju vida kod bolesnika s DME. Kombiniranim liječenjem nije postignuto dodatno poboljšanje VA.

Ključne riječi: *Dijabetički makularni edem; Deksametazonski implantat; Rutinska klinička praksa*