Clinical Outcomes of Dexamethasone Intravitreal Implantation for Recalcitrant Diabetic Macular Oedema Using ImageJ Software Analysis

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ABSTRACT

The aim of this retrospective observational study was to evaluate the efficacy of dexamethasone implant in the treatment of recalcitrant diabetic macular oedema in a real-world clinical setting.

Data was imported from patients' Ocular Coherence Tomography scans and imported into ImageJ software for quantitative segmental analysis by a masked observer. ImageJ was used to measure the intraretinal fluid volume and total central macular thickness. At baseline demographic information, previous treatment, number of implants, visual acuity, central macular thickness and analysis of intraretinal fluid using ImageJ analysis software were collected. Stata statistical analysis software was used to analysis the data.

Thirty-four eyes of 29 patients were included for analysis. The mean duration of diabetes mellitus was 19.8 years. The mean number of dexamethasone implants was 2.5 with a mean interval of 3.6 months. The greatest improvement in vision was demonstrated at two months where the mean gain was 4.6 letters ($p<0.001$). There was a significant decrease in central macular thickness from baseline to 12 months or the final patient visit (336.6 µm at baseline to 294.82 µm at final visit, $p<0.001$). At baseline the mean intraretinal fluid level was 421.1 μm^2 and a clinically significant decrease was found at 12 months or patients' last visit (103.06 microns, $p<0.05$).

The treatment of refractory or recurrent macular oedema with dexamethasone implant showed a significant improvement in visual acuity, central macular thickness and intraretinal fluid. The drug had minimal side effects in our patients and showed the added benefit of fewer injections required for re-treatment.

Keywords: dexamethasone, Ozurdex, diabetic macular oedema, central retinal thickness, intravitreal injection, retina, ImageJ

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INTRODUCTION

The worldwide estimated prevalence of people living with diabetes mellitus (DM) has risen rapidly from 108 million in 1980 to 422 million in 2014 and is projected to increase by a further 130 million cases by 2030.[1] Globally, diabetic retinopathy (DR) is the leading cause of visual disturbance and blindness in the working age population.[1,2] The leading cause of vision loss in patients with DR is attributed to diabetic macular oedema (DMO), which has been reported to affect between 3.8% and 13.9% of patients living with DM, although this range may represent an underestimation of the true prevalence due to lack of ophthalmic follow-up in many socially or physically disadvantaged patients with DM.[3-5] DMO will continue to challenge and impact the global health care system due to an increase in the aging population, the rising prevalence of the disease in emerging countries and the refractory nature of the ocular condition.[3,5-7] The choice of therapy is thereby critical as clinicians manage this chronic disease in a largely working and younger population.

DMO is characterised by fluid accumulation and thickening in the macular region due to the breakdown of the inner blood-retinal barrier, however the exact pathogenesis in the development of DMO is yet to be fully understood. Ischaemic, inflammatory and cellular metabolic pathways have previously been identified as having potential and interconnecting roles in the disease.[8-10] In the past decade, anti-vascular endothelial growth factor (VEGF) therapies have superseded laser photocoagulation in treating

DMO.[11-14] Focal and grid laser were used to prevent severe vision loss, however they were not effective in restoring visual acuity. Further, laser treatment resulted in serious complications including loss of central vision leading to central visual field scotomas due to laser scarring.[14-16]

Multi-centre studies have affirmed the effectiveness of VEGF inhibitors in the treatment of DMO.[14,17] The Diabetic Retinopathy Clinical Research Network (DRCR.net) Protocol T study compared the effectiveness of ranibizumab, aflibercept and bevacizumab in the treatment of DMO. Mean visual acuity at 24 months improved by 12.8 letters in the patients treated with aflibercept, 12.3 letters in those treated with ranibizumab and 10 letters in patients receiving bevacizumab. This comparative study supported the use of VEGF inhibitors for the treatment of DMO as they were found to increase visual acuity and decrease the need for laser photocoagulation. However, the refractory nature of the disease was shown in the RISE and RIDE studies, where DMO persisted in 23% of patients despite monthly ranibizumab injections. Variation in study outcomes suggests a need for alternative treatments therapies, in particular for patients who provided resistance or no response to anti-VEGF therapies.[18]

