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## RESEARCH ARTICLE

# Treatment patterns and persistence rates with anti-vascular endothelial growth factor treatment for diabetic macular oedema in the UK: A real-world study

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## Abstract

**Introduction:** Anti-vascular endothelial growth factors (anti-VEGFs) are considered standard of care therapy for diabetic macular oedema (DME). This study examined treatment patterns and outcomes in patients with DME treated with anti-VEGF therapy.

**Methods:** Using anonymized electronic medical record data collected from three UK sites, this retrospective cohort study assessed rates of anti-VEGF intravitreal injections in adults with treatment-naïve DME who received their first treatment between 1 September 2010 and 31 July 2018. The proportion of patients with at least one interval of at least 12 weeks between injections; the distribution of injection intervals; the discontinuation rates; and the number of anti-VEGF injection-, injection-free- and total visits were assessed during the first and second years of treatment.

**Results:** Overall, 1606 patient eyes with DME were included, with no minimum follow-up. During the first and second year of treatment, 63.2% and 73.1% of eyes had at least one anti-VEGF injection interval of at least 12 weeks, respectively. In the first and second years of treatment, the mean (standard deviation) numbers of injections were 7.7 (1.9) and 5.6 (2.2), with 14.2 (5.7) and 13.4 (6.4) total clinic visits, and 6.6 (5.0) and 7.8 (5.8) injection-free visits, respectively. In total, 27.8% of patient eyes discontinued treatment during the first 2 years.

**Conclusions:** The high number of clinic visits and high discontinuation rates demonstrate a significant unmet need for a treatment to enable sustainable extended injection intervals, while maintaining visual acuity. This could improve patient adherence and health-related quality of life for patients with DME.

## KEYWORDS

anti-VEGF, DME, health care delivery

## 1 | INTRODUCTION

In recent years, diabetes mellitus has become a global health problem. In 2019, 5.9% of the UK population had been diagnosed with diabetes.<sup>1</sup> Diabetic macular oedema (DME), which is defined as retinal thickening caused by the accumulation of intraretinal fluid, is the most common cause of visual impairment in patients with diabetes,<sup>2-4</sup> at a prevalence of 6.8–10.4%.<sup>5-8</sup> In 2014, approximately 21 million people had DME worldwide, a figure that is expected to rise with the increasing prevalence of diabetes.<sup>8</sup>

The European Society of Retina Specialists guidelines recommend the use of optical coherence tomography (OCT) combined with fluorescein angiography and fundus biomicroscopy to diagnose DME.<sup>9</sup> In combination with visual acuity (VA) measurements, OCT biomarkers (including central retinal thickness [CRT] and intraretinal fluid) and clinical examination are recommended for monitoring disease progression and supporting treatment decisions in clinical practice.<sup>9</sup> Although laser photocoagulation is still used to treat DME, anti-vascular endothelial growth factor (anti-VEGF) intravitreal injections are now considered the standard of care in eyes with centre-affecting DME affecting vision.<sup>10,11</sup> Anti-VEGF treatment initiation requires a loading phase of three or more consecutive monthly injections, followed by a maintenance phase during which intervals between injections are titrated to match the patient's needs.<sup>9,10</sup> Additional treatment (e.g. laser or steroid injection) may also be included.<sup>9,10</sup>

Clinical trials have demonstrated that improvements in VA are possible with adherence to fixed and frequent dosing regimens.<sup>12,13</sup> However, such regimens are associated with a high number of clinic visits and thus often impose high clinic and patient burdens.<sup>14,15</sup> Consequently, anti-VEGF therapies (aflibercept, ranibizumab and unlicensed bevacizumab) have flexible treatment recommendations (i.e. *pro re nata*, or fixed interval treat-and-extend dosing [T&E]), allowing clinicians to refine treatment intervals according to disease activity.<sup>9</sup> In the real-world clinical setting, both regimens are used depending on patients' needs and clinical capacity.

There is a need for better understanding of these treatment patterns and their relationship with functional outcomes, including their effect on VA, in a real-world setting. This non-interventional retrospective cohort study examined treatment patterns, persistence rates and change in VA in patients with DME during the first 2 years of treatment with anti-VEGF therapy in a real-world setting in the UK.

