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Predictors of Vision Loss After Lapse in Antivascular Endothelial Growth Factor Treatment in Patients With Diabetic Macular Edema

Meghana Chalasani, MD[1], Christopher Maatouk, MD[1,2], Jonathan Markle, MD[1], Rishi P. Singh, MD[1,3], and Katherine E. Talcott, MD[1]

Abstract

Purpose: To identify baseline characteristics that predict visual outcomes after a lapse in treatment among patients with diabetic macular edema (DME) who received intravitreal antivascular endothelial growth factor injections. **Methods:** In this retrospective study, patients with DME who had lapses in treatment of 3 months or longer were separated into 2 groups (stable vision, n = 201; vision loss, n = 61) based on an Early Treatment Diabetic Retinopathy Study vision loss threshold of 10 letters. Stepwise backward logistic regression was used to analyze baseline factors associated with vision loss and to create a predictive algorithm. **Results:** In the final regression model, the length of lapse in treatment (odds ratio [OR]; 1.15, 95% CI, 1.07-1.25), diabetic foot disease (OR, 3.02; 95% CI, 1.09-8.2), and Medicaid insurance (OR, 4.60; 95% CI, 1.20-18.7) were positively associated with vision loss ($P < .05$). Time since diagnosis of diabetic retinopathy (OR, 0.95; 95% CI, 0.91-0.99) was negatively associated with vision loss ($P < .05$). The final prediction model had a sensitivity of 20% and a specificity of 84%, with an area under the curve of 65%. **Conclusions:** For patients with DME at high risk for a lapse in treatment, baseline characteristics can help predict vision loss and guide management.

Keywords

diabetic macular edema (DME), diabetic retinopathy (DR), anti-VEGF, treatment lapse

Introduction

Diabetic retinopathy (DR), a leading cause of irreversible vision loss in adults globally, is a common complication of diabetes mellitus.[1,2] The pathogenesis of DR involves the degenerative effect of hyperglycemia and oxidative stress on blood vessels in the retina. Diabetic macular edema (DME) is a manifestation of DR that occurs as a result of the leakage of fluid through the blood–retinal barrier and the accumulation of subretinal fluid, which significantly contributes to visual impairment.[3] Optical coherence tomography (OCT) is now widely used to complement a physical examination in the diagnosis and monitoring of DME.[4,5] Progressive ischemic conditions that promote neovascularization, the hallmark of proliferative DR (PDR), result from inadequate glycemic control.[1] The management of metabolic-related comorbidities and maintaining glycemic control can help prevent and delay poor visual outcomes.[6]

The first-line treatment for DME is intravitreal injection of antivascular endothelial growth factor (anti-VEGF).[3] The chronic nature of DR necessitates consistent monitoring and treatment; therefore, the effectiveness of anti-VEGF treatment could be limited by lapses in care. Lapses in or discontinuation of treatment may result from many things, including comorbidities, difficulty in attending visits, and financial hardship.[7–9] A study by Weiss et al of 136 patients with DME[7] found that 46% of patients had at least 1 treatment lapse of more than 100 days from a scheduled follow-up while only 35% of the total patients always kept to the schedule. The reasons for missed appointments and therapy break-offs among patients with DME were summarized as most often being the result of other illnesses, personal issues, problems with the clinic, or no explanation given. Jansen et al[10] collected data on 37 401 appointments for

[1] Center for Ophthalmic Bioinformatics, Cole Eye Institute, Cleveland Clinic, Cleveland, OH, USA
[2] Department of Ophthalmology, University of Chicago Medical Center, Chicago, IL, USA
[3] Cleveland Clinic Martin Hospitals, Cleveland Clinic Florida, Stuart, FL, USA

Corresponding Author:
Katherine E. Talcott, MD, Cole Eye Institute, Cleveland Clinic, 9500 Euclid Ave, i-32, Cleveland, OH 44195, USA.
Email: talcotk@ccf.org

patients with DME in the United States and found that 14.32% were cancellations and 10.01% were no-shows. This study also found that patients with DME were more likely to miss appointments than patients with neovascular age-related macular degeneration (AMD).

Recent studies have attempted to determine the effect that lapses in anti-VEGF treatment have on visual outcomes in various ocular diseases. When evaluating relevant outcomes in DR, studies show variable results. In a study of 90 eyes with nonproliferative DR (NPDR) and DME that were lost to follow-up for at least 6 months, Matsunaga et al[11] found no significant decline in visual acuity (VA) after treatment was resumed. In a study of 170 participants with PDR or ME by Maguire et al,[12] more than one half (55.3%) of patients had at least 1 lapse in care of 8 or more weeks past a scheduled examination. These participants were more likely to have worse visual outcomes, with a median VA of −2 letters after 5 years compared with +5 letters in those who did not have a lapse in treatment.