Given that retinal inflammation plays a role in the development of DMO, anti-VEGF drugs may not effectively target the inflammatory molecules in all patients. Steroid therapies however, can simultaneously target inflammatory, angiostatic and anti-permeability pathways of the disease.[19] Triamcinolone acetonide is an anti-inflammatory drug used in the treatment of DMO. Chan, Mohamed, Shanmugam et al[20] have reported its efficacy for improving distance visual acuity by >5 LogMAR letters at two-years, achieved by 56% of eyes compared to 26% improvement in BCVA in the placebo group. Elevated intraocular pressure of >5 mmHg was seen in 68% of eyes treated with triamcinolone compared to 10% in the placebo group, suggesting a significant possible complication. The researchers also reported that repeat intravitreal injections of triamcinolone were not as effective in improving vision as the initial injection which remains a consideration due to the refractory nature of DMO.

Dexamethasone (DEX) implant (Ozurdex; Allergan Inc, Irvine, CA) is a sustained-release anti-inflammatory implant placed in the posterior cavity for the treatment of macular oedema secondary to DMO, vein occlusions and non-infectious uveitis. The anti-inflammatory properties of DEX appear six-fold stronger than triamcinolone, offering a significant potential alternative.[21] Clinical trials have shown the effectiveness and safety profile of DEX in the treatment of refractory DMO.[11,21-25] Although clinical trials provide a platform for evidence-based guidelines of treatment regimens, the rigid timelines may not translate easily to clinical practice due to the high burden on patients and their carers.[26,27]

Whilst real-life studies may be challenged by the potential of irregular monitoring, they provide the flexibility for modifying the treatment regimen. Understanding the usage pattern and visual outcomes of DEX in the real-world setting will provide insight into the disease and treatment process, particularly in chronic conditions with complex comorbidities such as diabetes mellitus.

The present retrospective case cohort study was conducted to provide a clearer understanding of the usage and efficacy of DEX treatment in a real-world clinical setting with an emphasis on DMO patients.

METHODS

This was a retrospective observational study of patients with with centre-involving DMO who were resistant to previous treatment modalities and needed a change in the therapy. All the patients attending the retinal clinic from March 2016 to January 2017 (the first 10 months of the DEX implant by the treating physician) were included in the analysis and were followed for a minimum of six months post initial treatment to a maximum of 12 months. Data were collected from the patients' clinic files.

All patients had refractory or recurrent DMO which was diagnosed using fundoscopy and optical coherence tomography (OCT). Patients were considered for DEX implant if diagnosed as a non-responder to previous intravitreal therapies including ranibizumab, aflibercept, bevacizumab or triesence for persistent DMO. The decision to re-treat was made at the discretion of the surgeon in accordance with clinical practice. Rescue vascular endothelial growth factor inhibitor intravitreal injections and the use of intraocular pressure (IOP) lowering agents were prescribed as required.

Retrospective data extraction included patient demographics (age, gender, duration of diabetes); the number of intravitreal injections prior to DEX implant; IOP and the presence of unexpected events during or after the injection procedures.

The primary outcome measure was best-corrected visual acuity (BCVA) measured using an Early Treatment Diabetic Retinopathy Study (ETDRS) chart and recorded in number of letters. Secondary outcome measures included central macular thickness (CMT) measured in microns, using high-definition OCT (Carl Zeiss Meditech AG, Germany); analysis of intraretinal (IR) fluid measured in μm^2; and IOP.

ImageJ analysis software[28] (National Institutes of Health, Bethesda, MD; available as a free download from http://rsb.info.nih,gov/ij/download.html) was used to calculate IR fluid. De-identified patient OCT images were extracted by a clinical orthoptist and given to a masked observer for quantitative segmental manual analysis using ImageJ. As part of this

procedure, the images were horizontally elongated and re-sized to a width of 4,029 pixels and a height of 1,024 pixels to allow for uniformity in all directions (Figure 1).

