

# Treatment of Diabetic Macular Edema or Macular Edema Following Retinal Vein Occlusion Based on Repeated Injection of the Dexamethasone Intravitreal Implant: A Retrospective Real-World Analysis

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**Purpose:** To assess the “real world” utility of repeated injection with the dexamethasone intravitreal implant (DEX) in routine practice.

**Methods:** This was a retrospective, single-center analysis of consecutive patients with diabetic macular edema, or macular edema following retinal vein occlusion, treated with DEX. None had received prior intravitreal steroid treatment. DEX was implanted as per the manufacturer’s instructions.

**Results:** Seventy-eight individuals (95 eyes) were included (50.0% female; mean age:  $68.1 \pm 12.4$  years; mean duration of macular edema:  $13.2 \pm 12.9$  months). Thirty-three eyes (34.7%) had received previous treatment with an anti-vascular endothelial growth factor (anti-VEGF) and/or laser. Thirty eyes (31.6%) underwent one round of DEX implantation; the remainder received 2–5 cycles (total: 225 cycles). Initial DEX treatment led to significant increases in visual acuity (VA) at 6 weeks (mean change: 4.6 letters;  $P=0.004$ ). Greater VA improvements during the first treatment cycle were associated with inferior baseline VA ( $P=0.02$ ), borderline associated with baseline central macular thickness (CMT;  $P=0.06$ ), and independent of prior anti-VEGF treatment ( $P=0.39$ ). In an analysis of all DEX injections, VA improvements were robust across cycles 1 and 2 but reduced in cycle 3 ( $P=0.03$ ). CMT improvements did not differ based on injection number ( $P=0.20$ ). Increases in intraocular pressure (IOP) were largest over the first 6 weeks (but rebounded towards baseline more rapidly) in cycle 1 versus cycles 2 and 3 ( $P<0.001$ ). IOP rises were typically manageable with topical medications.

**Conclusion:** This analysis confirms the broad utility of DEX and may inform decision-making in routine practice.

**Keywords:** corticosteroid, dexamethasone intravitreal implant, diabetic macular edema, intraocular pressure, retinal vein occlusion, visual acuity

## Introduction

The dexamethasone intravitreal implant (DEX) is a biodegradable, polymer-based drug delivery system designed to provide sustained release of the potent corticosteroid, dexamethasone, within the vitreous cavity for up to 6 months.<sup>1</sup> In selected patients with macular edema, it can be used to reduce inflammation by inhibiting fibrin deposition, capillary leakage and phagocytic migration, and by inhibiting the expression of vascular endothelial growth factor (VEGF), a promoter of vascular permeability.<sup>1,2</sup>

The efficacy and safety of DEX were first established in the Phase 3 MEAD<sup>3–5</sup> and GENEVA trial programmes.<sup>1,6</sup> As a result, indications for use in the United Kingdom include visual impairment due to diabetic macular edema (DMO) in patients who are pseudophakic or who are considered insufficiently responsive to or unsuitable for non-corticosteroid therapy; and macular edema following either branch or central retinal vein occlusion (RVO).<sup>2</sup>

From a practical perspective, the long duration of effect of DEX – and hence the reduced treatment burden on patients – may be an advantage compared with alternative, anti-VEGF treatments, such as bevacizumab, ranibizumab and aflibercept.<sup>7,8</sup> However, this must be weighed against other key considerations, including efficacy and safety within specific patient profiles.

Importantly, the efficacy and safety of DEX must be evaluated not just in clinical trials but also in the context of routine clinical practice. Increasing numbers of studies are now collecting “real-world data” across the globe,<sup>9–17</sup> but few such analyses have been performed in the United Kingdom. Furthermore, there are many important clinical questions that remain to be adequately addressed. These include considerations relating to the efficacy and safety of repeated administration of DEX and the potential for tachyphylaxis; the effect of prior treatment with an anti-VEGF on subsequent use of DEX; the impact of baseline visual acuity (VA) and central macular thickness (CMT) on efficacy; and the magnitude and time course of increases in intraocular pressure (IOP), a common safety concern with intravitreal steroid use. The purpose of the present study was to assess these questions in patients with macular edema treated using DEX in routine practice.

## Materials and Methods

### Study Design and Subjects

This was a retrospective analysis of consecutive patients for whom data were available, treated with DEX (Ozurdex 700 µg intravitreal implant in applicator; Allergan, an AbbVie company, Dublin, Ireland) at a single center between August 2014 and December 2020. Ethics Committee approval was not required because this was a retrospective, observational study. However, the research was performed in accordance with the Declaration of Helsinki, and all patients provided informed consent for treatment.

Eligible subjects were adults injected with DEX for either DMO or RVO. All were receiving their first course of intravitreal steroid treatment. Individuals were excluded if they were given DEX for other causes of macular edema, such as pseudophakic cystoid macular edema, uveitis or vasculitis.

Relevant DEX recipients were identified from treatment room diaries. Hospital records were then requested from the center’s Audit and Medical Records team. Optical coherence tomography data were gathered from the ImageNet software. Data were anonymized and stored on a secure Excel spreadsheet tool provided by the study sponsor.

### Treatments

All patients were treated with DEX as per the manufacturer’s instructions.<sup>2</sup> The eye was first locally anaesthetized, and the DEX implant was then placed into the vitreous cavity through the pars plana using a customized, single-use 22G applicator.

### Assessments

Details of the diagnosis and previous and current treatment(s) for DMO/RVO were collected for all included patients. Whenever available, measurements of VA, CMT and IOP were collated from baseline and all subsequent follow-up visits during the study period. In addition to increases in IOP, other complications were assessed throughout follow up.

