

Real Life Experience of Dexamethasone Implant in Refractory Diabetic Macular Oedema

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Purpose: The purpose of this retrospective study was to examine the efficacy of dexamethasone implant in refractory diabetic macular oedema (DMO) in real life settings.

Methods: In all, 24 eyes of 22 patients that required treatment with single or multiple intravitreal dexamethasone implants for refractory DMO were included in the study. Patients having macular oedema for another retinal disease were excluded from the study. The patient data were collected and analyzed retrospectively. As a demographic data age, gender, the type of diabetes and the duration of DMO were collected. Changes in central foveal thickness and the number of hyper reflective spots (HRS) were analyzed with Heidelberg SD-OCT. Furthermore, the best-corrected visual acuity (BCVA) and changes in the intraocular pressure (IOP) were measured.

Results: In all, 50.0% of the eyes with baseline BCVA 0.45 (± 2.4) lines in ETDRS LogMAR scale received only one implant during the follow-up of 332 (± 79) days. At the end of the follow-up, BCVA was 0.26 (± 2.0) lines. The other 50.0% of the eyes with baseline BCVA 0.64 (± 3.0) lines received the second implant in 156 (± 38) days. Central retinal thickness (CRT) at baseline was 333 (± 44) μm in the eyes with only one implant and 497 (± 125) μm in the eyes with 2 or more implants. IOP lowering medication was needed for 8.3% of the eyes. The decrease in the number of HRS was significant (8 ± 17 , $p=0.048$) in response to dexamethasone implantation.

Conclusion: The dexamethasone implant is a useful treatment in refractory DMO and HRS seen in the OCT might indicate inflammation in the retina.

Keywords: diabetic macular oedema, DMO, dexamethasone implant, hyper reflective spots, HRS, optical coherence tomography, OCT

Introduction

Diabetic macular oedema (DMO), one of the most severe complications of diabetes in the eye, is the leading cause of visual impairment in working-age population in developed countries. There are over 21 million people suffering from DMO in the world.¹ DMO is defined as thickening of the retina or appearance of hard exudates within 1 disc diameter of the center of the macula. Clinically significant macular oedema (CSME) was later described as thickening of retina within 500 μm center of the macula or hard exudate with adjacent retinal thickening within 500 μm center of the macula or a zone of retinal thickening 1 disc area or larger, any part of which is within 1 disc diameter of the center of the macula.²

Macular oedema is caused by dysfunction of blood-retinal barrier (BRB). BRB can be divided into inner and outer parts. Inner BRB is composed of tight junctions between vascular endothelial cells separating the vessel lumen from retinal glial

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cells (astrocytes and Müller cells). In addition, outer BRB is formed by tight junctions between retinal pigment epithelial (RPE) cells.³

BRB breakdown, leading to DMO is a multifactorial process. Vascular leukostasis, loss of pericytes, changes in tight junctions, endothelial dysfunction, up-regulation of vesicular transport, permeability of RPE cells and formation and accumulation of glycation end-products lead to DMO.³ Activation of protein kinase C by vascular endothelial growth factor (VEGF) is significant in DMO formation.^{4,5} Furthermore, inflammation is considered to be present in DMO and it is an important factor in BRB breakdown.⁶ Microglial activation starts at inner retinal layers and microglial aggregates are formed. These aggregates are thought to be hyper-reflective spots (HRS), seen in different retinal layers already at early stages of diabetic eye disease in spectral domain-OCT (SD-OCT), representing the inflammatory process in the retina.^{7–10}

Furthermore, the levels of inflammatory cytokines have shown to be increased in the vitreous in DMO patients and the treatment of refractory DMO with intravitreal corticosteroids has been found to be effective.^{11–14} Corticosteroids keep the integrity of the BRB and decrease the levels of inflammatory factors in the vitreous such as VEGF, Interleukin (IL)-6 and intercellular adhesion molecule (ICAM)-1.^{15–17} The aim of this study was to analyze real-life patients with refractory DMO treated with intravitreal dexamethasone implant. The dexamethasone implant Ozurdex[®] is a small corticosteroid implant injected in the vitreous. The implant dissolves slowly and releases medicine to treat the macular oedema. Ozurdex[®] has approved indications in the treatment of: DMO, branch retinal vein occlusion (BRVO), central retinal vein occlusion (CRVO) and non-infectious uveitis in adults. In previous studies, the dexamethasone implant has been shown to be effective in treating DMO with single or multiple injections. Also, the safety profile of the treatment is acceptable.¹⁸