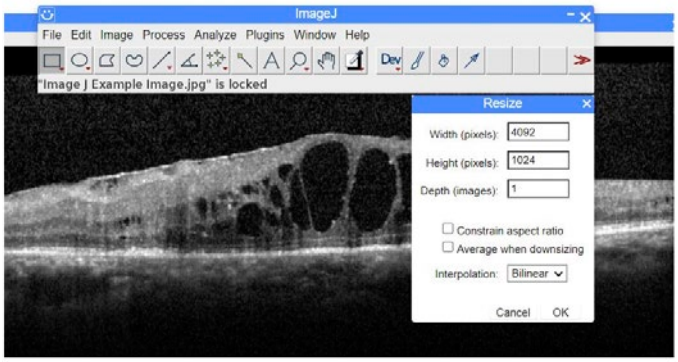

Figure 1. Image re-sizing using ImageJ software.

The cross-sectional area of the total macula, IR fluid, subretinal fluid and retinal pigment epithelium were derived. The inner limiting membrane, outer plexiform layer and retinal pigment epithelium were identified and marked using the polygon selection feature within ImageJ software to allow measurement of the inner macula. Central macular thickness is within 1.0 mm of the fovea and the total macular thickness in the central 6.0 mm surrounding the fovea. IR fluid was then identified and manually marked using polygon selection and measured to analyse the non-centre involving DMO.

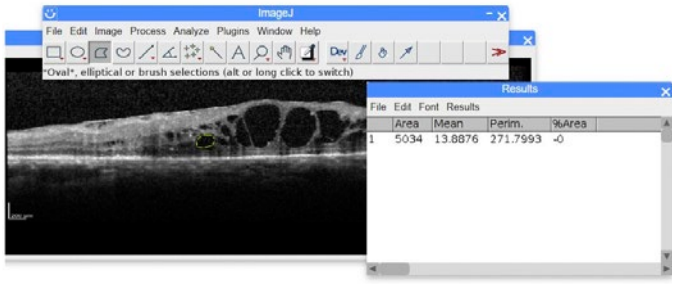

Figure 2. Marking and calculation of intraretinal fluid using ImageJ.

Data were analysed using Stata statistical analysis software version 12 (StatCorp LLC) and included descriptive analyses, correlations between outcome measures and linear regression with robust variance to allow for clustering between eyes and within patients.

RESULTS

Patients treated with DEX implant for centre-involving DMO in a routine clinical setting were studied. Thirty-four eyes of 29 patients treated with DEX implants for DMO were included for analysis. Baseline characteristics for the cohort are shown in Table 1. All patients received at least one DEX implant, with the mean number of implants reaching 2.5 ± 1.0 (SD) (range 1 to 4). The mean follow-up time was 8.33 months. Seventeen eyes (50%) received three or more implants during the review period. The mean interval between DEX implants was 3.6 ± 2.6 months (range 1 to 12).

Table 1. Patient baseline characteristics

n = 29	Mean (SD)	Range
Age (years)	67.9 (9.2)	45 – 88
Gender	Male n=20 (69%) Female n=9 (31%)	
Duration of diabetes (years)	19.8 (7.3)	6 – 37
Mean number of intravitreal injections prior to this study	5.7 (3.2)	1 – 14
Mean number of triesence injections prior to this study	1.2 (1.5)	0 – 5
Number of patients needing IOP-lowering treatment prior to this study	9 (34.0%)	
Mean BCVA (letters) at baseline	16.1 (9.2)	1 – 34
Mean CMT (μm) at baseline	336.6 (78.9)	196 – 480
Mean IR fluid area (μm^2) at baseline	421.1 (311.1)	45.0 – 1385.7
Mean IOP at baseline (mmHg)	14.8 (2.9)	11 – 26

Best-corrected visual acuity (BCVA)

The mean number of letters at baseline was 16.1 ± 9.2 and the change over time is shown in Figure 3. The greatest improvement in BCVA was demonstrated by patients at two months, where the mean gain was 4.6 letters or approximately one line of vision (p<0.001).