### Statistical Analysis

In the first series of analyses, data from follow-up visits after the first cycle of treatment with DEX were categorized according to the nearest study timepoint (6 weeks, 3 months, 6 months, 12 months, and 6-month intervals thereafter). If a patient had more than one follow-up visit within a given time interval, data were used from the visit closest to the study timepoint. Evaluations focused on changes in VA, CMT and IOP over time. As the same eyes were assessed on multiple occasions, all analyses were performed using multilevel, mixed regression methods. Two-level models were based on individual measurements nested with eyes. In addition to overall changes in endpoints over time, differences between patient subgroups were assessed; these analyses were performed by fitting the interaction between each subgroup and time, allowing changes to be quantified for each separately.

In a second series of analyses, each repeat treatment with DEX was considered to “reset” the time to zero (baseline), regardless of the injection number. Thus, for each cycle of treatment, the follow-up period continued until the time of the next DEX injection, or until the end of the study if no further injections were given. Again, analyses focused on changes in VA, CMT and IOP over time, and were performed using multilevel, mixed regression methods. Three-level models were based on individual measurements nested with each injection, and injections were in turn nested within eyes. In addition, the effect of repeated DEX injection was evaluated; multilevel regression methods were used, with differences in values over time by injection number assessed through the inclusion of time by injection number interaction terms in the model.

A *P*-value of <0.05 was considered to be statistically significant. In addition, descriptive statistics are provided throughout, including frequency and percentage for categorical variables, and mean, standard deviation and range for continuous variables.

## Results

### Baseline Characteristics and DEX treatments

A total of 78 patients (95 eyes) were included in the analysis (Table 1). Of these, 39 (50.0%) were female and 39 (50.0%) were male. The mean patient age was  $68.1 \pm 12.4$  years.

Among the 95 eyes, 48 (50.5%) had DMO and 47 (49.5%) had cystoid macular edema secondary to RVO. In patients with DMO, the mean duration of diabetes was  $16.8 \pm 12.1$  years. Across all 95 eyes, 68 (71.6%) were phakic and 27

**Table 1** Baseline Characteristics and DEX Treatments

Patients	N=78
Sex, n (%)	
Male	39 (50.0)
Female	39 (50.0)
Age, years, mean $\pm$ SD (range)	68.1 $\pm$ 12.4 (27–92)
Eyes	N=95
Diagnosis, n (%)	
DMO	48 (50.5)
CRVO	25 (26.3)
HRVO	3 (3.2)
BRVO	19 (20.0)
Lens status, n (%)	
Phakic	68 (71.6)
Pseudophakic	27 (28.4)
Duration of macular edema, months, mean $\pm$ SD (range)	13.2 $\pm$ 12.9 (1–48)
Previous treatments, n (%)	
Aflibercept	28 (29.5)
Ranibizumab	7 (7.4)
Laser	4 (4.2)
None (treatment naïve)	62 (65.3)
Visual acuity, letters, mean $\pm$ SD (range)	54.7 $\pm$ 16.2 (5–80)
Visual acuity, logMAR category, n (%) <sup>a</sup>	
< 0.3	13 (13.8)
0.3–1.2	75 (79.8)
> 1.2	6 (6.4)

(Continued)

**Table 1** (Continued).

Central macular thickness, $\mu\text{m}$ , mean $\pm$ SD (range) <sup>a</sup>	508 $\pm$ 128 (249–839)
Central macular thickness category, n (%) <sup>a</sup>	
< 400 $\mu\text{m}$	19 (20.2)
$\geq$ 400 $\mu\text{m}$	75 (79.8)
Macular volume, $\text{mm}^3$ , mean $\pm$ SD (range) <sup>a</sup>	10.6 $\pm$ 2.2 (7.3–18.6)
Intraocular pressure, mmHg, mean $\pm$ SD (range) <sup>b</sup>	15.5 $\pm$ 3.6 (10–32)
Number of DEX treatments received, n (%)	
1	30 (31.6)
2	26 (27.4)
3	21 (22.1)
4	10 (10.5)
5	8 (8.4)

Notes: <sup>a</sup>N=94. <sup>b</sup>N=73.

**Abbreviations:** BRVO, branch retinal vein occlusion; CRVO, central retinal vein occlusion; DEX, dexamethasone intravitreal implant; DMO, diabetic macular edema; HRVO, hemi-retinal vein occlusion; logMAR, logarithm of the minimum angle of resolution; SD, standard deviation.

(28.4%) were pseudophakic, and the mean duration of macular edema was  $13.2 \pm 12.9$  months. Sixty-two eyes (65.3%) were treatment-naïve; the remaining 33 (34.7%) had received previous treatment with an anti-VEGF and/or laser. Baseline measurements of VA, CMT, macular volume and IOP are provided in [Table 1](#).