Methods

The research was conducted according to the ethical standards of the Declaration of Helsinki. The patient consent statement was not required in this retrospective study. Kuopio University Hospital approved the study with organization permit and the hospital policy of confidentiality was followed. Retrospective analysis for 24 eyes of 22 patients was made in Kuopio University Hospital, Department of Ophthalmology in 2014. All the patients got intravitreal dexamethasone implant treatment for

previously diagnosed DMO in the year 2013. The inclusion criteria were: DMO with no improvement in BCVA with anti-VEGF therapies and more than 3 months from previous laser and surgical operations. Exclusion criteria were: other retinal diseases evoking macular oedema. Several ophthalmologists with experience in technique gave the injections. Technique-related complications or infections or hemorrhages were not reported. The schedule of observation after injections was planned case-specifically.

The age, gender, type of DM, previous ocular surgeries and treatments were checked. The intraocular pressure (IOP) was measured with Goldmann applanation tonometry (Haag-Streit, Bern, Switzerland). The OCT images were taken with Heidelberg Spectralis[®] SD-OCT (Heidelberg Engineering, Heidelberg, Germany) and analyzed with Heidelberg Eye Explorer version 1.9.10.0. Two individual examiners analyzed the OCT images. The central retinal thickness (CRT) was measured. The HRS were calculated at foveal cross-section and 3 upper and 3 lower sections within papilla diameter from the fovea. Because of refractory DMO the inner nuclear layer (INL), the outer plexiform layer (OPL) and the outer nuclear layer (ONL) of the retina were analyzed. The other retinal layers were excluded to avoid miscalculation in the number of HRS, since other findings in OCT such as hard exudates and blood vessels were prominent in these layers. HRS were calculated from the OCT image before the first dexamethasone implant and compared to the OCT image at the control visit 61 days after. The results were analyzed with IBM SPSS Statistics version 21 (SPSS Inc., Chicago, IL).

Paired samples *t*-test was used to calculate the differences in BCVA and CRT values after normality tests. Pearson's correlation was calculated with BCVA and CRT values. The tables and figures were made with GraphPad Prism version 5.0. (GraphPad software, Inc.).

The patients were divided into two groups for statistical analysis. The group 1 composed of patients who managed only with one implant and the group 2 composed of patients who needed the second or the third implant.

Results

The analysis of efficacy and the number of implantations show that 50.0% of the eyes did not need any additional therapy for DMO during the follow-up of 332 (± 79) days. The mean ETDRS BCVA at baseline with both groups was 0.54 (± 2.7) lines. In the follow-up of 138 (± 35) days, the BCVA was stable 0.4 (± 3.2) (Figure 1). After the first implant treatment, 50% of the eyes received the second

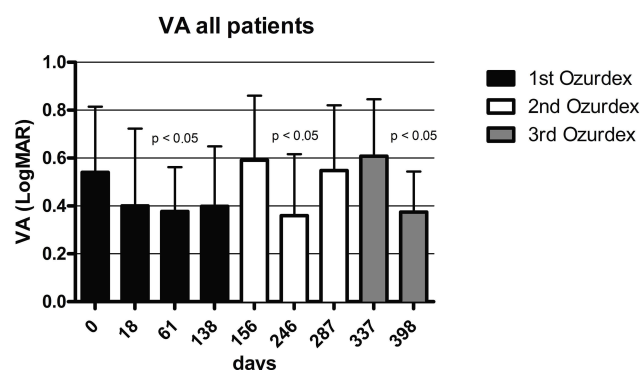


Figure 1 Visual acuity (VA) of all patients.