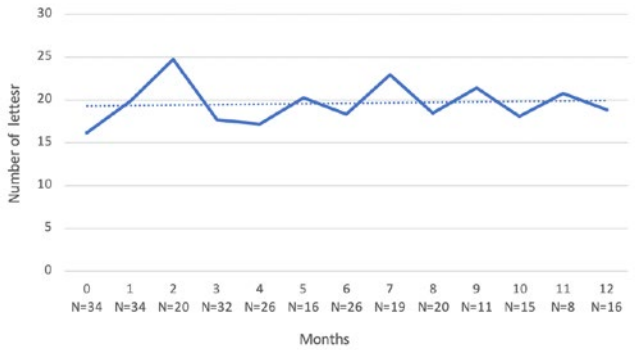

Figure 3. Mean change in BCVA over time.

The proportion of eyes achieving >5 and >10 letter improvement at 1, 3, 6, 9 and 12-months is shown in Table 2. No patients lost greater than 10 letters at any time-point.

Table 2. Proportion of eyes gaining 5 and 10 letters at respective time intervals

	1 month	3 months	6 months	9 months	12 months
Number of eyes with data	34	32	26	11	16
>5 letter gain (%)	32.4	20.9	17.7	26.5	26.5
>10 letter gain (%)	14.7	14.7	11.8	14.7	14.7

Central macular thickness

Mean CMT over 12 months is shown in Figure 4. The mean CMT at baseline was 336.6 µm and this improved to 294.82 µm (± 65.0 µm). 'Last visit attended' data was used for the final 12-month analysis, a statistically significant decrease in overall CMT (p<0.001).

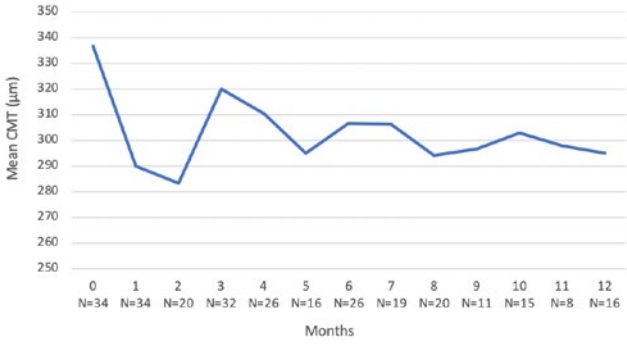

Figure 4. Mean central macular thickness change over time.

There was a significant correlation between both baseline CMT and total number of DEX injections with the final CMT at 12 months. This represented a moderately positive relationship for both variables (baseline CMT: r=-0.39, p=0.02; DEX: r=-0.51, p=0.04). This was similarly significant at 1 and 2 months following the initial DEX injection (r=-0.592, p=0.0002; r=-0.563, p=0.0098, respectively). Change in CMT from baseline and change in BCVA from baseline is shown in Figure 5.

Change in CMT is moderately positively correlated with change in BCVA; thicker CMT was associated with poorer VA.

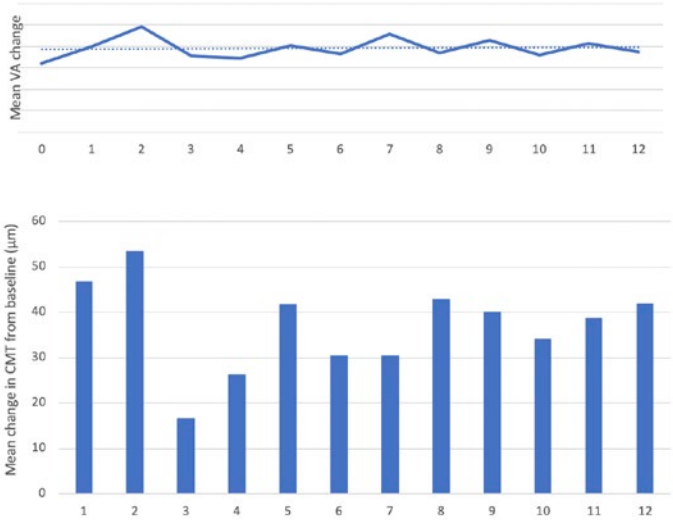

Figure 5. Mean change in CMT and corresponding mean VA change.