Yalamanchili et al[13] examined outcomes in 164 patients having treatment and evaluation for DME. One half of the patients had at least a 3-month lapse in anti-VEGF treatment for DME and did not have any significant differences in central subfield thickness (CST) or VA measurements 6 months after the lapse compared with controls who did not have a lapse in treatment.

The current study assessed patients with DME who had a significant change in vision after a lapse in evaluation and treatment. Our primary aim was to investigate baseline clinical and demographic characteristics and identify relevant risk and protective factors for vision change after an unintended lapse in DME management.

Methods

This analysis was performed at Cole Eye Institute, Cleveland, OH, USA, using a comprehensive chart review of the electronic medical record. These methods were approved by the Cleveland Clinic Institutional Review Board. The study included adults at least 18 years of age with a diagnosis of DR (PDR or NPDR), DME, and/or retinal edema according to International Classification of Diseases (ICD), 9th edition, and ICD, 10th edition, codes. Patients who had received at least 1 anti-VEGF injection before a lapse in treatment and had an unintended lapse in follow-up for at least 3 months were also included. The time limit was 3 calendar months from a patient's previous visit. Patients who had a lapse in treatment of at least 3 months per provider recommendation and those with other unrelated retinal diseases, including pathologic myopia, AMD, and choroidal neovascularization in the study eye, were excluded. Only the first lapse was evaluated for patients with multiple lapses in treatment. For patients with bilateral disease, only 1 eye was included in this study at random using a random number generator.

Patients were separated into 2 groups according to whether they had vision loss or stable vision. Their characteristics were compared, and a chart review was performed. A significant loss of vision was defined at the first appointment after a lapse in treatment as a loss in best-corrected VA (BCVA) of at least 10 Early Treatment Diabetic Retinopathy Study (ETDRS) letters. BCVA was obtained in standardized examination rooms using protocol refraction and an ETDRS chart. The choice of 10 letters was based on considerable vision loss while allowing for a reasonable sample size. During data collection, assessors were blinded to the outcome of vision loss and stable vision.

Categorical variables included type of insurance, severity of DR, type of anti-VEGF agent, smoking status, and history of the following comorbid conditions: obesity, diabetic foot disease (ulcer or osteomyelitis of the foot attributed to diabetes), neuropathy, nephropathy, chronic kidney disease, hypertension, hyperlipidemia, myocardial infarction or stroke, and atherosclerotic disease. Continuous variables included the length of treatment lapse, time since DR diagnosis, number of total injections, glycosylated hemoglobin (HbA_{1c}) within 1 year of the last treatment before a lapse in treatment, body mass index, serum creatinine, and estimated glomerular filtration rate within 3 years of the last treatment before a lapse in treatment.

Statistical Analysis

Multiple imputation was used to address missing data of individuals with incomplete medical records. Categorical variables were summarized by frequency (%) and compared using χ^2 tests. Discrete variables were summarized with the mean ± SD and compared using independent *t* tests. To further assess factors associated with vision loss after a treatment lapse, multiple logistic regression using the previously stated categorical and continuous variables was performed to identify factors significantly associated with vision loss. Stepwise backward logistic regression was used to create a prediction algorithm optimized using Akaike information criteria to predict patients at higher risk for vision loss. The algorithm was trained on 80% of patients and tested on the remaining 20%; its efficacy was evaluated using the area under the curve (AUC) from the receiver operator characteristics curve and calculation of its sensitivity and specificity. All analysis was performed using R software (version 4.2.1, R Project for Statistical Computing). Statistical significance was set at $P = .05$.

Results

The study comprised 262 patients who met the inclusion criteria and were analyzed; 61 patients were in the vision loss group and 201 patients were in the stable vision group. The mean patient age was 61 years; 44.7% were women and 61.1% were White. The groups were similar in age, distribution of racial groups, and sex ($P > .05$) (Tables 1 and 2).

Among baseline characteristics, the mean lapse in treatment was greater in the vision loss group (9.2 ± 9.5 months) than in the stable vision group (5.8 ± 3.4 months) ($P < .001$) (Table 1). The groups also differed significantly in their distribution across insurance groups ($P = .01$) (Table 2). In the vision loss group,

Table 1. Baseline Analysis of Continuous Variables.