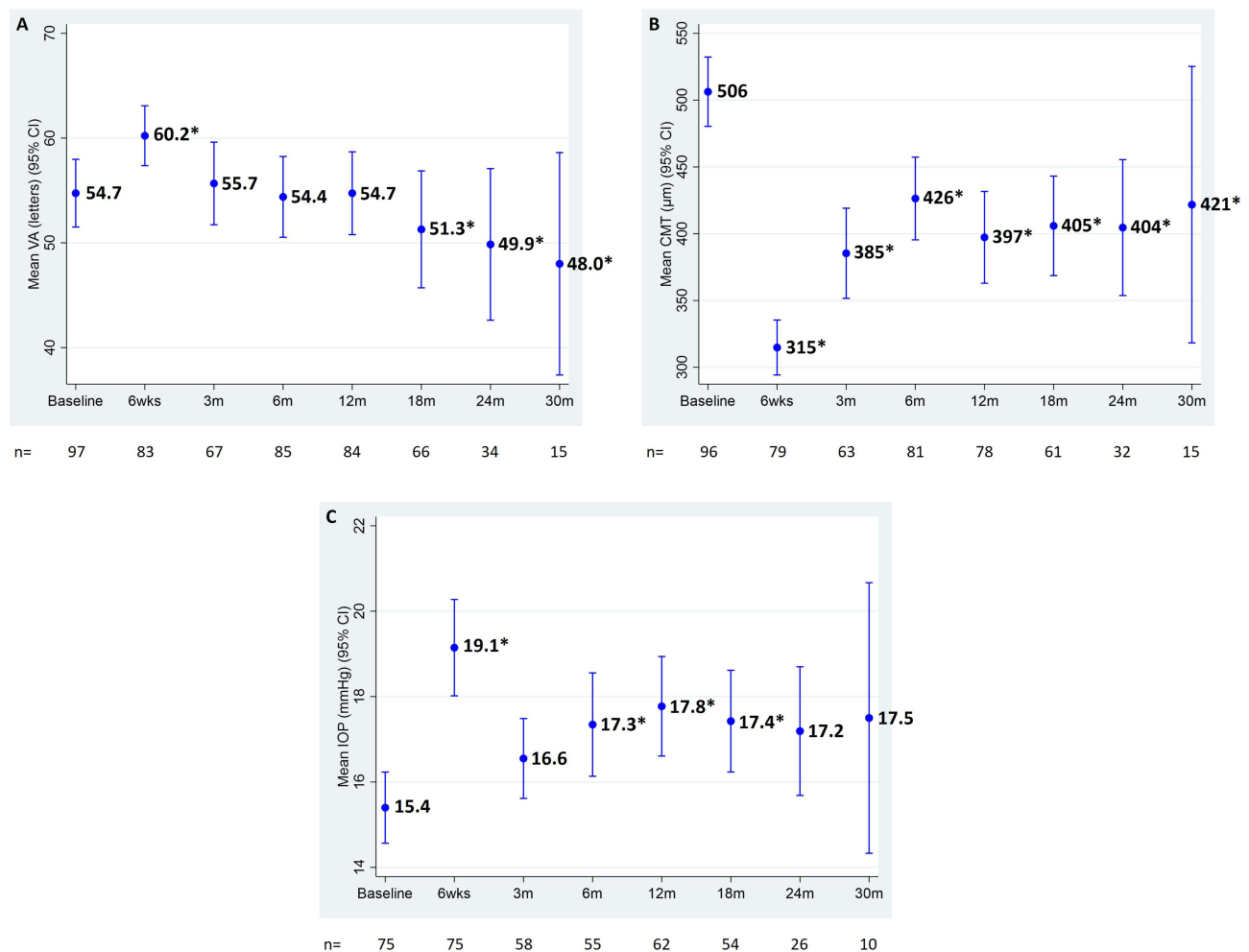
All 95 eyes were injected with DEX. Thirty (31.6%) received only one round of treatment, and the remaining 65 (68.4%) underwent between two and five cycles ([Table 1](#)). In total, 225 injection cycles were administered. The mean duration of follow-up was  $20.0 \pm 8.4$  months.

Five eyes (5.3%) also received one or more cycles of treatment with aflibercept during the follow-up period, and 2 (2.1%) were treated using laser. Aflibercept was initiated on a case-by-case basis in individuals with inadequate response to DEX, while laser was used following development of secondary proliferative retinopathy.

## Overall Time Course of Key Measurements

[Figure 1](#) shows the time course of mean VA, CMT and IOP measurements from baseline (first injection of DEX) to 30 months, irrespective of subsequent treatments received. At 6 weeks, mean VA was significantly increased compared with baseline, rising from  $54.7 \pm 16.2$  to  $60.1 \pm 13.2$  letters (mean change: 4.6 letters; 95% confidence interval [CI]: 1.4, 7.8;  $P=0.004$ ) ([Figure 1A](#)). This effect was no longer statistically significant at 3 months (mean change from baseline: 1.4 letters; 95% CI:  $-2.0, 4.8$ ;  $P=0.41$ ), and was lost from that point onwards. Mean CMT decreased significantly from baseline ( $508 \pm 128 \mu\text{m}$ ) to 6 weeks ( $316 \pm 92 \mu\text{m}$ ), with a mean change of  $-195 \mu\text{m}$  (95% CI:  $-230, -160$ ;  $P<0.001$ ) ([Figure 1B](#)). Reductions in CMT from baseline remained statistically significant all the way out to 30 months. Mean IOP increased from baseline ( $15.5 \pm 3.6 \text{ mmHg}$ ) to 6 weeks ( $19.2 \pm 5.0 \text{ mmHg}$ ), with a mean change of 3.6 mmHg (95% CI: 2.6, 4.7;  $P<0.001$ ) ([Figure 1C](#)). Increases from baseline were numerically smaller at subsequent timepoints but remained statistically significant out to 18 months (except at the 3-month timepoint;  $P=0.07$ ).

