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ARTICLE

Real-world management and long-term outcomes of diabetic macular oedema with good visual acuity

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Abstract

Purpose To evaluate the management and long-term outcomes of patients with diabetic macular oedema (DMO) and good initial visual acuity in real-world settings.

Methods We reviewed 122 eyes of 100 patients with treatment-naive DMO and initial best-corrected visual acuity (BCVA) of 20/25 or better. We assessed clinical characteristics, logMAR BCVA, central subfield thickness (CST), cumulative intravitreal injections and laser treatments at yearly intervals, and characteristics at time of initial treatment. Linear mixed effects models were used to identify predictors of visual outcomes.

Results At presentation, mean BCVA was 0.057 ± 0.048 logMAR (Snellen 20/23) and mean CST was 288 ± 57 µm. After a median follow-up of 3 years, 51% of eyes underwent treatment. More eyes underwent intravitreal injection as initial treatment (54%), but lasers were initiated at an earlier time and at better BCVA. Final BCVA was associated with better BCVA ($P < 0.001$) and earlier timing ($P = 0.017$) at initial treatment, but not CST at first treatment ($P = 0.634$) or cumulative number of injections or lasers ($P = 0.441$–0.606).

Conclusion DMO with good initial visual acuity should be monitored closely, as delay in treatment initiation is associated with worse visual outcomes. BCVA at time of initial treatment is the strongest determinant of final visual acuity.

Introduction

Diabetic macular oedema (DMO) is a common ocular complication of diabetes resulting from disruption of the blood–retinal barrier and accumulation of fluid in the retina, which can lead to vision loss and blindness if untreated. The Wisconsin Epidemiologic Study of Diabetic Retinopathy reports that 29% of patients who have had diabetes for at least 20 years develop DMO [1]. Current treatments for DMO consists of intravitreal anti-vascular endothelial growth factor (VEGF) pharmacotherapies and focal or grid laser photocoagulation [2], as well as ancillary therapies including intravitreal corticosteroids, subthreshold micropulse laser [3–6], and pars plana vitrectomy [7, 8]. While multiple pivotal randomised prospective studies have demonstrated the efficacy of anti-VEGF agents with or without focal/grid laser as first-line treatment for DMO [9–14], most of these studies only evaluated patients with best-corrected visual acuity (BCVA) of 20/32 to 20/40 Snellen equivalent or worse. Among eyes with centre-involving DMO and presenting BCVA of 20/25 or better in the Early Treatment Diabetic Retinopathy Study (ETDRS), 27% of eyes treated with prompt focal laser therapy lost five or more ETDRS letters compared with the 40% of eyes that were observed, supporting the role of early intervention [15]. However, this study relied on clinical examination to define "clinically significant" DMO threatening the central macula, and neither optical coherence tomography (OCT) or anti-VEGF therapy was available at the time. The more

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recent prospective Protocol V study from the Diabetic Retinopathy Clinical Research (DRCR) Retina network randomised 702 participants with centre-involving DMO with BCVA of 20/25 or better to initial management with aflibercept, laser photocoagulation, or observation only. The study found that eyes that were initially observed did not undergo significant vision loss after 2 years compared with prompt intervention with anti-VEGF [16]. However, this study did not evaluate long-term outcomes beyond 2 years, and the patients were generally healthier and more motivated—the mean haemoglobin A1c (HbA1c) was 7.6 and patients were followed closely and underwent immediate aflibercept treatment for any >10 letters decrease in visual acuity. To better understand the management of DMO with good initial visual acuity in real-world settings, we performed a retrospective cohort analysis of eyes with treatment-naive, centre-involving DMO and baseline BCVA of 20/25 or better to assess the clinical factors associated with long-term visual and anatomic outcomes, and the impact of early versus delayed intervention.