### Key Points/Highlights

- This retrospective cohort study of three UK clinics found that 27.8% of patient eyes with diabetic macular oedema (DME) discontinued treatment during 2 years of anti-VEGF therapy.
- During year one, 63.2% of eyes reached at least one injection interval of  $\geq 12$  weeks. However, only 18.3% of eyes had 2 or more consecutive intervals of  $\geq 12$  weeks.
- These data highlight the burden of DME and demonstrate an unmet need for long-acting treatments to reduce disease burden on patients and healthcare providers.

## 2 | PARTICIPANTS AND METHODS

### 2.1 | Study design and population

This retrospective, non-interventional cohort study assessed treatment with intravitreal injections of anti-VEGF agents in treatment-naïve patients with DME who received their first anti-VEGF (aflibercept, ranibizumab or unlicensed bevacizumab) injection between 1 September 2010 and 31 July 2018 (the index period). The study was conducted using anonymized electronic medical record (EMR) data collected from three medical retina clinics in NHS hospitals in the UK. All sites used a single EMR system (Medisoft Ophthalmology EMR; Medisoft Limited), which allowed patient data to be aggregated and normalized. Patient identifiers, site and clinician data were pseudonymized. The use of de-identified patient data was approved by the Medical Lead and Caldicott Guardian at each site. Patient informed consent was not required.

Eligible patients were at least 18 years old on the date of their first injection (index date), had a recorded DME diagnosis on the index date or during the previous 180 days, and received at least one anti-VEGF injection during the follow-up period for the study eye(s). In this study, patients were considered treatment naïve if they had not received an anti-VEGF injection in the 180 days before the index date. Patient eyes were excluded if they had received anti-VEGF, intravitreal steroid or macular laser treatment, or had a diagnosis of neovascular age-related macular degeneration, retinal vein occlusion or any other exudative maculopathy, in the 180 days before the index date. The eye was the unit of analysis; thus, a patient might have one or two study eyes.

## 2.2 | Outcomes

The primary outcome was the proportion of eyes with at least one injection interval of at least 12 weeks in the first year (months 0–12) of treatment. Secondary outcomes included: the proportion of eyes with injection intervals of at least 12 weeks during the second year of treatment (months 13–24); the duration of injection intervals during the first and second year of treatment; the number of anti-VEGF injection-, injection-free- and total visits during months 0–3, 0–6, 0–12 and 13–24 of treatment; the anti-VEGF treatment discontinuation rate; and the proportion of patients who switched index therapy within the first and second years of treatment. Injection-free visits were defined as any clinic visit without an injection recorded in the EMR. Treatment discontinuation was defined as when anti-VEGF injections were not re-introduced for at least 180 days after the last injection, with a record of a clinic visit during that period. The time to treatment discontinuation was defined as the time to the first day that treatment was stopped (i.e. the day after the final injection).

Changes in VA and CRT from baseline to months 3, 6, 9 and 12 were also evaluated as secondary outcomes. OCT biomarker data were available from one of the three sites (site A) and were used to assess the association between CRT and VA and the change from baseline in these parameters. CRT data were extracted from OCT images as part of a sub-study separate from the EMR data analysis.

The number of anti-VEGF injection-, injection-free- and total visits during months 0–3 and 3–12 were also analysed by whether patients received treatment for one (unilateral) or both (bilateral) eyes, using the following subgroups: patients treated unilaterally at the index date (those who received no treatment in the second eye during the 360 days after treatment of the first eye), patients treated bilaterally at the index date (those received treatment for the second eye during the 0–90 days after treatment of the first eye) and patients who initiated bilateral treatment during the study (those who received treatment for the second eye during the 91–360 days after treatment of the first eye).