A regression analysis was performed to examine whether VA varied over time following initial DEX treatment for various subgroups of patients (based on previous anti-VEGF treatment and baseline CMT and VA). Owing to differences between subgroups in mean baseline VA values, this analysis was focused on changes in VA relative to baseline ([Figure 2](#)). Improvements in VA following initial DEX treatment were numerically lower in patients with previous anti-VEGF treatment versus those with no previous anti-VEGF treatment, but this difference was not statistically significant ( $P=0.39$ ) ([Figure 2A](#)). There was a borderline significant association between baseline CMT and subsequent changes in VA following initial DEX treatment; patients with baseline CMT  $< 400 \mu\text{m}$  maintained improvements in VA beyond 3 months whereas those with baseline CMT  $\geq 400 \mu\text{m}$  did not ( $P=0.06$ ) ([Figure 2B](#)). Finally, changes in VA over time



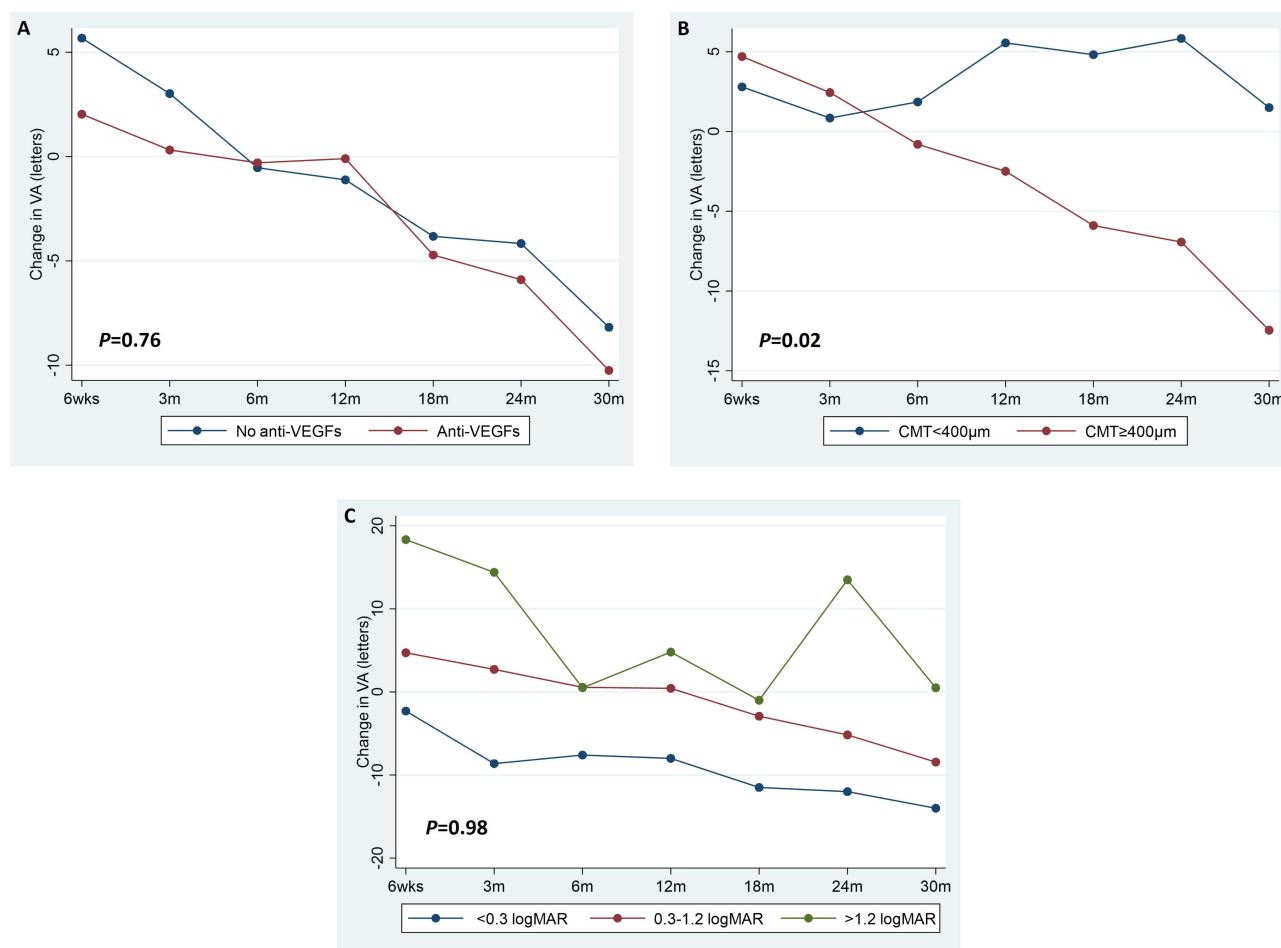
**Figure 1** Time courses of mean VA, CMT and IOP measurements. Analysis of mean VA (A), CMT (B) and IOP measurements (C) from baseline to 30 months. \* $P < 0.05$  vs baseline.

**Abbreviations:** CI, confidence interval; CMT, central macular thickness; IOP, intraocular pressure; m, months; VA, visual acuity; wks, weeks.

following initial DEX treatment were found to be dependent on baseline VA values ( $P=0.02$ ) (Figure 2C). Patients with a baseline VA  $< 0.3$  logarithm of the minimum angle of resolution (logMAR) showed no improvements in VA following initial DEX treatment, whereas those with baseline VA 0.3–1.2 logMAR (the majority of individuals included in this analysis) showed improvements lasting 3–6 months; patients with VA  $> 1.2$  logMAR at baseline showed the largest improvements in VA over the first 3 months, although this finding must be caveated by the particularly small size of the group.