Methods

Patient selection

We reviewed the medical records of 2262 patients diagnosed with diabetic retinopathy (ICD9 code 250.XX or ICD10 codes E11.311, E11.321×, E11.331×, E11.241×, E11.251X, and E11.37XX) who were seen at the University of California, Davis Health System between March 8th, 2007 to March 8th, 2018. We included only eyes with centre-involving DMO confirmed on spectral-domain OCT imaging who had BCVA of 20/25 or better at initial diagnosis and no prior treatments, and at least 1-year of follow-up visits with SD-OCT imaging. Eyes with a history of ocular surgery or ocular comorbidities such as age-related macular degeneration, retinal vein, and artery occlusion, end-stage glaucoma, vitreomacular traction (VMT), or retinopathies unrelated to diabetes were excluded. Eyes with medically controlled glaucoma, posterior vitreous detachment, and vitreomacular adhesion without VMT were not excluded. This study was approved by the Institutional Review Board of University of California, Davis and was conducted in accordance with the tenets of the Declaration of Helsinki.

We recorded baseline demographics and clinical data including age, sex, treating provider, presence of visual symptoms, type of diabetes, and severity of diabetic retinopathy as documented by the physician at the time of diagnosis. We also recorded HbA1c levels, BCVA, lens status, cataract types and grades, central subfield thickness (CST) based on OCT imaging, and cumulative number and type of intravitreal injections or laser treatments at yearly follow-up visits. Data were collected from follow-up visits that are closest to, and within 90 days, of 12-month intervals from the initial visit, until the most recent available annual visit, up to a total of 4 years. Data beyond 4 years were not collected due to the small proportion of subjects with 5 or more years of follow-up. Snellen readings for BCVA were converted to a logarithm of the minimal angle of resolution (logMAR) scale for statistical analyses. Cataract types and grades were based on the treating physician's exam documentation, which were classified on a lens opacity scale of 0–3 for nuclear, cortical, and posterior subscapsular cataracts. Pseudophakic eyes were classified separately, and eyes that underwent cataract extraction surgery during the study period were classified as phakic prior to surgery and pseudophakic after surgery. Severity of diabetic retinopathy was classified as mild non-proliferative diabetic retinopathy (NPDR), moderate NPDR, severe NPDR, non-high-risk PDR, and high-risk PDR, based on physician documentation. CST was automatically measured as the average retinal thickness from the central 1 mm diameter circle cantered on the fovea, based on the ETDRS grid, using either Cirrus HD-OCT (Carl Zeiss Meditec) or Spectralis HRA + OCT instrument (Heidelberg Engineering). All OCT measurements were verified for accuracy of grid centration and retinal layer segmentation. We also recorded the length of time (in weeks) from first presentation to which the patient received the first laser treatment or intravitreal injection, the first type of laser and/or injection received, and the BCVA and CST values at the time of treatment initiation. Types of laser treatments included focal/grid laser or subthreshold micropulse laser. Types of intraocular injections included 1.25 mg bevacizumab, 0.3 mg ranibizumab, 2 mg aflibercept, 2–4 mg triamcinolone, and 0.7 mg intravitreal dexamethasone implants.

Statistical analysis

Statistical methods were chosen to account for varying lengths of follow-up, varying providers, as well as the inclusion of patients that had both eyes qualify under the study criteria. The relationships between changes over time in VA or CST and patient baseline and disease characteristics were modelled using linear mixed effects models. These models included fixed effects for the indicated baseline/patient characteristic, year, the interaction between the indicated characteristic and year, and VA or CST at baseline, and a random effect for patient. The relationships between VA or CST at the final visit and treatment characteristics were likewise modelled using linear mixed effects models, including fixed effects for the indicated treatment characteristic, provider, lens status (phakic vs. pseudophakic), cortical, nuclear, and posterior subcapscular cataract grades, and year of last visit, and a random effect

for patient. Analyses were conducted using R, version 3.5.3 (R Core Team, 2019), with linear mixed effects modelling conducted using the R packages lme4 (version 1.1–21) and lmerTest (version 3.1–0).

Results

Demographics and baseline characteristics

We identified 122 eyes of 100 patients with treatment-naive, centre-involving DMO and baseline BCVA of 20/25 or better. Mean age at presentation was 62.1 ± 12.3 years, with more men than women (63 vs. 37%), and majority of subjects with type 2 diabetes (94%). Most eyes were asymptomatic at the time of diagnosis (82%), and most eyes had mild (61%) to moderate (15%) NPDR (Table 1). Mean baseline BCVA was 0.056 ± 0.038 logMAR (Snellen equivalent 20/23), which was not associated with any baseline characteristics including age, sex, symptoms at presentation, type of diabetes, diabetic retinopathy severity, or baseline CST, likely due to the homogeneity of visual acuities at baseline (Supplemental Table 1). Mean CST at presentation was 288 ± 57 µm. Female sex was associated with 30.6 µm lower CST compared with males ($P = 0.004$). No other baseline characteristics such as, age, symptoms, diabetes type, or diabetic retinopathy severity were associated with baseline CST (Supplemental Table 2).