implant in 156 (± 38) days with BCVA 0.59 (± 2.7) lines. At the first control, 90 days after the second implant BCVA was 0.36 (± 2.6) lines (day 246). The effect of the second implant was lost in 132 (± 19) days (day 287). 25 % of the eyes received the third implant 181 (± 38) days after the second implant with BCVA 0.6 (± 2.4) lines (day 337). The latest control during the follow-up was 61 days after the third implant when BCVA was 0.37 (± 1.7) lines (day 398). The BCVA improved 0.19 (± 2.0) lines ($n=5$) ($p=0.087$) in the vitrectomized eyes and in the non-vitrectomized eyes the BCVA improved 0.16 (± 2.4) lines ($n=19$) ($p=0.01$) with one dexamethasone implant.

The demographic data of the patients are shown in Table 1.

In the group 1 the mean duration of DMO before the treatment was 23.0 (± 24.7) months and the baseline BCVA was 0.45 (± 2.4) ETDRS LogMAR lines (Figure 2). In addition, the baseline CRT was 333 (± 44) μm . The improvement in BCVA with one implant was 0.19 (± 0.8) lines ($p=0.000$), and the decrease in CRT 34 (± 36) μm ($p=0.022$). The end point BCVA was 0.26 ± 2.0 lines. The follow-up time with these patients was 332 (± 79) days (Figure 2).

As shown in Table 1, almost all patients in the group 2 had type 2 diabetes. The mean duration of DMO in these patients before the treatment was 29 (± 24) months, which was not statistically higher than in the group 1 ($p=0.56$). The baseline BCVA was 0.64 (± 3.0) lines with no significant difference from the baseline BCVA of group 1 (0.19 ± 1.2 lines, $p=0.114$, $n=22$). The baseline CRT in the group 2 was 497 (± 125) μm and, in contrast to the BCVA values, the difference in the baseline CRT between groups 1 and 2 was statistically significant (164 ± 46 μm , $p=0.007$). However, there was no statistically significant correlation

Table 1 Demographic Data (Standard Deviation)

Demographic Data	All Patients	Group 1	Group 2
Patients	22	12	10
Eyes	24	12	12
Age	65.6 (10.6)	67 (14)	64 (4)
Gender F/M	8/14	5/7	3/7
DM type 1	22.7%	33.3%	8.3%
DM type 2	77.3%	66.7%	91.7%
Duration of DMO in months	26.1 (23.8)	23.0 (24.7)	29.0 (24.0)
Previous number of injections			
Bevacizumab	4.4 (2.9)	3.8 (2.4)	5.1 (3.3)
Triamcinolone	0.5 (0.7)	0.3 (0.5)	0.6 (0.9)
Laser			
Macular	54.0%	42.7%	66.7%
Peripheral	50.0%	33.3%	66.7%
Pseudophakic	54.0%	58.3%	41.7%
Vitrectomy done	20.8%	25.0%	16.7%

Abbreviations: DM, diabetes mellitus; DMO, diabetic macular oedema; F, female; M, male.

between BCVA and CRT values in groups 1 and 2 in any of the time points during the study.

In the group 2, improvement in BCVA after the second implant was 0.23 (± 1.9) lines ($p=0.001$, $n=12$), and after the third implant 0.23 (± 2.1) lines ($p=0.0225$, $n=6$) (Figure 3). The decrease in CRT after the second implant was statistically significant ($179 \pm 136 \mu\text{m}$, $p=0.042$, $n=5$) while after the third implant this response was no longer observed ($129 \pm 105 \mu\text{m}$, $p=0.053$, $n=5$) (Figures 4 and 5).