Multiple regression analysis was undertaken to eliminate confounding factors to the change in CMT, final CMT and the initial change at 1 month. There were no significant variables predicting the change in CMT at 1 month (p=0.29) or final change in CMT (p=0.85).

Intraretinal fluid level

The mean IR fluid level at baseline was 421.1 μm² (SD ± 311.1) and a clinically significant decrease was noticed at 12 months or patients' last visit (103.06 μm², p<0.05). The IR fluid change is shown at each time-point in Figure 6.

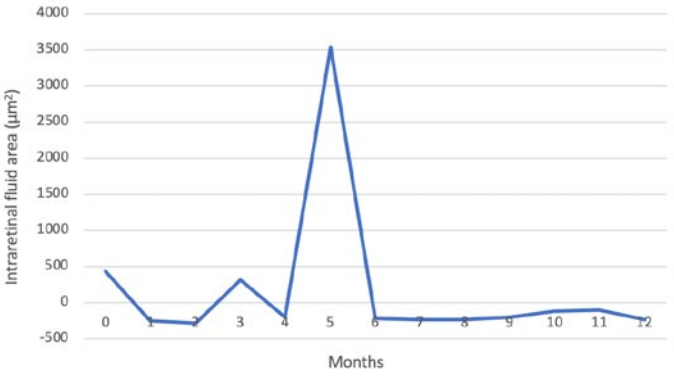

Figure 6. Mean intraretinal fluid level change over time.

Age at baseline and overall change in IR fluid area at final visit presented a significant moderately positive relationship (r=0.641, p<0.001). There was a statistically significant positive correlation between CMT and IR fluid levels at each monthly interval (p<0.05). The strength of the relationship was relatively weak at 5 months (r=0.231), increasing to a strong relationship at 12 months (r=0.857).

Intraocular pressure

The mean IOP at baseline and the change over time is shown in Figure 7. Following DEX injections, 20.5% of eyes showed a significant increase in IOP (p=0.041) over 12 months, requiring treatment. Patients were generally prescribed IOP-lowering medication when IOP measured above 25 mmHg. Five eyes were treated with topical medication, while two eyes underwent selective laser trabeculoplasty. Only one patient (one eye) required continuation of topical treatment at the final visit.

Nine eyes were on IOP-lowering medication prior to DEX treatment and continued therapy throughout the period of this retrospective review. It is worth noting that six of these eyes (66.7%) had previously been treated with triesence intravitreal injections.

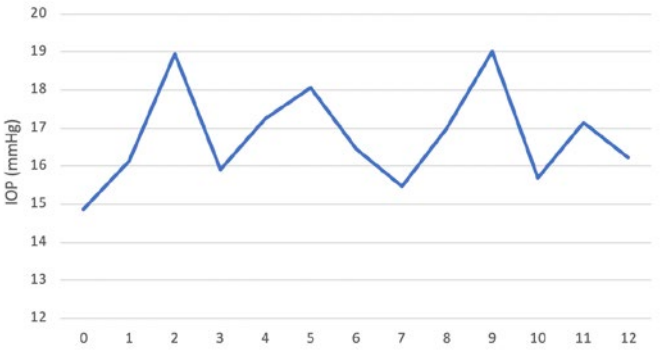

Figure 7. Mean IOP change over time.

DEX implant re-treatment indication

The number of eyes requiring re-treatment with DEX implant was highest at month-3 from baseline, when 18 eyes required another implant. The number of eyes requiring re-treatment over time is shown in Figure 8.