## Time “Reset” Analysis

A second series of analyses were performed based on resetting the time to baseline on each occasion that patients received repeat treatment with DEX (based on 225 total injection cycles; Figure 3). At 6 weeks following each DEX injection, mean VA was significantly increased compared with baseline, rising from  $51.4 \pm 17.3$  to  $56.1 \pm 16.0$  letters (mean change: 4.3 letters; 95% CI: 2.6, 6.0;  $P < 0.001$ ) (Figure 3A). This was no longer statistically significant at 3 months although there was a trend towards improvement (mean change from baseline: 2.0 letters; 95% CI: 0.0, 4.0;  $P=0.05$ ). Increases from baseline in mean VA were lost at subsequent timepoints. Mean CMT measurements were significantly decreased from baseline ( $503 \pm 130 \mu\text{m}$ ) at 6 weeks ( $345 \pm 117 \mu\text{m}$ ; mean change:  $-160 \mu\text{m}$ ; 95% CI:  $-182, -138$ ;  $P < 0.001$ ) and at 3 months ( $403 \pm 141 \mu\text{m}$ ; mean change:  $-101 \mu\text{m}$ ; 95% CI:  $-126, -76$ ;  $P < 0.001$ ) (Figure 3B). This effect

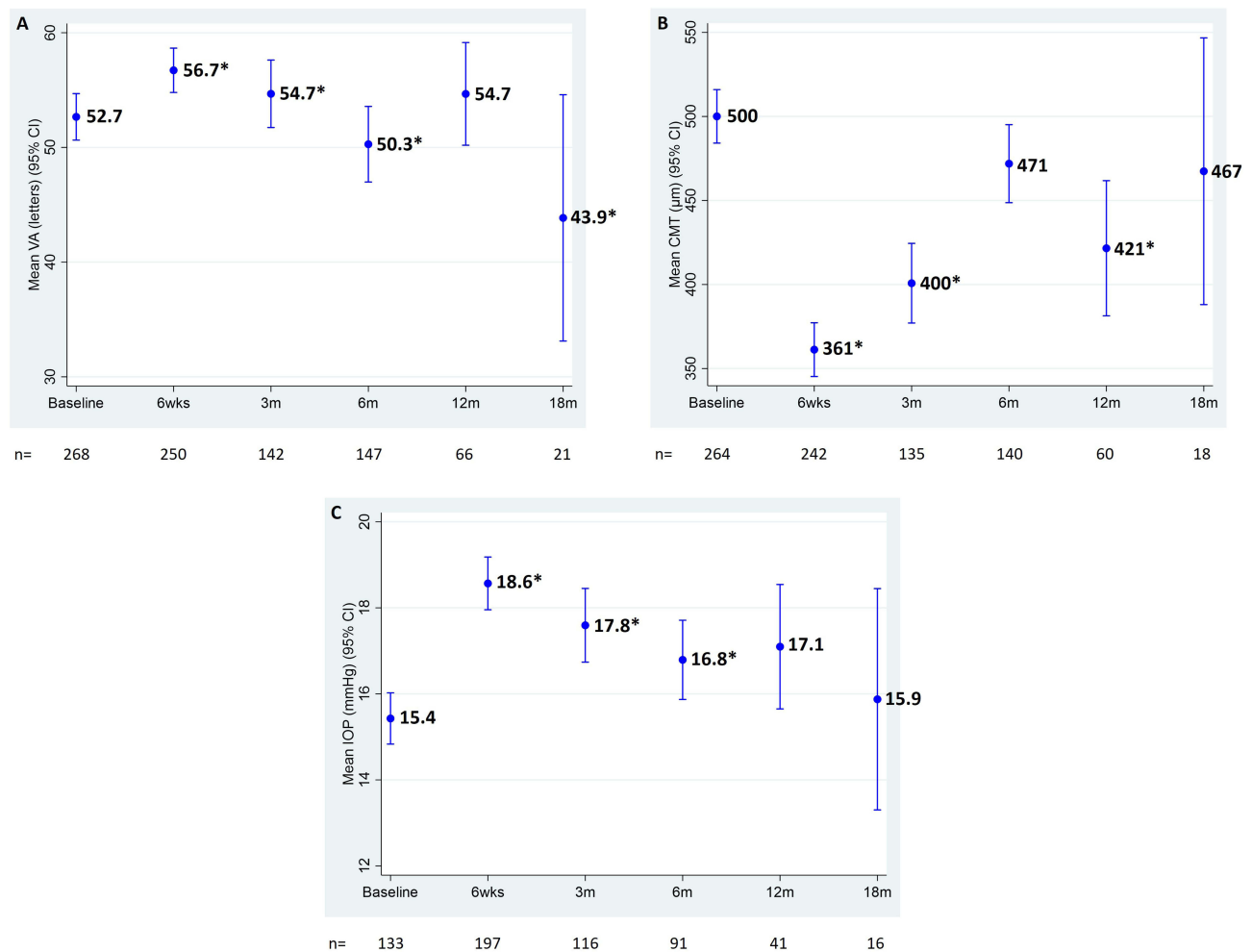


**Figure 2** Regression analysis of changes in VA from baseline in patient subgroups. Analysis based on previous anti-VEGF treatment (yes/no; **(A)**), CMT at baseline (< 400 μm; **(B)**), and VA at baseline (< 0.3 / 0.3–1.2 / > 1.2 logMAR; **(C)**).