## 2.3 | Statistical analyses

Descriptive summary statistics (*n* [%], mean, standard deviation [SD]) were used to describe the following: the proportion of patients (eyes) that had injection intervals of less than 8 weeks (0–52 days), 8–12 weeks (53–80 days), at least 12 weeks ( $\geq 81$  days), at least 16 weeks and at least 20 weeks during the first and second years of treatment; the number of anti-VEGF injection-, injection-free- and total visits during the first and second years of treatment; change from baseline in VA

**TABLE 1** Baseline demographics and characteristics of patients with DME

Demographic or characteristic	Site A <sup>a</sup> ( <i>n</i> = 179)	Overall ( <i>N</i> = 1263)
Age, mean (SD)	67.3 (11.9)	65.7 (12.9)
Men, <i>n</i> (%)	116 (64.8)	756 (60.0)
Patients treated, <i>n</i> (%)		
Unilaterally	116 (64.8)	920 (72.8)
Bilaterally	63 (35.2)	343 (27.2)
VA		
Overall ETDRS letters, mean (SD)	63.4 (14.7) <sup>b</sup>	61.3 (16.8) <sup>c</sup>
Patients with <33 ETDRS letters, <i>n</i> (%)	10 (4.1)	102 (6.9)
Patients with 33–73 ETDRS letters, <i>n</i> (%)	165 (68.5)	986 (66.3)
Patients with >73 ETDRS letters, <i>n</i> (%)	66 (27.4)	400 (26.9)

Abbreviations: DME, diabetic macular oedema; ETDRS, Early Treatment Diabetic Retinopathy Study; OCT, optical coherence tomography; SD, standard deviation; VA, visual acuity.

<sup>a</sup>OCT biomarkers were available at one of the three sites (site A).

<sup>b</sup>*n* = 241.

<sup>c</sup>*n* = 1488.

(estimated by decimal VA converted to Early Treatment Diabetic Retinopathy Study [ETDRS] letters) and CRT during the first year of treatment; and the proportions of patients (eyes) that discontinued or switched treatment during the first 2 years.

Two-sided 95% confidence intervals (CIs) were derived for the proportion of patients (eyes) with at least one injection interval of at least 12 weeks during the first year of treatment with anti-VEGF agents. Kaplan–Meier methods were used for the analysis of time-to-event, which included time from initiation of anti-VEGF therapy to discontinuation or switching. Generalized estimating equations were used to estimate the quarterly least-squares mean change from baseline in VA, for months 3–24, using eyes as the unit of analysis and each patient as a group. Pearson correlation coefficients were calculated to assess the correlation between CRT change from baseline and VA change from baseline to months 3–12.

## 3 | RESULTS

In total, 1606 eyes with DME from 1263 patients were eligible for inclusion in the study. Baseline characteristics, including those of patients from site A, are given in Table 1. At baseline, the mean (SD) VA was 61.3 (16.8) ETDRS letters.

Overall, 920 (72.8%) and 343 (27.2%) of patients were treated unilaterally and bilaterally, respectively. Of unilaterally treated patients, 655 (71.2%) had a follow-up period of at least 12 months (Table S1). Of bilaterally treated patients, 200 (58.3%) had a follow-up period of at least 12 months, of which 45 (22.5%) initiated bilateral treatment during the study and 155 (77.5%) received bilateral treatment at the index date.

During the first 2 years of treatment, 1096 eyes (68.2%) continued and 447 eyes (27.8%) discontinued treatment, respectively. Some eyes switched to laser treatment (0.1%,  $n = 1$ ), steroid injections (3.9%;  $n = 62$ ) or another anti-VEGF agent (8.5%,  $n = 137$ ) (Figure 1). Of the 343 patients who were treated bilaterally, 71 discontinued treatment in both eyes, 171 patients remained on treatment in both eyes and 3 patients were switched to corticosteroids in both eyes. The remaining 98 patients had a different treatment status in each eye at the end of the second year of treatment (e.g. one eye discontinued and the other eye remained on index therapy).