Variable	Mean ± SD		*P* Value
	Vision Loss (n = 61)	Stable Vision (n = 201)	
Age (y)	58.6 ± 15.5	61.7 ± 10.6	.08
Time since DR diagnosis (mo)	11.6 ± 9.5	14.3 ± 13.1	.13
Time since diabetes diagnosis (y)	13.7 ± 7.2	14.1 ± 8.5	.73
Time since first injection (mo)	10.3 ± 9.8	10.7 ± 9.8	.75
Length of lapse (mo)	9.2 ± 9.5	5.8 ± 3.4	<.001[a]
Total injections (n)	4.9 ± 3.9	5.2 ± 4.7	.68
Visual acuity before lapse (ETDRS letters)	66.8 ± 14.5	68.0 ± 13.6	.57
CST before lapse (μm)	333 ± 110	341 ± 117	.67
Cube volume before lapse (μm)	10.8 ± 1.7	10.7 ± 2.0	.67
Cube average thickness before lapse (μm)	314 ± 48	310 ± 55	.64
BMI	32.9 ± 7.6	32.2 ± 8.0	.54
HbA_{1c} (%)	8.2 ± 2.6	7.6 ± 2.1	.07
Serum creatinine (mg/dL)	1.15 ± 1.45	1.03 ± 1.62	.63

Abbreviations: BMI, body mass index; CST, central subfield thickness; ETDRS, Early Treatment Diabetic Retinopathy Study; HbA_{1c}, hemoglobin A_{1c}.
[a]Statistically significant ($\alpha = .05$).

Table 2. Baseline Analysis of Categorical Variables.

Variable[a]	Percentage		*P* Value
	Vision Loss (n = 61)	Stable Vision (n = 201)	
Insurance			.01[b]
Medicaid	19.7	7.0	
Medicare	60.7	60.7	
Private	18.0	24.4	
None	1.6	7.9	
Diabetic neuropathy	47.5	33.8	.07
Female sex	47.5	43.8	.71
Race			.34
White	54.1	63.2	
Black	34.4	29.8	
Other	11.5	7.0	
Right eye	47.5	51.7	.67
Anti-VEGF type			.58
Bevacizumab before lapse	32.8	24.9	
Aflibercept before lapse	13.1	15.4	
Ranibizumab before lapse	4.9	3.5	
No injection at appointment before lapse	32.8	24.9	
Smoker			.43
Current	8.2	5.5	
Former	50.8	44.8	
Never	41.0	49.8	
Comorbidity			
Obesity	60.7	59.7	1.00
Insulin	72.1	69.2	.34
PDR	18.9	24.6	.30
Diabetic foot disease	21.3	11.9	.10
Chronic kidney disease	42.6	35.3	.38
Hypertension	90.2	92.5	.74
Hyperlipidemia	82.0	78.6	.70
Stroke or myocardial infarction	9.8	13.4	.60
Atherosclerotic disease	26.2	32.3	.46

Abbreviations: Anti-VEGF, antivascular endothelial growth factor; PDR, proliferative diabetic retinopathy.
[a]For variables with more than 2 categories, all categories are shown and the χ^2 test was used to assess for differences in distribution among categories.
[b]Statistically significant ($\alpha = .05$).

60.7% of patients had Medicare, 19.7% had Medicaid, 18.0% had private insurance, and 1.6% had no insurance. These proportions significantly differed from those in the stable vision group, in which 60.7% of patients had Medicare, 7.0% had Medicaid, 24.4% had private insurance, and 8.0% had no insurance.

Patients were similar in respect to history of comorbid conditions, including obesity, diabetic neuropathy, foot disease, chronic kidney disease, as well as the distribution of DR severity diagnoses ($P > .05$) (Table 2). Table 3 shows the ophthalmologic characteristics of patients in both groups after a lapse in treatment.

The optimized logistic regression model included type of insurance, history of diabetic foot disease, length of treatment lapse, time since DR diagnosis, and total injections received before a lapse in treatment (Table 4). The odds of vision loss were reduced by 5% per month since DR diagnosis ($P = .02$). The length of treatment lapse was associated with significantly higher odds of losing vision by 15% per month ($P = .0008$).

Table 3. Ophthalmologic Characteristics of Patients in Each Group After Treatment Lapse.