Management of DMO with good visual acuity

The median follow-up duration was 3 years, with 51% of patients receiving some form of treatment during follow-up. The median time from presentation to first treatment of any type was 9.5 weeks (Fig. 1a), with mean logMAR 0.22 ± 0.25 (Snellen equivalent 20/33) and mean CST of 356 ± 103 µm at the time of intervention. More patients underwent an intravitreal injection (54%) than laser treatment (46%) for initial management (Table 1), and included anti-VEGF therapy (54.8%), followed by focal/grid laser (32.3%), subthreshold micropulse laser (11.3%), and only one patient receiving an intravitreal steroid (1.6%). For eyes that received an intravitreal injection first, the median time to first intravitreal injection was 35.5 weeks (Fig. 1b), with mean logMAR 0.3 ± 0.3 (Snellen equivalent 20/40) and mean CST 382 ± 107 µm at the time of the first injection (Table 1). For those that underwent laser treatment first, the median time to the laser was 16.5 weeks (Fig. 1c), with mean logMAR 0.2 ± 0.2 (Snellen equivalent 20/31.7) and mean CST 328 ± 81 µm at the time of the first laser (Table 1). These data suggest that while intravitreal injections were the most common first intervention, laser treatments were initiated earlier and at better BCVA and CST.

Table 1 Baseline and follow-up characteristics of DMO with good visual acuity

Baseline patient characteristics	
Mean age (years)	62.1 ± 12.3
Sex (%) (male/female)	63/37
Diabetes type (%) (type 1/type 2)	6/94
Baseline eye characteristics	
Symptoms (%) (present/absent)	18/82
Laterality (%) (right/left)	46/54
Diabetic retinopathy severity (%)	
NPDR (mild/moderate/severe)	61/15/11
PDR (non-high-risk/high-risk)	11/2
Mean BCVA (logMAR)	0.057 ± 0.048
Mean CST (µm)	288 ± 57
Follow-up characteristics	
Median follow-up (years)	3
% Eyes receiving any treatment	51
First treatment type (%) (injection/laser)	54/46
Mean cumulative # injections	
Year 1	0.4
Year 2	1.2
Year 3	2.0
Year 4	3.1
Mean cumulative # lasers	
Year 1	0.3
Year 2	0.5
Year 3	0.7
Year 4	0.8
Median time (weeks)	
To first treatment	9.5
To first injection	35.5
To first laser	16.5
Mean BCVA (logMAR)	
At first treatment	0.22 ± 0.25
At first injection	0.3 ± 0.3
At first laser	0.2 ± 0.2
Mean CST (µm)	
At first treatment	356 ± 103
At first injection	382 ± 107
At first laser	328 ± 81

BCVA best-corrected visual acuity, *CST* central subfield thickness, *NPDR* non-proliferative diabetic retinopathy, *PDR* proliferative diabetic retinopathy

Visual outcomes of DMO with good visual acuity

During the follow-up period, BCVA decreased by 0.046 ± 0.013 logMAR units per year based on a linear mixed effects model (Fig. 2a), while CST measurements did not vary significantly over time across the cohort (Fig. 2b). The visual decline showed a marginal association with cortical cataract