**Abbreviations:** CMT, central macular thickness; logMAR, logarithm of the minimum angle of resolution; m, months; VA, visual acuity; VEGF, vascular endothelial growth factor; wks, weeks.

remained statistically significant out to 12 months ( $424 \pm 153 \mu\text{m}$ ; mean change:  $-63 \mu\text{m}$ ; 95% CI:  $-95, -30$ ;  $P < 0.001$ ). Mean IOP increased significantly from baseline ( $15.6 \pm 3.5 \text{ mmHg}$ ) to 6 weeks ( $18.7 \pm 4.4 \text{ mmHg}$ ; mean change:  $2.9 \text{ mmHg}$ ; 95% CI:  $2.1, 3.7$ ;  $P < 0.001$ ) and 3 months ( $17.7 \pm 4.7 \text{ mmHg}$ ; mean change:  $1.8 \text{ mmHg}$ ; 95% CI:  $0.8, 2.7$ ;  $P < 0.001$ ) (**Figure 3C**). However, increases from baseline in mean IOP were no longer statistically significant from 6 months onward.

VA data were then analyzed according to whether each DEX injection was the patient's first, second or third cycle of treatment (**Figure 4**). Mean VA increased between baseline and 6 weeks, irrespective of injection number – from  $54.7 \pm 16.2$  to  $60.1 \pm 13.2$  letters ( $+5.4$  letters) after the first injection, from  $54.2 \pm 13.7$  to  $59.6 \pm 10.9$  letters ( $+5.4$  letters) after the second injection, and from  $49.1 \pm 18.7$  to  $52.9 \pm 18.3$  letters ( $+3.8$  letters) after the third (**Figure 4A**). However, at subsequent timepoints, mean VA values were substantially lower after the third DEX injection compared with the first or second injection; as a result, a regression analysis found that there was a significant difference in changes in VA based on injection number ( $P = 0.03$ ). With regard to CMT, this was consistently decreased from baseline after the first, second or third injection (**Figure 4B**). Between baseline and 6 weeks, mean CMT fell from  $508 \pm 128$  to  $316 \pm 92 \mu\text{m}$  ( $-192 \mu\text{m}$ ) after the first injection, from  $481 \pm 137$  to  $360 \pm 119 \mu\text{m}$  ( $-121 \mu\text{m}$ ) after the second injection, and from  $509 \pm 143$  to  $355 \pm 133 \mu\text{m}$  ( $-154 \mu\text{m}$ ) after the third. Furthermore, at subsequent timepoints, the trajectory was similar irrespective of injection number. Regression analysis found that there was no significant difference in changes in CMT over time based on injection number ( $P = 0.20$ ).



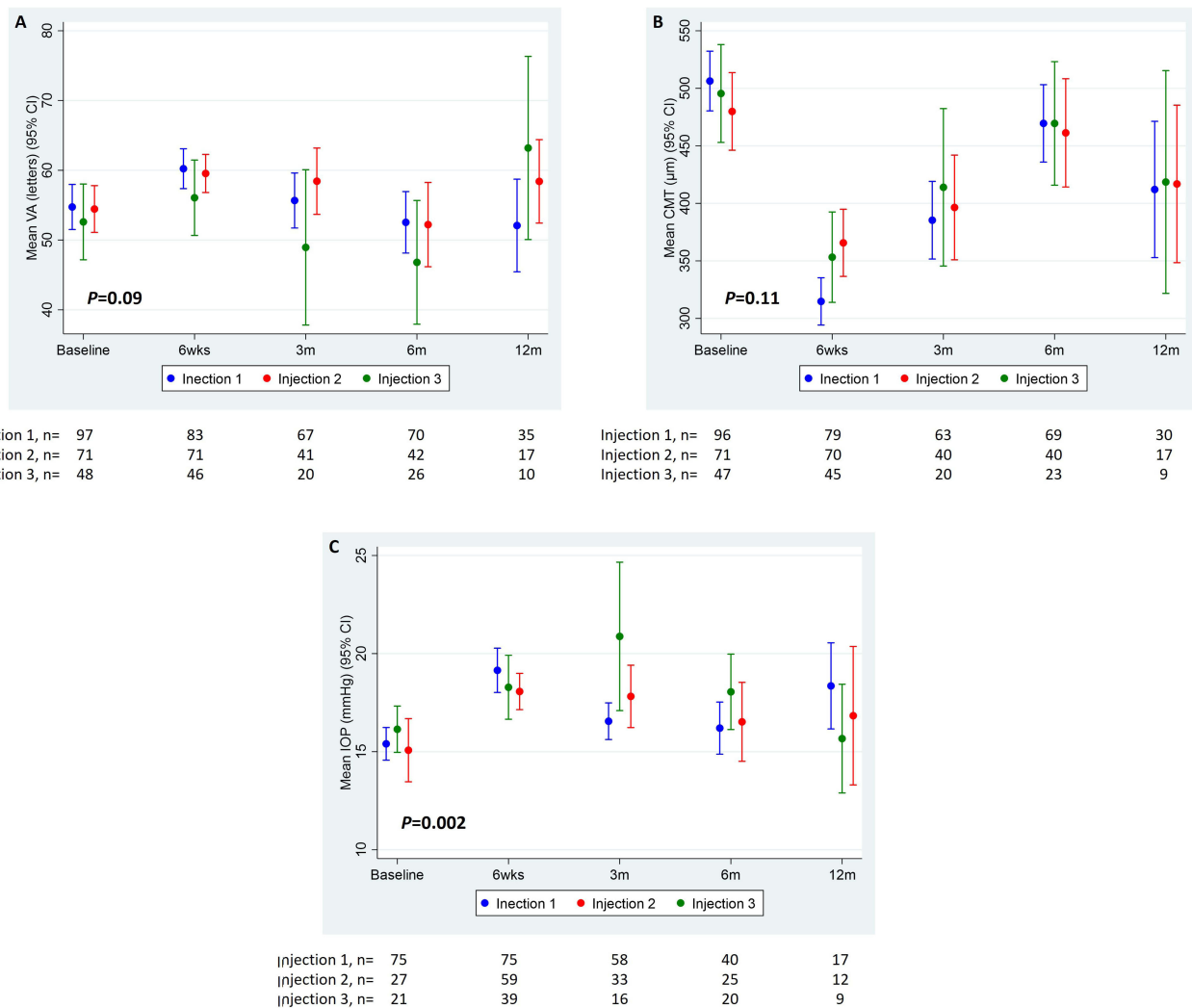
**Figure 3** Time courses of mean VA, CMT and IOP measurements with a time reset after each cycle of DEX treatment. Analysis of mean VA (A), CMT (B) and IOP measurements (C) from baseline to 18 months with a “resetting of the clock” to zero (baseline) on each occasion that patients received repeat treatment with DEX. \* $P < 0.05$  vs baseline.