Variable	Vision Loss (n = 61)	Stable Vision (n = 201)
Mean after lapse (ETDRS letters) ± SD	44.9 ± 19.9	68.5 ± 13.1
Mean CST after lapse (μm) ± SD	429 ± 155	356 ± 125
Mean cube volume after lapse (μm) ± SD	11.9 ± 2.8	11.6 ± 2
Mean cube average thickness after lapse (μm) ± SD	332 ± 77	320 ± 6
Patients who received injection at visit after lapse, n (%)	50 (82.0)	142 (70.6)

Abbreviations: CST, central subfield thickness; ETDRS, Early Treatment in Diabetic Retinopathy Study; VA, visual acuity.

Table 4. Baseline Differences Between Vision Loss Group and Stable Vision Group Among Predictors Included in a Simplified Regression Model.

Variable	Regression Estimate (Odds Ratio)	95% CI		Regression *P* Value
		Low	High	
Length of lapse	1.15	1.07	1.25	.0008[a]
Time since DR diagnosis	0.95	0.91	0.99	.02[a]
Total injections	1.08	0.98	1.19	.11
Diabetic foot disease	3.02	1.09	8.2	.03[a]
Insurance				
Private		Reference Level		—
Medicaid	4.60	1.20	18.7	.03[a]
Medicare	2.02	0.77	6.09	.18
None	0.47	0.02	3.39	.52

Abbreviation: DR, diabetic retinopathy.
[a]Statistically significant (α = .05).

Patients with a history of diabetic foot disease had an increased risk for vision loss by a factor of 3.02 ($P = .03$). Patients with Medicaid insurance had significantly higher odds of vision loss than with patients with private insurance (odds ratio [OR], 4.60; $P = .03$) (Table 4). However, the odds of vision loss in patients with Medicare or no insurance were similar to those of individuals with private insurance ($P = .18$ and $P = .52$, respectively). The total number of injections received before a lapse in treatment was not significantly associated with vision loss ($P = .11$).

When applied to the testing data, the optimized model had a sensitivity of 20% and a specificity of 84% (Table 5), with an AUC of 65.6% in the receiver operator characteristics curve (Figure 1). Accordingly, the model's positive predictive value was 33% and the negative predictive value was 73%, which was superior to the complete model's predictive ability, as determined by its lower AUC of 59.5% (Supplemental Table S1 and Supplemental Figure S1).

Table 5. Confusion Matrix of Optimized Prediction Algorithm on Testing Dataset.

Parameter	Observed		Predictive Value
	Vision Loss	Stable Vision	
Vision loss	3	6	Positive 33%
Stable vision	12	32	Negative 73%
Sensitivity/ specificity	Sensitivity 20%	Specificity 84%	—

Conclusions

This study identified baseline medical and ophthalmic history factors that predict loss of vision in patients with DME after a lapse in treatment of at least 3 months. We found that patients with longer lapses in treatment and a history of diabetic foot disease were at higher risk for vision loss after lapses in treatment and follow-up. Medicaid insurance was also associated with an increased risk for vision loss compared with private insurance. In addition, a longer time since DR diagnosis was found to be a significant protective factor in the final regression. These findings indicate that factors present before a lapse in treatment can influence vision loss after a lapse in treatment.

It is intuitive that longer lapses in treatment lead to worsened visual outcomes, and it is reasonable to infer that pathologic changes result from lengthier lapses in treatment, leading to vision loss. Of note, the vision loss group exhibited significant heterogeneity in the length of treatment lapses, with a mean of 9.2 ± 9.5 months. There may not be a direct relationship between the length of lapse in treatment and the subsequent probability of vision loss; however, an association between the 2 may be appreciated.

Although the literature on factors predicting vision loss is sparse, there are studies that support our findings. Zhou et al[14] found that patients whose appointments were delayed during the COVID-19 pandemic had higher odds of worsened VA and increased edema than patients whose appointments were kept. Wubben et al[9] conducted a study of 13 eyes with PDR or NPDR, with or without DME, that had a median lapse in treatment of 12 months. Of the patients, 77% lost at least 3 lines of VA, despite treatment of visual complications that arose on follow-up. More information regarding the reversibility of the effects of a lapse in treatment would be gained by monitoring patients' responses after treatment is resumed. Studies by Yalamanchili et al[13] and Matsunaga et al[11] found that VA is overall reversible when treatment is resumed after lapse lengths of approximately 6 months and 11 months, respectively.