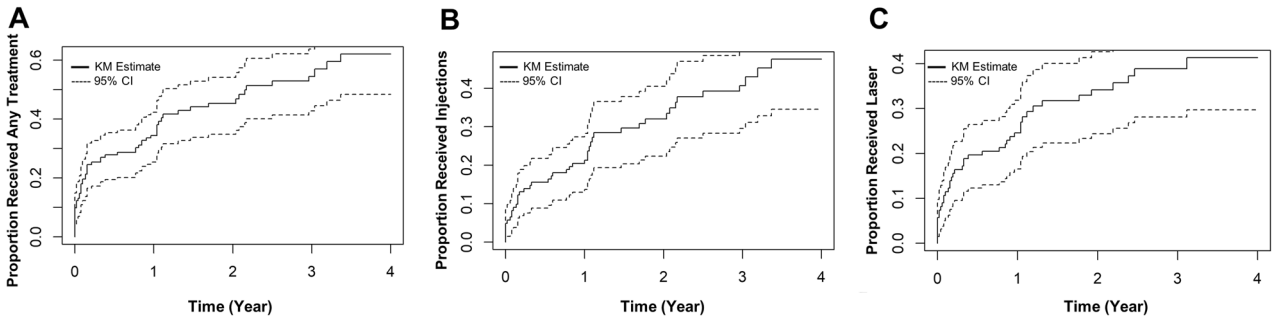

Fig. 1 Kaplan–Meier plots of the proportion of eyes with diabetic macular oedema and initial BCVA ≥ 20/25 that received any treatment (**a**), injections (**b**), or laser (**c**). The solid line shows the KM estimate of the proportion of treated subjects, and the dashed lines show 95% CI. CI confidence interval, ERM epiretinal membrane, KM Kaplan–Meier

grade ($P = 0.044$), but not with any baseline characteristics such as age, sex, symptoms, diabetes type, retinopathy severity, or CST at presentation; or other time-varying factors such as HbA1c, nuclear sclerosis, or posterior subcapsular cataract grades (Table 2).

Next, we evaluated how management strategy impacted visual acuity outcomes. Interestingly, while the cumulative number of treatments, including either injections or lasers, did not significantly impact visual outcomes ($P =$ 0.441–0.606), there was a strong association between BCVA at the time of initial treatment and final visual acuity ($P < 0.001$). Each 0.1 logMAR unit decrease in visual acuity at the time of initial treatment was associated with 0.469 (95% CI 0.319–0.663) logMAR unit decrease in final BCVA (Table 3). The rate of visual decline was slower in eyes treated when BCVA was 20/25 or better (0.028 ± 0.023 logMAR units/year), compared with eyes that were not treated (0.046 ± 0.021 logMAR units/year) or treated when BCVA was worse than 20/25 (0.064 ± 0.025 logMAR units/year) (Fig. 2c). There was also an independent association between timing of initial treatment and final visual acuity ($P = 0.017$), with each 1-week delay in initiating therapy associated with a 0.014 (95% CI 0.003–0.024) logMAR unit worsening in final vision (Table 3). Visual outcomes were not impacted by whether an injection or laser was chosen as initial therapy ($P = 0.114$). Among eyes that first underwent injection or laser treatment, there was a similarly strong association between better BCVA or earlier timing of intervention with better visual outcomes (Table 3). Neither the type of anti-VEGF agent used ($P = 0.468$) or modality of laser ($P = 0.545$) impacted visual outcomes within their respective subgroup analyses. Although CST at the time of first treatment did not affect final vision ($P = 0.634$), retinal thickening was also associated with worse visual outcomes in eyes that underwent laser therapy ($P = 0.026$). Together, our findings suggest that among clinical factors evaluated in this study, better BCVA at the time of initiating treatment is the strongest determinant of visual outcomes in eyes with DMO and good initial visual acuity.

Discussion

The timing for initiating treatment for eyes with DMO and good initial visual acuity has been an area of great interest for retinal specialists. While interstitial fluid and retinal thickening may damage the cellular components of the central macula responsible for high acuity visual function, patients with good visual acuity or without symptoms are often reluctant to undergo therapy based solely on anatomic findings. The ETDRS showed that 27% of eyes with centre-involving DMO and BCVA ≥ 20/25 treated with focal or grid laser lost five or more letters at 2 years compared with 40% in the observation group, supporting prompt intervention with laser therapy [15]. The DRCR Protocol I further showed that only 4% of subjects receiving anti-VEGF therapy lost five or more letters at 2 years, although that study was limited to eyes with BCVA of 20/32 or worse [9]. The prospective, randomised DRCR Protocol V study suggests that eyes with DMO and initial BCVA of 20/25 or better may be initially observed without prompt anti-VEGF therapy [16]. However, the study was limited to 2 years of follow-up, and patients enrolled in prospective clinical trials are generally healthier and more motivated to follow closely. In our study, we evaluated the real-world management of a large cohort of eyes with treatment-naive DMO and initial visual acuity ≥20/25 over a 10-year period and assessed their long-term visual outcomes up to 4 years of follow-up. The mean baseline HbA1c in our cohort was 8.76, compared with the mean HbA1c of 7.6 in Protocol V. The proportion of eyes that received intravitreal injections was 38% at 2 years, which is similar to the 25–34% that received aflibercept in eyes randomised to initial observation or laser in Protocol V. However, our cohort of patients underwent slow visual decline of 0.046 logMAR units (~1/2 Snellen line) per year, while those in protocol V remained largely stable near 20/20, suggesting that real-world patients with DMO and good initial visual acuity who were not closely monitored in clinical trial settings may suffer some visual loss over 3–4 years.