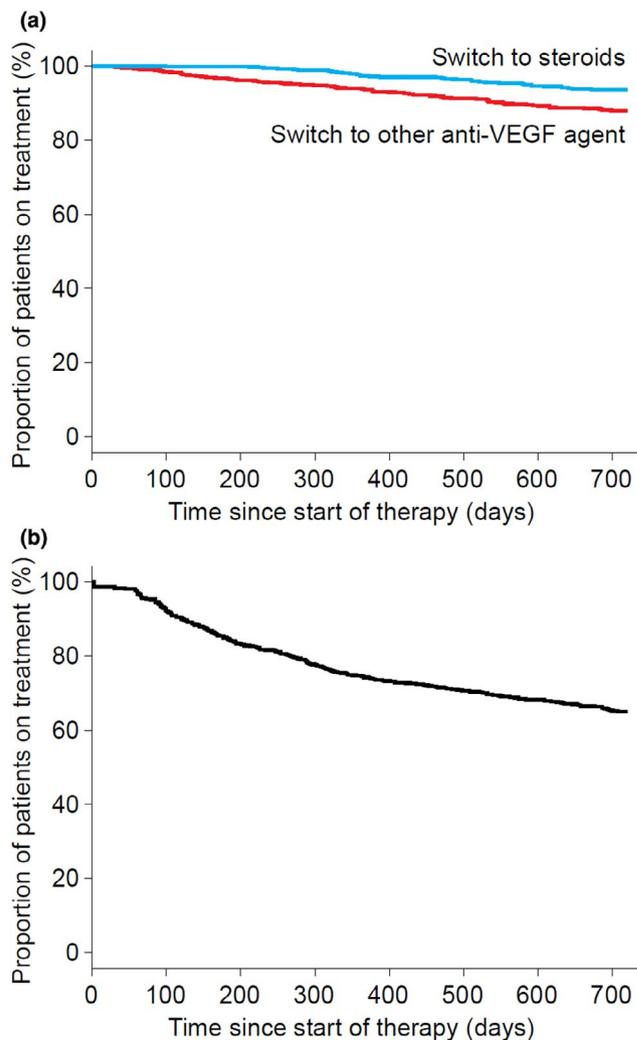
### 3.1 | Distribution of maximum injection intervals

During the first year of anti-VEGF treatment, 63.2% ( $n = 674$ , 95% CI 60–66) of eyes had at least one injection interval of at least 12 weeks (Figure 2). Of these eyes, 53.3% had only one injection interval of at least 12 weeks (Table 2). In the first year of treatment, 55.7% of injection intervals were between 4 and 6 weeks, and 8.0% of eyes had injection intervals of under 8 weeks. Injection intervals of 16 and 20 weeks were achieved by 34.3% and 15.7% of eyes. A small proportion of eyes achieved this more than once in the first year of treatment (4.9% and 1.1%, respectively). The mean (SD) VA gain from baseline at the time when extension of injection intervals was initiated was 5.8 (10) ETDRS letters.

In patients with a follow-up period of at least 24 months, most eyes had at least one injection interval of at least 12 weeks during the second year of treatment (<8 weeks: 5.1%; 8–12 weeks: 21.8%;  $\geq 12$  weeks: 73.1%) (Table S2). Of these eyes, the majority had only one or two intervals of this duration (Table 2); however, 32.6% of eyes had at least two consecutive intervals of at least 12 weeks.

### 3.2 | Number of anti-VEGF injections and clinic visits

In total, 8169 anti-VEGF injections were given during the first year of the study period. During the first 3 and 6 months of anti-VEGF treatment the mean (SD) numbers of injections were 3.1 (0.7) and 4.9 (1.1) per patient eye,



**FIGURE 1** Time to (a) switch from index VEGF agent to a different VEGF agent or steroid treatment and (b) discontinuation. Discontinuation of treatment was defined as when anti-VEGF injections were stopped and not re-introduced for  $\geq 180$  days. The patient must have had a record of a clinic visit during that period. VEGF, vascular endothelial growth factor

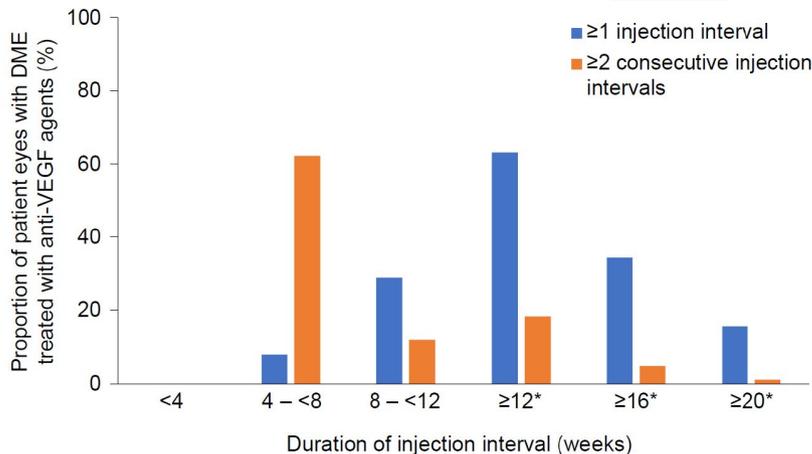
respectively. The mean (SD) numbers of injections per patient eye were 7.7 (1.9) and 5.6 (2.2) in the first and second years, respectively.