A longer time since diagnosis of DR was found to be protective and may be secondary to increased stability of the condition by the time a lapse in treatment occurs. It has since been well-established that early detection and treatment of DR can reduce the risk for severe vision loss.[15] In the context of a lapse in treatment, perhaps more time since diagnosis relates to earlier diagnosis and treatment and subsequent achievement of better control of DME

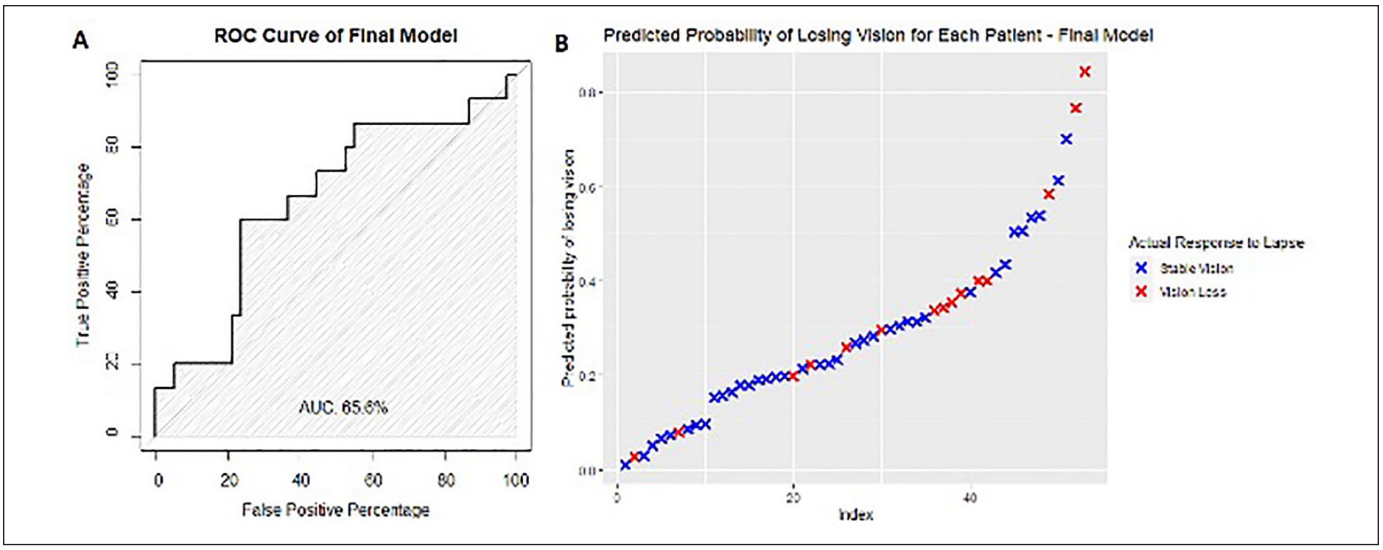

Figure 1. (A) Receiver operating characteristic curve of the final optimized model on testing data shows an area under the curve of 65.6%. (B) The plot of predicted probabilities of vision loss for each patient. In an ideal model, patients who lost vision after a lapse in treatment should have a predicted probability of >0.50.
Abbreviations: AUC, area under the curve; ROC, receiver operator characteristics curve.

before a lapse in treatment. The duration of disease itself may also be the reason behind stable vision, as reported in previous studies that found the treatment burden in clinical practice diminishes over time in patients with DME.[16,17] The baseline variability in time since DR diagnosis was likely related to the outcome of a significant increase in the risk for vision loss. Interestingly, we would have expected that patients with better glycemic control, reflected by HbA_{1c}, would have fewer or less severe microvascular complications.[18] However, we did not identify a correlation between HbA_{1c} and a change in BCVA in this study.

Diabetic foot disease as a predictor of vision loss in patients with DME may be explained by similar pathophysiology among the conditions. Both diabetic foot disease and DR are microvascular complications of diabetes, with the presence of diabetic foot disease likely indicating advanced disease. One would expect that diabetic nephropathy and neuropathy would also be significant predictors of vision loss; however, no such associations were found. Kovarik et al[19] found that 88.2% of admitted patients with diabetic foot ulcers or osteomyelitis had concurrent DR. In addition, renal disease was independently associated with DR, with an OR of 3.86 ($P < .05$). Similarly, Romero et al[20] compared the presence of overt nephropathy to the incidence of DME. Patients with a history of diabetic foot disease and lapse in treatment for DME may comprise an overlapping population with significant barriers to care.