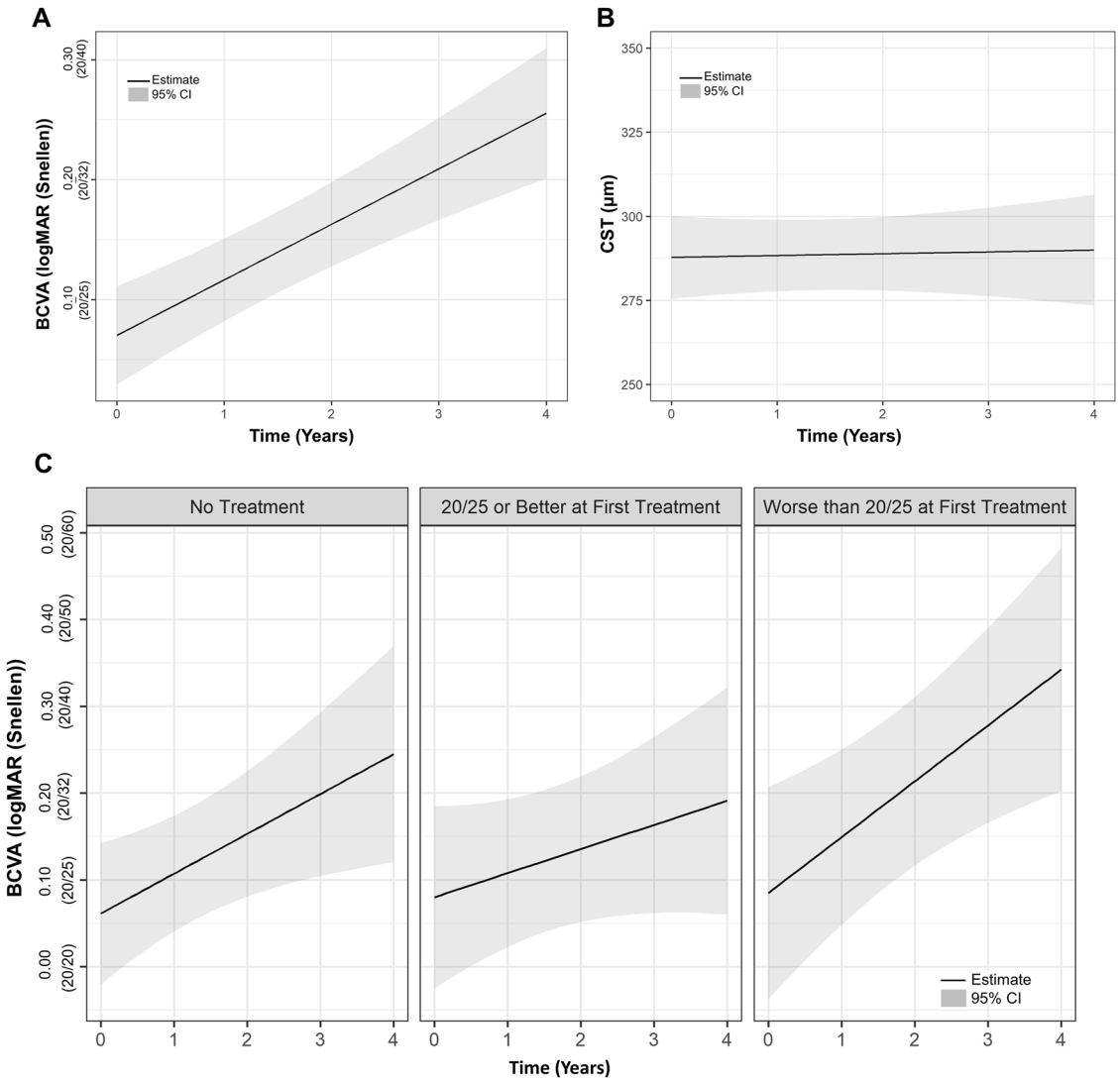

Fig. 2 Linear plots of long-term visual (**a**) and anatomic outcomes (**b**) of eyes with diabetic macular oedema and initial BCVA ≥ 20/25. The solid lines on the plot shows the fit from a linear mixed effects model of BCVA or CST, with a fixed effect for year and random effects for subject and eye. The estimated rate of change in BCVA is 0.046 logMAR/year, with a 95% CI of (0.033 logMAR/year, 0.059 logMAR/year), $P < 0.001$. The estimated rate of change in CST is 0.53 µm/year, with a 95% CI of (−3.29 µm/year, 4.39 µm/year), $P = 0.784$. **c** Linear plots of subgroup analyses of BCVA change over time in eyes that received no treatment (left), ≥20/25 at first treatment (centre), and <20/25 at first treatment (right). The solid lines show the fits from a linear mixed effects model of BCVA, with fixed effects for year, vision at first treatment, and their interaction, and random effects for subject and eye. The shaded grey areas for all graphs show simultaneous 95% CI for the fits. BCVA best-corrected visual acuity, CI confidence interval, CST central subfield thickness

Unlike Protocol V where patients randomised to initial observation or laser were given prompt aflibercept treatment for a two-line decrease in visual acuity, the patients in our retrospective study were managed based on the clinician's discretion. In this setting, approximately half of our patient cohort underwent either intravitreal injection or focal/grid laser during the follow-up period, with a median time of 2.5 months to initiating some form of therapy in these eyes. Although intravitreal injections were more commonly performed as initial therapy, laser treatments tended to be initiated at an earlier time (median 16.5 vs. 35.5 weeks), and at better BCVA (mean Snellen 20/32 vs. 20/40), possibly because laser