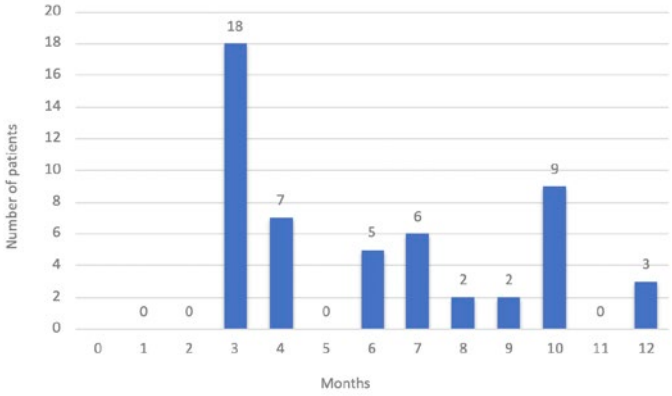

Figure 8. DEX implant re-treatment over time.

Anti-VEGF rescue treatment

Eight eyes (23.5%) underwent additional 'rescue' treatment with other intravitreal injections at follow-up. Five eyes (71.4%) received greater than one additional injection. The mean overall improvement in BCVA of eyes undergoing DEX implants was 3.2 letters, as opposed to 2.1 letters for eyes requiring rescue intravitreal injections. The change in CMT from the baseline reading was not statistically different between eyes requiring rescue treatment and eyes that did not, by the final visit. The decision to treat with other intravitreal injections was varied. Some patients were returned to rescue treatment if DMO presented earlier than 12 weeks post DEX implant. One patient showed macular ischemia on fluorescein angiography and was returned to anti-VEGF drugs to help promote vascular flow through the deep capillary plexus and the foveal avascular zone.