**Abbreviations:** CI, confidence interval; CMT, central macular thickness; DEX, dexamethasone intravitreal implant; IOP, intraocular pressure; m, months; VA, visual acuity; wks, weeks.

To investigate whether lens status might be a factor affecting VA in subsequent treatment cycles, a comparison was made of changes in VA and CMT between phakic and pseudophakic eyes during the first, second and third treatment cycles. During cycle 1, mean improvements in VA were similar at 6 weeks in both phakic and pseudophakic eyes, but were more durable at subsequent time points in phakic eyes ( $P=0.04$ ). However, there was no difference in mean CMT changes in cycle 1 based on lens status. Crucially, there were no significant differences between phakic and pseudophakic eyes in the time courses of either VA or CMT changes after the second or third DEX injection ( $P > 0.05$ ).

Thus, in summary, VA improved substantially in treatment cycles 1 and 2 but less during cycle 3, whereas CMT was reduced in all three treatment cycles; there were no major differences in the tachyphylaxis pattern between phakic and pseudophakic eyes, suggesting that lens status may not explain the diminishing improvements in VA during subsequent DEX treatment cycles despite continued CMT reductions.

With regard to IOP, the general trend was similar after the first, second and third treatment cycle (Figure 4C), but regression analysis suggested a significant interaction between injection number and the time course of IOP ( $P < 0.001$ ). Indeed, mean increases in IOP from baseline to 6 weeks appeared to diminish with each progressive treatment cycle: first injection,  $15.5 \pm 3.6$  to  $19.2 \pm 5.0$  mmHg (+3.7 mmHg); second injection,  $15.4 \pm 3.8$  to  $18.3 \pm 3.6$  mmHg (+2.9 mmHg); third injection,  $16.1 \pm 2.9$  to  $18.6 \pm 5.2$  mmHg (+2.5 mmHg). In addition, at 3 and 6 months, mean IOP values rebounded back towards baseline more rapidly after the first injection compared with subsequent cycles.



**Figure 4** Regression analysis of key endpoints over time depending on DEX injection number. Analysis of mean VA (A), CMT (B) and IOP (C) over 12 months following DEX injections 1, 2 and 3.

**Abbreviations:** CI, confidence interval; CMT, central macular thickness; DEX, dexamethasone intravitreal implant; IOP, intraocular pressure; m, months; VA, visual acuity; wks, weeks.

### Safety

Mean increases in IOP following DEX injection have already been discussed. In most cases, these increases were not clinically significant; at 6 weeks after DEX injection (initial or repeat), an IOP of  $\geq 21$  mmHg was recorded in 48 of 183 cases (26.2%). One patient with an adverse event of increased IOP required treatment with bilateral peripheral iridotomy. In addition, 5 patients were noted to develop a cataract during follow up. There were no treatment-related serious adverse events.

### Discussion

In this retrospective observational study, we have demonstrated clinically and statistically significant improvements in VA and CMT following DEX treatment in a real-world cohort of patients with DMO or RVO. At 6 weeks after the first injection, mean changes in VA and CMT were +4.6 letters and  $-195 \mu\text{m}$ , respectively. These improvements align with those observed in other recent real-world studies.<sup>12–17</sup> For both outcome measures, peak effectiveness was observed at 6 weeks post-treatment. This is a little earlier than in other analyses, which typically found that the effects of DEX on VA and CMT peaked at 2–3 months.<sup>1,12,14–17</sup> Nonetheless, the pattern we observed broadly corresponds with the established



pharmacokinetics of DEX, with the highest concentrations in the retina and vitreous humor occurring during the first 2 months after implantation.<sup>18</sup> Interestingly, decreases in CMT were particularly sustained in the present analysis – remaining significant out to 12 months, even in patients who were not re-treated. The prolonged durability of CMT decreases compared with VA improvements may be linked to disease-related disruptions in retinal architecture, leading to functional loss; thus, in spite of sustained reductions in CMT with DEX treatment, the retina may not regain fully functional microcircuitry and hence VA improvements are less durable.

With regard to mean IOP – the key safety measure assessed – this peaked at 6 weeks after initial treatment with DEX (mean value: ~19 mmHg) and subsequently declined. Around a quarter of patients experienced an IOP of  $\geq 21$  mmHg, which is often considered to be the approximate upper limit of normal.<sup>19</sup> These cases were mostly managed with topical IOP-lowering medication; one individual underwent bilateral peripheral iridotomy, possibly relating to IOP increases and accelerated cataract maturation.