treatments are perceived as better tolerated, exhibiting greater durability, and requiring less frequent follow-up visits. Also, anti-VEGF therapies may be favoured in eyes with foveal fluid, where visual acuity is more likely to be compromised, while laser photocoagulation may be better suited for non-foveal oedema. While our study did not distinguish between fluid type, amount, or location, a more robust analysis of OCT findings may provide additional insight into imaging features that could guide the management of these eyes [14].

An important finding in our study is the strong association between visual acuity at first treatment and visual

Table 2 Clinical characteristics associated with visual outcomes in DMO with good visual acuity

	Category or increment	Coefficient (95% CI)[a]	*P*-Value
Baseline characteristics			
Age	1 year	0.253 (−0.181, 0.69)	0.256
Sex	Female vs male	0.008 (−0.009, 0.024)	0.382
Symptoms	Present vs. absent	−0.494 (−1.059, 0.063)	0.085
DM type	Type 2 vs. type 1	−0.082 (−0.995, 0.853)	0.861
DR severity	1 level	0.063 (−0.136, 0.258)	0.534
Baseline CST	50 µm	−0.108 (−0.282, 0.063)	0.219
Time-varying characteristics			
A1C	1	−0.029 (−0.162, 0.104)	0.671
Nuclear cataract grade	1 level	0.265 (−0.063, 0.597)	0.117
Cortical cataract grade	1 level	0.361 (0.013, 0.71)	0.044*
Posterior subcapsular cataract grade	1 level	0.28 (−0.556, 1.119)	0.515

*$P < 0.05$, statistically significant

[a]For categorical variables, coefficient is the difference between categories in the rate of change over time in VA (in units of 0.1 logMAR) between categories. For continuous variables, coefficient is the change in the rate of change of time in VA (in units of 0.1 logMAR) for the indicted change in the continuous variable

Table 3 Treatment parameters associated with visual outcomes in DMO with good visual acuity