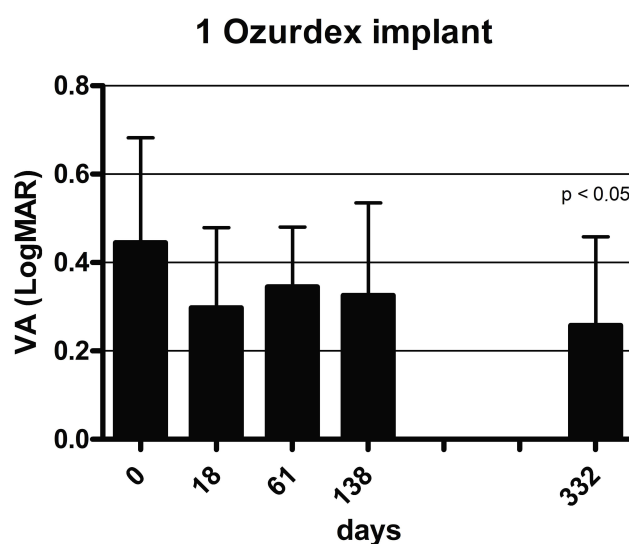


Figure 2 Visual acuity (VA) of the patients that managed with one dexamethasone implant.

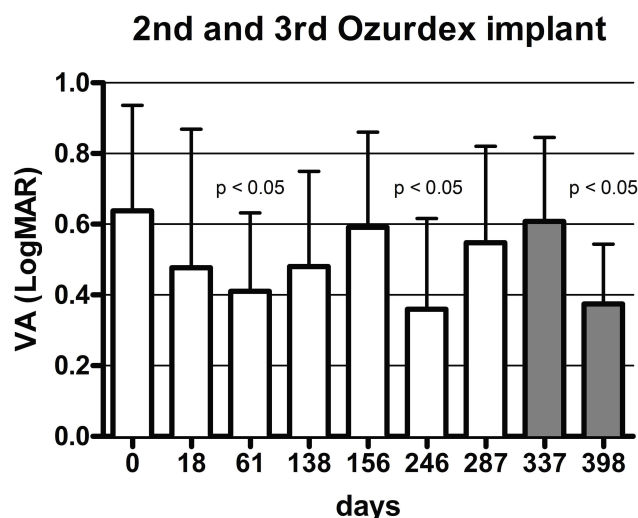


Figure 3 Visual acuity (VA) of the patients that needed two or three dexamethasone implants. The second implant was injected at day 156 and third implant at day 337.

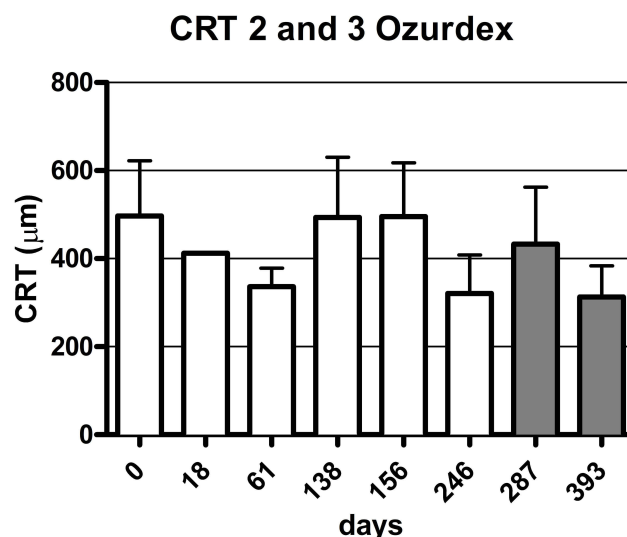


Figure 5 Central retinal thickness (CRT) of the patients that needed two or three dexamethasone implants.

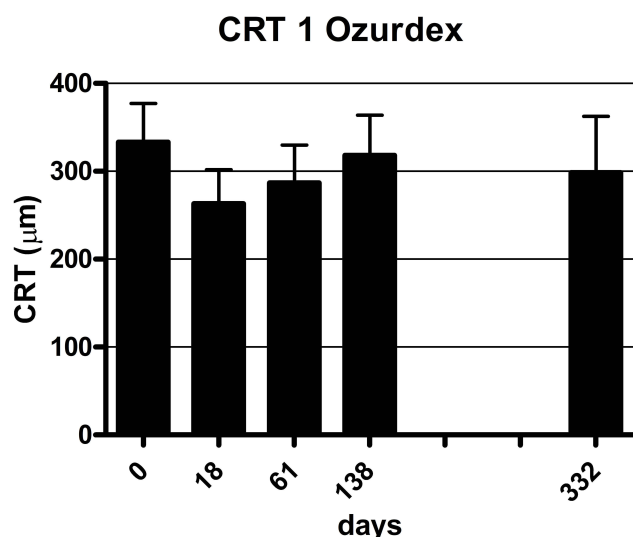


Figure 4 Central retinal thickness (CRT) of the patients that managed with one dexamethasone implant.