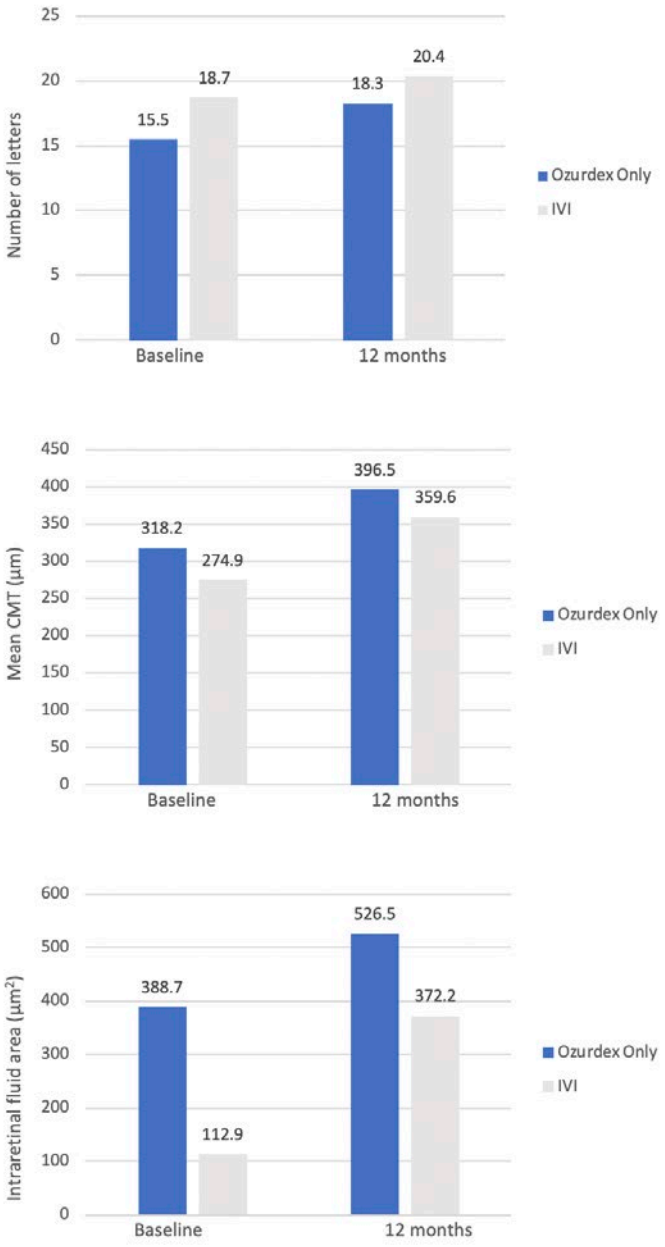

Figure 9. Change in vision, mean intraretinal fluid and mean CMT in 'Ozurdex only' and IVI groups at baseline and at 12 months.

Adverse events

There were minimal side-effects reported by patients. The most common adverse event reported by four eyes (11.7%) was an intermittent 'stick' in front of their visual axis. In all patients, this reported adverse event resolved between one and three-weeks post implant, when the implant appeared to settle into the vitreous cavity. One eye developed a vitreous haemorrhage, which resolved spontaneously, and one eye was diagnosed with a lamellar hole not requiring treatment.

DISCUSSION

Diabetic macular oedema continues to represent a significant burden on both patients and the health care system.[3] The expected increase in the incidence of this chronic disease, particularly in working-age patients, represents a specific clinical challenge for ophthalmologists to optimise the treatment of the condition. Positively, our understanding of pathogenesis and treatment of DMO has evolved in recent times. The introduction of VEGF inhibitors has provided anatomical and visual benefits over focal laser therapy, however this has represented a significant increase in clinic visits with corresponding financial strains and time implications for patients and their carers. The ideal treatment would provide a balance of positive visual and safety outcomes against an extended period of efficacy.[14,20,24,26,29-34]

The most significant visual gains demonstrated by the patients in this study were at two months following the initial implant (mean, 4.6 letters). However, the mean improvement in visual acuity at 12 months was not as high (mean, 3.0 letters). Visual outcomes reported in DEX studies show that patients often cannot maintain the improvement and may return to baseline values. Vision can be complicated by associated variables including, but not limited to the duration of DMO, presence or development of cataract during the review period and prior treatment.[25,37,38]

A study by Ou, Brown, Payne et al[39] reported that a medium negative correlation between CMT and BCVA exists in patients with DMO, suggesting that a decrease in CMT will result in an improvement in BCVA. In contrast, other studies suggest that a reduction in CMT does not indeed translate to a visual benefit.[23,35-37,40] Baseline retinal thickness may correlate better with baseline visual acuity than to post-treatment retinal thickness and visual acuity outcomes. The limitations in visual gains are likely related to existing trauma and damage at neural and retinal levels[23,35-37,40] The improvement in visual acuity is central to the ongoing discussion of DMO treatment, that is, what is the best time to begin treatment, what represents the most appropriate frontline treatment, when to provide additional options and the development of long-term visual goals for patients. As our understanding of contributing pathophysiological factors increases, it would be expected that the ability to optimise visual and anatomic outcomes will similarly improve.

The mean CMT at baseline in our study was 336.7 ± 76.9 microns, significantly decreasing to 294.8 ± 65.0 microns at the final visit. Similar real-world assessments of DEX implants for DMO have indicated greater improvements in CMT.[11,32,41] Lam, Albiani, Yoganathan et al describe a mean peak improvement of 190.9 ± 23.5 microns in their DMO sub-group following the final DEX implant.[24] Malclès, Dot, Voirin et al[33] retrospectively analysed 128 eyes of 89 patients and found a mean decrease of 171 microns at 3 years follow-up. This cohort included almost a quarter of treatment-naive patients which impacted the findings. A multi-centre phase IV study by Singer, Dugel, Fine et al[13] reported a mean peak improvement of 137.7 microns at 12 months albeit with significant variation between the various sub-group analyses including lens status, duration of DMO, additional treatment and history of vitrectomy. Our results broadly match those reported by Pareja-Ríos, Fuente-Rodríguez, Bonaque-González et al[42] who reported an overall mean decrease of 49.6 microns in their cohort of refractory DMO patients. Baseline CMT values reported in these studies were considerably higher than our group which may have impacted the potential range of improvement on this parameter.