The key objective of the present analysis was to assess important clinical questions around the use of DEX in a real-world setting. In particular, we aimed to better understand the impact of VA and CMT values at the initiation of treatment on subsequent effectiveness. With regard to the former, previous studies have suggested that mean VA improvements with DEX are larger in patients with worse VA at baseline.<sup>14,15,17</sup> Our data support this notion, with a clear hierarchy of increasing effectiveness from baseline VA  $< 0.3$  logMAR (no improvement in VA with DEX) to baseline VA 0.3–1.2 logMAR (the majority of patients; improvements with DEX lasting 3–6 months) to baseline VA  $> 1.2$  logMAR (very large improvements, albeit based on low n values) ( $P < 0.02$ ). The impact of baseline CMT on the subsequent effectiveness of DEX has not been extensively studied previously. In the present analysis, patients with baseline CMT  $< 400$  or  $\geq 400$   $\mu\text{m}$  experienced substantially different VA time courses following initial DEX injection: while both groups showed clinically significant improvements over the first 3 months, those with baseline CMT  $< 400$   $\mu\text{m}$  maintained these gains for many months afterwards, whereas those with CMT  $\geq 400$   $\mu\text{m}$  did not. This difference was borderline statistically significant ( $P = 0.06$ ), and might be related to disruption of microscopic architecture and possible permanent alteration of central retinal functionality in those with higher baseline CMT.

We also analyzed the impact of previous treatment with an anti-VEGF on the effectiveness of subsequent DEX injection. Although improvements in VA were numerically superior in treatment-naïve individuals, this did not reach statistical significance – possibly owing to the modest number of patients who had received prior anti-VEGF therapy. Several previous studies found that VA improvements with DEX were greater in patients who were previously treatment-naïve.<sup>10,12,13,15,16</sup> On the flipside, a recent analysis of data from an international registry found no effect of prior treatment on VA improvements following DEX injection in 204 patients with DMO;<sup>17</sup> however, the comparison was made at 12 months, which is later than other studies (assessing VA at 1–6 months post-treatment), potentially masking short-term effects.

A regression analysis was also made of the impact of repeat DEX treatment and the potential for tachyphylaxis. We found no indication of significantly decreasing effects on CMT with repeat treatment, but there was an association between injection number and the time course of VA: improvements at 6 weeks were similar for the first, second and third injection, but the effect was less durable after the third treatment compared with the first two. Our findings align with two other recent real-world studies suggesting that improvements in CMT remain durable through multiple cycles of DEX injection whereas increases in VA may decline somewhat with repeat treatment.<sup>13,16</sup> For example, in an analysis of 141 patients with DMO, improvements in VA were similar for each of the first three cycles of treatment but were reduced following the fourth.<sup>13</sup> The primary cause of these decrements in VA improvement may have been ongoing maturation of cataracts during repeated steroid injection rather than any inherent decrease in the efficacy of DEX. However, the tachyphylaxis pattern in the present work was broadly consistent across both phakic and pseudophakic eyes (albeit caveated by the modest number of pseudophakic eyes included [ $n = 27$ ]), suggesting that it cannot be entirely explained by accelerated cataract progression due to DEX.

With regard to the impact of repeat treatment on IOP, phase 3 trials<sup>3,5</sup> and previous real-world studies<sup>13,16</sup> have typically found no relationship between injection number and the overall incidence or magnitude of increases in IOP. By contrast, in the present work, we found that the pattern of IOP increases evolved with repeat treatment – with a greater short-term (6-week) increase and then a rapid rebound back towards baseline after the first DEX injection, compared with

a lower peak but slower tail-off following subsequent injections. This effect could be related to altered resistance to aqueous outflow, which is an important aspect of steroid-induced IOP rises.

We must acknowledge the strengths and weaknesses of the present study. Its key strength is the focus on “real world” outcomes in a largely unselected population treated with DEX in routine practice. However, this design also brings limitations, including considerable inter-patient variations in DEX treatment course over time (as well as the introduction of non-DEX treatments in a small number of cases) and some missing follow-up data on outcome measures and on minor adverse events (eg, injection discomfort, which was not recorded). In addition, the study had a retrospective, single-center design with no control group, and included modest numbers of patients; the results are consistent with our practical experience, but further large, prospective, multicenter studies would be welcome, particularly focusing on possible tachyphylaxis.

## Conclusions

This study suggests that DEX is an effective and safe treatment for macular edema. Improvements in VA were robust regardless of prior therapy, but were greater in patients with worse VA at baseline. There was no evidence of significant tachyphylaxis over the first three injection cycles with regard to CMT improvements; for VA, the magnitude of short-term benefit was also durable, although this tailed off more rapid during the third treatment cycle. Additional studies may be required to assess these effects further, including for treatment cycles beyond a third injection. Nonetheless, the present analysis confirms the broad utility of DEX and may help to inform decision making in normal clinical practice.

## Acknowledgments

The authors wish to thank Timothy Ryder, DPhil, of Biological Communications Limited (London, United Kingdom) for writing and editorial assistance, funded by AbbVie. We also thank Paul Bassett, MSc, of Statsconsultancy Limited (Amersham, United Kingdom) for statistical analysis, funded by AbbVie. This project was considered to be ‘non-research’, and therefore a R&D and NHS REC application was not required.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

## Funding

Writing and editorial assistance was provided by Timothy Ryder, DPhil, of Biological Communications Limited (London, United Kingdom) and funded by AbbVie at the request of the investigator. Statistical analysis was provided by Paul Bassett, MSc, of Statsconsultancy Limited (Amersham, United Kingdom) and funded by AbbVie.

## Disclosure

The authors declare that they have no conflicts of interest in this work.

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