The HRS were seen as more numerous and prominent in the OCT images before dexamethasone treatment compared to the OCT images after the treatment in both groups

(Figure 6). At the baseline, the mean number of HRS in all cross-sections was (67 ± 20) and, after one implant, at the control visit 61 days later, the mean number of HRS was significantly lower $(59 \pm 22, p=0.048)$ (Table 2). The difference in the mean number of HRS at baseline between groups 1 and 2 was statistically significant $(15.75 \pm 8.7, p=0.089)$. In the group 1, the decrease in the number of HRS after the treatment was not significant $(5 \pm 18, p=0.409)$. However, in the group 2, the decrease was significant $(12 \pm 14, p=0.042)$. The difference in the number of HRS was not statistically significant between DM1 and DM2 patients.

When looking at the morphological changes in the OCT images, there were some differences between patients in the group 1 and group 2. In the group 1, oedema was composed of a few large parafoveal cysts. In contrast, in the group 2 diffuse cystic oedema was seen (Figure 7).

The mean IOP values are presented in Figure 8. In 3 eyes IOP increased over 10 mmHg. Increased IOP was treated successfully with IOP lowering medication in all 3 eyes.

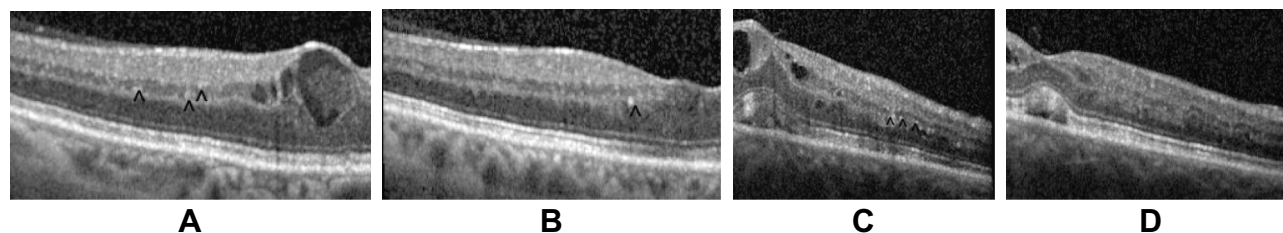


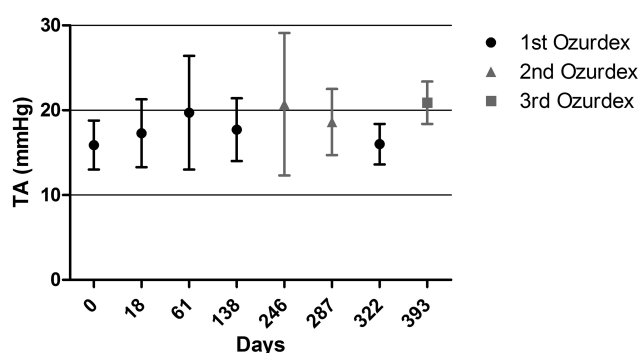
Figure 6 Hyper-reflective spots (HRS) in the inner nuclear layer (INL) and in the outer plexiform layer (OPL) are seen more prominently in the OCT before the dexamethasone implant. Magnification of Group 1 (A and B) and Group 2 (C and D) OCT pictures.