The total numbers of clinic visits per patient eye were slightly higher in the first year than the second (mean [SD], 14.2 [5.7] vs. 13.4 [6.4], median [interquartile range], 13 [11, 16] vs. 11 [9,17]). The mean (SD) numbers of injection-free visits per patient eye were 6.6 (5.0) and 7.8 (5.8) in the first and second years, respectively.

### 3.3 | Change in VA and CRT

During the 2-year follow up period, the maximum least-squares mean VA gain from baseline ranged from 1.2

**FIGURE 2** Maximum durations of consecutive injection intervals during the first year of treatment with anti-VEGF agents. \*Categories not mutually exclusive. DME, diabetic macular oedema; VEGF, vascular endothelial growth factor



≥1 injection interval, n (%)	0 (0.0)	85 (8.0)	308 (28.8)	674 (63.2)	366 (34.3)	167 (15.7)
≥2 injection intervals, n (%)	0 (0.0)	664 (62.2)	128 (12.0)	195 (18.3)	52 (4.9)	12 (1.1)

**TABLE 2** Injection intervals during the first and second years of treatment with anti-VEGF agents

Number of injection intervals with a duration of ≥12 weeks	Patient eyes with DME treated with anti-VEGF agents, n (%) <sup>a</sup>	
	12 months' follow-up (n = 674)	24 months' follow-up (n = 348)
1	359 (53.3)	143 (41.1)
2	257 (38.1)	139 (39.9)
3	56 (8.3)	58 (16.7)
4	2 (0.3)	8 (2.3)

Abbreviations: DME, diabetic macular oedema; VEGF, vascular endothelial growth factor.

<sup>a</sup>Injection intervals were not required to be sequential.

(month 3) to 8.3 (month 24) ETDRS letters. The mean VA remained above baseline VA throughout the entire treatment period (Figure S1). The mean (SD) gain from baseline in VA was 6.3 (9.9), 7.8 (9.6), 8.3 (11.1) and 8.9 (11.3) at months 3, 6, 9 and 12, respectively.

When CRT was assessed as part of a sub-study, the mean (SD) change from baseline in CRT was -112.6 (109.1), -116.7 (106.3), -131.2 (121.9) and -133.5 (122) μm at months 3, 6, 9 and 12, respectively. The correlation between change from baseline in CRT and VA during the post-index period was moderate at each of these time points (month 3,  $r = -0.43$ ; month 6,  $r = -0.43$ ; month 9,  $r = -0.36$ ; month 12,  $r = -0.48$ ) (Figure 3).

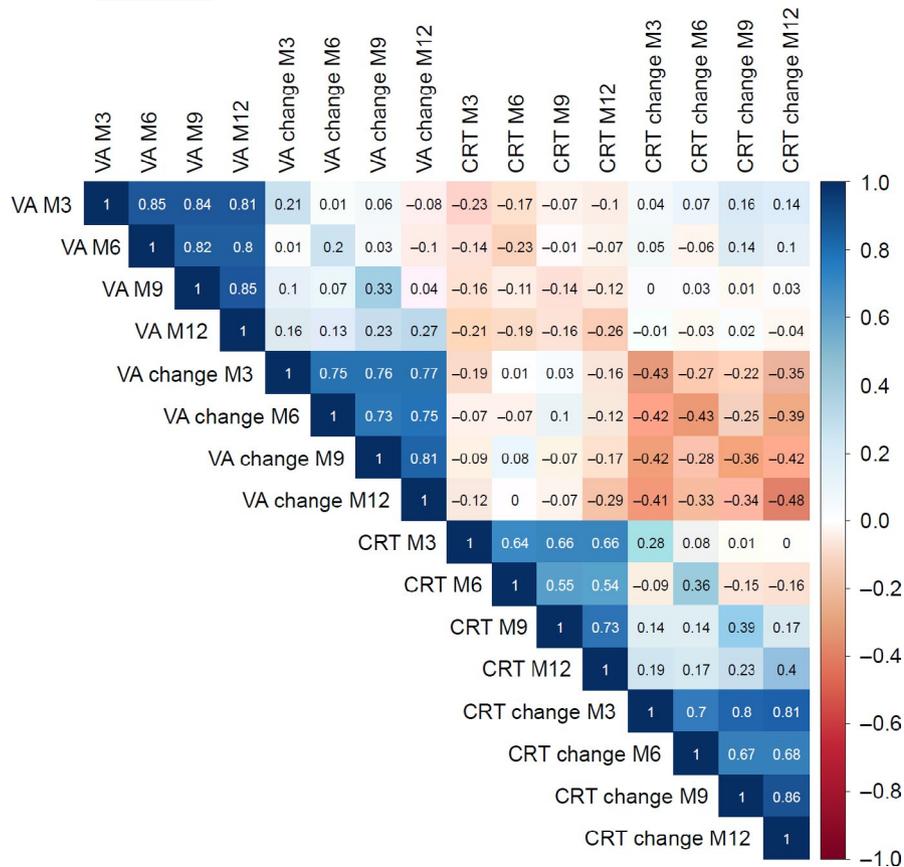
### 3.4 | Patients with DME grouped by unilateral or bilateral treatment