The largest reduction in CMT occurs at one month following each injection, however the effect of DEX starts to diminish with time. Peak efficiency is thought to be at less than two months albeit the drug has been identified in patients up to 6 months.[21] Pacella, Romano, Turchetti et al[25] reported a regression to baseline values for both CMT and visual acuity, although generally an improvement was maintained by patients with recalcitrant DMO. Malclès et al[33] described a reduction in the need for re-treatment with time suggesting an extension of effect. The extension between treatments may suggest an accumulation over time of the drug within the vitreous, although an increase in effect does not appear to occur over time.[43,44]

The analysis of IR fluid using ImageJ represents a novel assessment in patients with DMO. Persistent scattered IR fluid with or without increased CMT may hinder visual outcomes in patients with DMO. Therefore, measuring CMT using OCT in addition to measuring recalcitrant IR fluid using ImageJ provides insight into the effect of IR fluid on treatment outcomes. Analysis of a larger area around the macula compared to standard OCT (approximately 5 mm compared to 1 mm) may present a clearer understanding of the classification and change in retinal morphology, particularly following treatment.

Whilst the measurement of OCT can evaluate macular thickness, additional morphological biomarkers are not conventionally considered. Namely, the presence and measured amount of IR fluid may have a significant impact on visual function. Therefore, investigation and treatment of additional biomarkers such as IR fluid may be useful in maintaining long-term retinal function. Our study found a correlation between CMT and IR fluid values and helps confirm IR fluid as a potential marker. At baseline the mean IR fluid level was 421.10 μm^2 with a clinically significant drop at 12 months to 103.06 μm^2. Incorporating a more accessible and faster method to measure volume will assist in increasing the practical use of software technology such as ImageJ.

The cohort was the first set of patients treated with DEX implant by a single surgeon. In the initial phase of treatment, the treating physician cautiously switched some patients back to anti-VEGF therapy to avoid patients potentially developing resistance to DEX and hence limiting their treatment options. As treatment progressed and the functionality of DEX was better understood, fewer patients were switched to other therapies. Hence, confirming that real-life patient management requires adjustable treatment options compared to more formal trials.

Safety remains paramount to any treatment. Our study demonstrated minimal side-effects following implantation, and as with many other studies, suggests that DEX implants maintain a strong ocular and systemic safety profile.[2,8,13,21,22,26,30,38,45] Ocular hypertension remains a consideration following injections. In our study, 20.5% of eyes required treatment to reduce IOP during the review period. Only a single patient who required topical medication following DEX implantation remained on treatment by the final visit suggesting a transient increase and successful management of IOP-related effects.

CONCLUSION

Patients in our study had an average of 2.5 DEX implants and prior to treatment with DEX, had a mean of 5.7 intravitreal injections. The benefits of decreasing the number of injections and treatment visits on quality of life and adherence to treatment is well known.[32,46-51] Reducing the number of treatments and visits represents a significant possible reduction in treatment burden and financial cost to the patients and carers.

DEX implant re-treatment was highest at month 3 (34.6%) followed by month 10 (17.3%). Re-treatment did not have the constraints of trial protocols where most studies have a fixed re-treatment schedule at 4 or 6-month intervals. Whilst patients in this study were already resistant to other treatments and the study was a retrospective observation, it is possible that 4 to 6-month intervals may be too long to treat patients safely. Eyes in this study were followed for a minimum of 6 months and maximum of 12 months, which may explain why re-treatment tapered off after month 9. Further research is required to identify optimum treatment intervals.

Our cohort represented the initial patients treated with DEX implants by a single surgeon under the same conditions, presenting a clear picture of real-world treatment in patients with refractory diabetic macular oedema. The findings of this study are consistent with many other published studies on several variables, and we found that dexamethasone implant

improved both best-corrected visual acuity and central macular thickness with a good safety profile and minimum adverse events.

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