Table 2 Accumulation of Hyper-Reflective Spots (HRS) (Standard Deviation)

Hyper-Reflective Spots (HRS)					
	All patients	Group 1	Group 2	DM1	DM2
Baseline	67 (20)	74 (22)	58 (12)	62 (16)	69 (21)
Treated	59 (22)	69 (13)	45 (25)	55 (22)	60 (23)

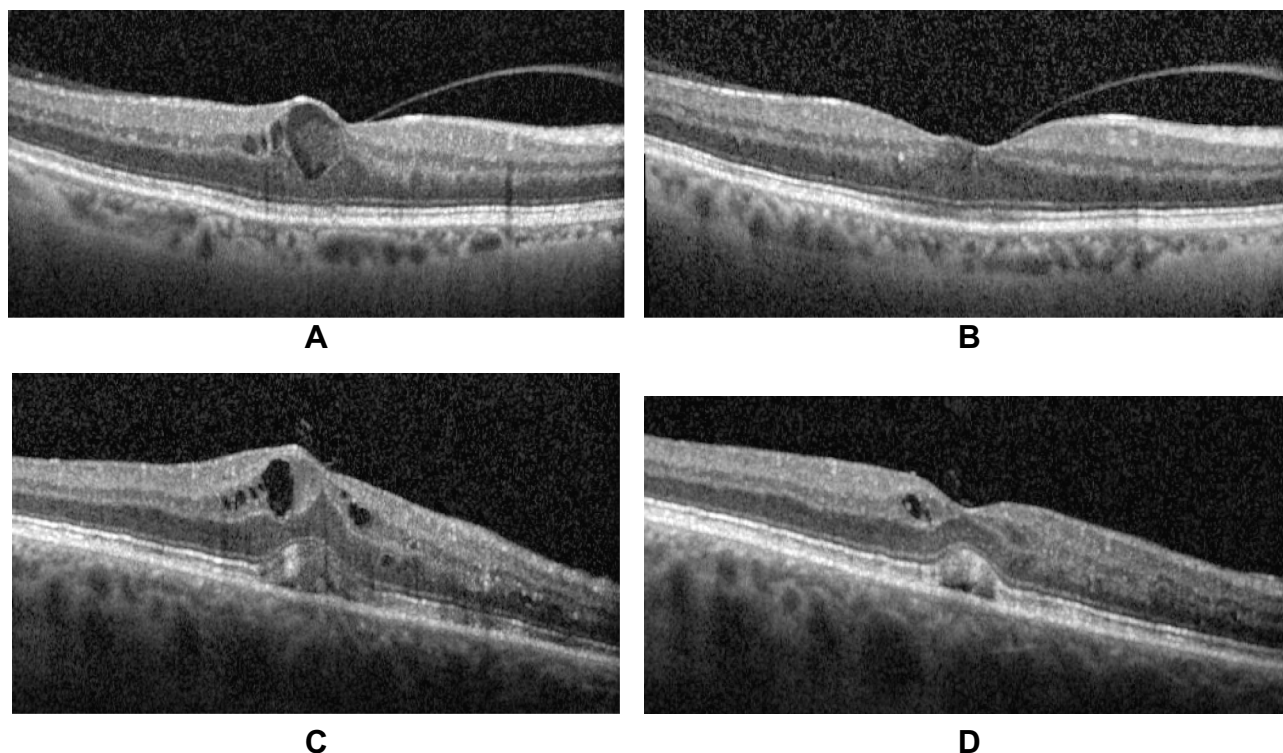
Discussion

In this retrospective real-life study, we analyzed if dexamethasone implant would be beneficial for refractory DMO in patients with no response to anti-VEGF therapies. The number of patients especially in sub-analyses was small and further studies are needed to confirm these findings. Beneficial response was defined as a significant increase in BCVA. Based on the results, the effect of the treatment seems to be relatively good, especially in patients with lower CRT values at the baseline. Furthermore, patients with large parafoveal cysts seem to benefit more from the treatment than those with diffuse DMO, although in earlier studies with other intravitreal therapies, large macular cysts have been shown to be a poor prognostic factor for retinal

**Figure 8** Intraocular pressure (IOP).

function.¹⁹ These different findings might be due to inflammatory factors behind different clinical entities of DMO, which are recently poorly understood.

Looking at the differences between groups 1 and 2, the duration of DMO in the group 2 was longer than in the group 1, but the difference was not significant ($p=0.56$). However, there was a trend of better response and lower number of implantations with a shorter duration of DMO in both groups. This has also been shown in previous studies, where better results were confirmed with early intervention.^{20,21}

**Figure 7** The OCT before and after dexamethasone implant. Group 1 (parafoveal cysts) before (A) and after (B) the dexamethasone implant. Group 2 before (C) and after (D) the dexamethasone implant.