Patients who were treated bilaterally at the index date were slightly younger and had worse VA than those who

received unilateral treatment or changed to bilateral treatment. Other baseline characteristics were similar between patients who were treated unilaterally or bilaterally at baseline and those who changed to bilateral treatment during the first year (Table S1). The mean numbers of injections in months 0-3 and months 3-12 were similar between subgroups (Table S3). Patients who were treated bilaterally at the index date had the highest total number of visits.

## 4 | DISCUSSION

This non-interventional, retrospective study of patients attending UK NHS clinics reports real-world treatment patterns, discontinuation rates and treatment outcomes in eyes treated with anti-VEGF therapy for DME. During the first and second years of treatment, most eyes had at least one anti-VEGF injection interval of at least 12 weeks (year 1, 63.2%; year 2, 73.1%). The number of clinic visits



**FIGURE 3** Pearson correlation coefficient between change from baseline in CRT and change from baseline in VA over 12 months of treatment with anti-VEGF agents (site A). OCT biomarkers were available at one of the three sites (site A). CRT, central retinal thickness; M, month; OCT, optical coherence tomography; VA, visual acuity; VEGF, vascular endothelial growth factor

observed during the first two years of treatment were high (year 1, 14.2; year 2, 13.4). In addition, 27.8% of patient eyes discontinued treatment during the first 2 years.

The proportion of eyes with at least one anti-VEGF injection interval of at least 12 weeks observed in the current study is in line with those attained in clinical trials. A Swiss T&E study of 75 treatment-naïve eyes with DME reported maximum injection intervals between 4 and 14 weeks and a mean injection interval of 8.5 weeks.<sup>16</sup> Clinical trials have demonstrated that frequent and fixed injection intervals are associated with the best outcomes for patients with DME.<sup>12,13</sup> However, these regimens often impose high clinic and patient burden.<sup>13–15</sup>

The mean number of injections per patient eye observed in the first 3 months of treatment (3.1 injections) indicates that patients attending UK NHS clinics received loading doses in accordance with label recommendations and clinical guidelines of treatment with anti-VEGF therapy. The mean number of injections per patient eye in the first year of treatment (7.7 injections) was similar to those observed in the POLARIS (7.4 injections)<sup>17</sup> and the Moorfields Eye Hospital studies (6.7 injections).<sup>18</sup> In addition, the majority (55.7%) of injections within the first 3 months were administered in intervals of 4–6 weeks, suggesting that patients were adequately treated.

Owing to the heterogeneity of the data, it was not possible to determine whether *pro re nata* or T&E regimens

were applied at these sites. The high number of total clinic visits and moderate number of injection-free visits observed may be due to other ocular and general comorbidities, and suggest that treatment for DME was individualized. Patients with diabetes have complex comorbidity profiles, including cerebrovascular and cardiovascular diseases, which might not allow injections to be given at certain times,<sup>19,20</sup> and may contribute to the total number of clinic visits. These patients also have high healthcare utilization.<sup>20</sup> In addition, fewer injections were given in the second year of treatment than the first (mean, 5.6 vs. 7.7), although the total number of injection and injection-free visits remained high (mean, 13.4 vs. 14.2). These data further highlight the need for longer-acting treatments to reduce the burden of DME on patients and healthcare providers.