	Category or increment	Coefficient (95% CI)[a]	*P*-Value
Treatment pattern			
Cumulative injections	One injection	0.033 (−0.085, 0.155)	0.606
Cumulative laser	One laser	−0.2 (−0.717, 0.286)	0.441
Treatment Initiation			
Type of first ANY treatment	Injection vs. laser	0.736 (−0.093, 1.589)	0.114
Time to:			
First treatment	1 week	0.014 (0.003, 0.024)	0.017*
First injection	1 week	0.016 (0.005, 0.028)	0.021*
First laser	1 week	0.012 (0.002, 0.022)	0.041*
BCVA at:			
First treatment	0.1 logMAR	0.469 (0.319, 0.663)	<0.001*
First injection	0.1 logMAR	0.582 (0.414, 0.756)	<0.001*
First laser	0.1 logMAR	0.516 (0.319, 0.727)	<0.001*
CST at:			
First treatment	50 µm	0.048 (−0.123, 0.229)	0.634
First injection	50 µm	0.037 (−0.228, 0.294)	0.811
First laser	50 µm	0.604 (0.549, 0.653)	0.026*

*$P < 0.05$, statistically significant

[a]For categorical variables, coefficient is the difference between categories in VA at the final visit (in units of 0.1 logMAR). For continuous variables, coefficient is the change in VA at the final visit (in units of 0.1 logMAR) for the indicated change in the continuous variable

outcomes—each line of BCVA increase at time of intervention was associated with ~0.5 line gain in final vision. Better visual outcomes were also associated with starting therapy earlier, but not with any baseline characteristics (demographics, symptoms, diabetes type, or severity of retinopathy), time-varying factors (HbA1c or cataract severity), total treatment burden (total injections or lasers), or CST at the time of first treatment. Hence, our results suggest that delayed treatment of DMO with good initial vision may lead to worse visual outcomes, and that initiating treatment based on BCVA may be the most important determinant of final visual acuity. These findings

complement Protocol V findings, emphasising the need for close monitoring and prompt treatment despite the option to initially observe DMO with good initial visual acuity. Our results also support the use of visual acuity rather than anatomy as the primary determinant or threshold for initiating treatment.

Due to its retrospective nature, our study lacks the granularity of data to understand the clinical circumstances for treatment decisions, frequency or pattern of treatments, injection strategy (e.g. as-needed or treat-and-extend), switching between anti-VEGF agents, or interactions between lasers and injections. We also cannot conclude that earlier intervention would have improved the outcomes of eyes with delayed treatment. Finally, the lack of statistical difference between initiating injections vs. laser therapy or different types of injections does not imply equivalence, so we cannot conclude if starting with one treatment may be superior to another. Since prolonged anti-VEGF therapy may have secondary effects in eyes with DMO [17], care should be taken when inferring treatment decisions from retrospective analyses.

Beyond the longer duration of follow-up, our study is strengthened by the use of linear mixed effects models that adjusted for cataract grade to account for changes in lens opacity which may impact eyes with good visual acuity, and for provider identity to account for different treatment preferences of individual physicians. The study is limited by its retrospective design, which includes (1) a diversity of intervention practice patterns, (2) reliance on physician documentation of exam findings, (3) visual acuity measurements using Snellen rather than ETDRS charts, and (4) inclusion of two different commercial SD-OCT instruments for CST measurements. Nevertheless, consistent with studies in other retinal conditions where early intervention may improve visual outcomes [18], our findings supports the importance of closely monitoring patients with DMO and good baseline visual acuity, and the need to initiate therapy promptly if visual acuity declines to maximise long-term visual outcomes.

Summary

What was known before

- Anti-VEGF agents and focal/grid lasers are effective treatments for diabetic macular enema (DMO), but most prospective clinical trials evaluated only patients with best-corrected visual acuity (BCVA) of 20/32 or worse. In eyes with DMO and BCVA of 20/25 or better, the DRCR Protocol V study showed that initial observation may be a reasonable strategy, if aflibercept were given for any worsening in BCVA.

What this study adds

- In real-world settings, eyes with DMO and initial BCVA greater than or equal to 20/25 undergo gradual visual decline, with 51% of eyes undergoing treatment at 3-year median follow-up. Visual outcomes were strongly associated with better BCVA at the time of treatment initiation, with each line of BCVA increase at time of intervention associated with ~0.5 line gain in final vision. This study suggests that DMO with good initial visual acuity should be monitored closely, as delay in treatment initiation may be associated with worse visual outcomes.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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