In the group 2, patients had more than 1 implants during the follow-up. The treatment was equally efficient after the second and the third implant compared to the first one ($p < 0.05$), both looking at the BCVA and CRT values (Figures 3 and 5). Also, at the end of the study, the response in BCVA and CRT values was as good as in group 1 patients after one implant. The eyes with better BCVA at the beginning managed better with one implant than those with worse BCVA at the baseline although the difference in the baseline BCVA between group 1 and group 2 was not statistically significant. Furthermore, the eyes that managed with only one implant during the follow-up in group 1 had significantly lower CRT at the baseline than those needing the second or the third implant in group 2.

In the group 1, the CRT value was significantly decreased but the absolute median value was only 34 ± 36 μm . In contrast, in the group 2, the absolute decrease was 179 ± 136 μm after the second and 129 ± 105 μm after the third implant. In addition, the significant improvement in BCVA was similar after all treatments. Previous studies reveal that the lower CRT values do not correlate with better BCVA, since the malfunction of the retinal glial cells and possible ischemia or retinal atrophy may decrease the BCVA permanently.^{22,23} The fact that a relatively small decrease in CRT value was seen with significant improvement of BCVA in group 1 might suggest that in these patients potential protective mechanisms in the eye have more effect on the oedema resolution than in more chronic cases in group 2. Although the HRS, considered as inflammatory cells, were more numerous in group 1 than in group 2, but the decrease in the number of the HRS was significant only in group 2. Furthermore, in the group 2, most patients have type 2 diabetes and the number of HRS were higher with DM2 patients than DM1 patients but the difference was not statistically significant. Type 2 diabetes has in recent years been linked to chronic, low-grade inflammation^{24–26} leading to a more complicated disease with more persistent inflammatory reaction also in the retina, where more aggressive anti-inflammatory treatment might be needed to achieve good results.

There is a lot of debate going on with the nature of HRS, whether the origin of the spots is inflammatory or whether the spots are hard exudates. The HRS might be precursors of hard exudates but they can also be seen independently without the formation of hard exudates.^{27,28} In previous studies, HRS have shown to be involved in the refractory DMO.⁷ Furthermore, as seen in the previous studies, the decrease in

the number of HRS seen in this study after dexamethasone treatment suggests that HRS might be inflammatory.^{8,10} The differentiation of HRS and hard exudates especially in refractory DMO can be difficult. Further studies with naive patients would give more precise information about the nature and clinical importance of HRS.

In the group 2, where the response to the treatment was similar to group 1, but the effect was lost significantly faster, the decrease of HRS after the treatment was significant. This suggests that a bigger number of HRS might indicate a more chronic nature of DMO and the disappearance of the spots reflects the response to the treatment.

54% of the patients were pseudophakic when dexamethasone was implanted (Table 1). In this study, there was no statistical difference in the BCVA or CRT between phakic and pseudophakic eyes after the treatment. However, with a longer follow-up, the influence of developing cataract must be considered as a complicating factor in measuring BCVA. In addition, intravitreal corticosteroids might cause IOP increase.^{22,29,30} In this study, IOP was increased in three eyes and it was treated successfully with IOP lowering medication.

There was no statistical difference in the BCVA or CRT between vitrectomized and non-vitrectomized eyes after the treatment. The efficacy has been equal also in other studies even though the clearance of intravitreal drugs is accelerated after vitrectomy.³¹

Conclusion

In conclusion, dexamethasone implant is a useful treatment in DMO in patients who do not benefit from anti-VEGF injections. In addition, numerous HRS in OCT images could be considered as a morphological sign of chronic and more aggressive disease. Anti-inflammatory treatments may be needed to achieve satisfying results in these cases.

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Author Contributions

All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

Dr Tommi Karttunen reports grants from Allergan Norden AB, during the conduct of the study. Dr Kati Kinnunen

reports grants from Allergan, during the conduct of the study. The authors declare that they have no other conflicts of interest in this work.

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