Insurance type (specifically Medicaid) leading to worse visual outcomes after a lapse in treatment is a unique finding that may suggest involvement of a social determinant of health. A baseline comparison of insurance types among patients in the vision loss group and stable vision group was found to be significantly different; a greater proportion of patients in the vision loss group had Medicaid coverage. Studies of patients with Medicaid have previously found barriers associated with decreased adherence to DR examinations.[21] Nguyen et al[22] found that low-income patients and those on Medicaid had greater odds of vision-threatening forms of DR than high-income patients and those with private insurance. Similar findings from Malhotra et al[23] showed an association between patients living in lower income communities and receiving fewer anti-VEGF injections. Our findings corroborate those results within the context of a lapse in treatment. These patients are also more likely to have lapses in treatment and suffer worse consequences from those lapses.

When comparing predicted outcomes with actual outcomes, our model has greater accuracy at predicting which patients would experience stable vision compared with those who would develop vision loss, as evidenced by higher specificity and negative predictive value and low sensitivity and positive predictive value. However, the predictive ability using our current data is low, as shown by the low AUC of 65.6%. This may result from the selective exploration of variables that were not inclusive of all factors involved in the relationship between a lapse in treatment and vision loss. To accurately predict patients at high risk for vision loss after a lapse in treatment, further exploration of contributing factors is necessary.

Limitations of our case-control study include its retrospective nature of comprehensive chart review, meaning that factors such as laboratory values could not be drawn at the time of the lapse in treatment and instead had to be imputed or gathered from the nearest result date. The intraclass correlation coefficient between assessors in chart review was not calculated for this study. Patients' reasons for lack of follow-up were unknown, which limits our contextual understanding of lapses in treatment. In addition, other ocular comorbidities (eg, cataracts and glaucoma) were not accounted for, and these could have affected the VA after a lapse

in treatment. Patients with PDR may have developed complications, such as vitreous hemorrhage, neovascular glaucoma, or retinal detachment, which may or may not have been documented as a rationale behind patients' vision loss.

Evaluating previous treatments with focal laser and panretinal photocoagulation as well as other factors that may be associated with stable vision is an area for future study. The OCT machines used at our institution may have varied in the measurements of CST, cube volume, and cube average thickness, as has been shown with different OCT modalities.[24,25] Our study assessed vision loss over the period of the treatment lapse; however, we are unable to draw conclusions about longer term effects of a lapse in treatment for DME, especially after anti-VEGF therapy is resumed.

The results may also not be generalizable internationally because data regarding insurance types are specific to the US healthcare system. The focus of this study was lapses in treatment of DME with anti-VEGF injections specifically; however, future research may focus on how lapses in other treatment modalities, such as steroids and laser therapy, affect vision outcomes.[3,26]

In summary, our study identified predictors for vision loss after a treatment lapse of at least 3 months in patients with DME. An increased length of lapse in treatment, a history of diabetic foot disease, and Medicaid insurance put patients at greater risk for worse visual outcomes after a lapse in treatment. Patients with a greater duration since diagnosis before a lapse in treatment had better visual outcomes than their counterparts. Further exploration is needed to identify the longitudinal effect of treatment lapses among patients with DME.

From a clinical standpoint, these factors may identify patients who should receive earlier rescheduling efforts or more robust outreach before their scheduled appointments. Although collaborative, patient-centered care is always the objective, the findings in this study highlight the patients who experience worse VA or stable vision with a lapse in treatment. With anti-VEGF agents having different properties and with advances in extended treatment formulations, the careful identification of patients who may benefit from longer acting agents has promise in terms of improving adherence to DME treatment. Ophthalmologists should consider these predictors when creating a collaborative treatment and follow-up plan.

Ethical Approval

Ethical approval for this study was obtained from the Cleveland Clinic Institutional Review Board (#18-1488)

Statement of Informed Consent

Informed consent was not required for this retrospective study, which was determined to not affect patient treatment.

Declaration of Conflicting Interests

Dr. Singh reports personal fees from Alcon, Apellis, Asclepix, Bausch + Lomb, Genentech/Roche, Gyroscope, Novartis, and Regeneron. Dr. Talcott reports personal fees from Apellis, EyePoint, and Genentech/Roche and research fees from RegenxBio and Zeiss. None of the other authors declared potential conflicts of interest with respect to the research, authorship, and/or publication of the article.

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ORCID iDs

Meghana Chalasani https://orcid.org/0000-0002-0733-1051
Katherine E. Talcott https://orcid.org/0000-0003-0458-4181

Supplemental Material

Supplemental information is available online with this article.

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