The mean VA at baseline (61.3 ETDRS letters) observed in this study was higher than in previous studies, including the POLARIS and Moorfields Eye Hospital studies (59.4 ETDRS letters and 56.4 ETDRS letters, respectively).<sup>17,18</sup> It is possible that improved access to care and changes to guidelines in recent years were factors underlying the differences observed between this study and previous studies. Patients included in the present study initiated treatment by July 2018, whereas previous studies were conducted before anti-VEGF therapy for DME was introduced into routine clinical practice.<sup>9</sup> VA gains from baseline observed

in the present study were within the confidence intervals of VA gains reported in the Diabetic Retinopathy Clinical Research Network study.<sup>21</sup>

The importance of the number of injections on visual outcomes is well established.<sup>14,16,22</sup> In this study, patients with DME maintained their visual gain (>6 ETDRS letters) for up to 2 years, which may indicate that the number of injections were appropriate. The magnitude of gain was similar to those observed in clinical trials (4.4–8.0 ETDRS letters).<sup>16–18,23</sup> A modest negative correlation was observed between the improvements in VA and reductions in retinal thickness, which is consistent with previously reported correlations.<sup>24,25</sup> In addition to retinal thickness, other factors such as disorganization of retinal layers or ellipsoid zone disruption affect functional outcomes in DME. Further studies are required to assess the disorganization of retinal morphology in DME in a larger cohort.

Overall, 8.5% and 3.9% of patient eyes switched index therapy to either another anti-VEGF agent or steroids, respectively. This is consistent with a recent publication from the Fight Retinal Blindness! Registry, which reported a switching rate of 5.0% by the end of the first year of treatment.<sup>26</sup> However, in a retrospective Danish study with a follow-up of 2–4 years, 25.4% of eyes switched to another intravitreal therapy.<sup>24</sup> This may be owing to differences in the protocols and follow-up periods between the studies. Furthermore, in the present study, 27.8% of patient eyes discontinued treatment during the first 2 years of treatment; the reasons for treatment discontinuation were unknown. In the Fight Retinal Blindness! study, the discontinuation rate in treatment-naïve eyes with DME was lower (15.9%;  $n = 61$ ).<sup>26</sup> However, it should be noted that the sample size ( $n = 383$ ) was smaller than for the present study.

The present study had several strengths, which include the use of the same EMR system for each study site to collect data on VA, date of visit and treatment, the eye treated, and the administered drug. A limitation of this study was that it was based on only three sites; therefore, it is possible that the findings captured here are not representative of all patients with DME in the UK. However, a recent real-world study of patients with DME from 21 UK sites who were treated with aflibercept reported similar VA gains and identified high discontinuation rates, noting that retention of patients with DME is challenging in a clinical setting.<sup>27</sup> An additional limitation of the current study is that data were included if a diagnosis of DME was present in the EMR system. The validity of this diagnosis was not verified at the point of care. Therefore, it is possible that not all patients with DME were captured or that some patients were mis-coded. In addition, eyes without an anti-VEGF injection for 6 months before the index date were deemed treatment-naïve. However, it is unlikely that the EMR system was in use for a substantial amount of

time before the introduction of anti-VEGF therapy into clinical practice, and therefore patients included in the study were likely to be treatment-naïve. Furthermore, it was not possible to determine the reasons for discontinuation of treatment or follow-up. Additionally, the sample size for patients with CRT data was limited.

DME incurs a significant healthcare burden in the UK, as demonstrated by the high number of clinic visits over 2 years observed in this study. A quarter of patients discontinued treatment during the first year. Although the improvements in VA observed in this study were similar to those reported in randomized controlled trials, the total number of visits was high for all treatment groups. These data demonstrate the requirement for therapeutic solutions that enable sustainable extended injection intervals without compromising the morphological and functional benefits. This could improve patient adherence and lessen the burden on both healthcare providers and on patients and their carers.

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## SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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