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The Short-term Effect of a Single Lapse in Anti-Vascular Endothelial Growth Factor Treatment for Diabetic Macular Edema Within Routine Clinical Practice



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• **PURPOSE:** Diabetic macular edema (DME) is a leading cause of vision loss in diabetics. Anti-vascular endothelial growth factor (VEGF) therapy has been shown to be an effective treatment option for DME, although the injections are costly and require frequent visits, which increases the risk for unintended treatment lapses. The aim of this study is to characterize the effects of an unintended treatment lapse in patients with DME undergoing anti-VEGF therapy.

• **DESIGN:** Retrospective, comparative case series.

• **METHODS:** This retrospective chart review compared patients seen in a multicenter institutional practice with DME exhibiting an unintended minimum 3-month lapse in anti-VEGF treatment, with a control group of DME patients receiving regular anti-VEGF treatment without lapses. The primary outcome was difference in central subfield thickness (CST) between the control group and the treatment lapse group at 6 months following treatment lapse.

• **RESULTS:** A total of 164 patients were evaluated, 82 patients in the treatment lapse group and 82 patients in the control group. The average age was 65 years, and the average lapse in treatment was 6.2 ± 3.5 months (range 3-24 months). Comparison of data between the lapse and control groups revealed no significant differences in CST ($359.9 \pm 108.3 \mu\text{m}$ and $335.4 \pm 94.6 \mu\text{m}$, respectively, $P = .066$) or in visual acuity (66.5 ± 14.3 and 68.9 ± 14.5 , respectively, $P = .136$). Limitations included a relatively small sample size, retrospective nature, and only a single lapse being evaluated.

• **CONCLUSIONS:** An unintended, single, relatively short-term lapse in anti-VEGF treatment in patients with DME did not appear to result in significant anatomic

or visual compromise upon resumption of regular follow-up and treatment. (*Am J Ophthalmol* 2020;219:215–221. © 2020 Published by Elsevier Inc.)

DIABETIC RETINOPATHY (DR) IS A LEADING CAUSE of visual impairment in patients with diabetes, affecting 93 million people worldwide.¹ DR is a microvasculopathy that occurs as a long-standing complication of poorly controlled diabetes mellitus. Vascular endothelial growth factor (VEGF) as well as other angiogenic and proinflammatory factors are released as a result of inflammation and oxidative stress secondary to high glucose levels in diabetes mellitus. These factors result in increased permeability of retinal blood vessels, resulting in DR and diabetic macular edema (DME).

Therapeutic options for DME include laser and anti-VEGF injections.^{2–4} Previous randomized studies have shown an average interval of 1 to 2 months between anti-VEGF injections with a high frequency of injections in the first few years of treatment.^{5–7} The DRCR retina network conducted a randomized controlled trial in 660 patients with DME treated with anti-VEGF agents on an as-needed basis.⁸ The study showed that all 3 anti-VEGF agents (bevacizumab, ranibizumab, and aflibercept) led to improved VA and anatomic improvement over 2 years, with 11–20 injections received within the first 2 years of treatment. These regular visits can become burdensome for patients, contributing to compliance challenges. It has been shown in previous studies that patients who do not receive treatment for 6 months or more may experience poorer long-term outcomes, including worsening visual acuity (VA) and increased central macular thickness.^{1,9}

Noncompliance with appointments for DME is common. A retrospective study published in 2017 identified that 46% of patients with DME experienced treatment lapses greater than 100 days.¹⁰ Another study following patients treated for DME with anti-VEGF injections in routine clinical practice demonstrated a loss to follow-up (defined as 12 months without follow-up office visits after an intravitreal injection) rate of 25.3%.¹¹ In particular among racial groups, Hispanic patients were the most likely to be lost to follow-up, and patients with an annual gross

Accepted for publication Jun 30, 2020.

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income less than \$50,000 were more likely to be lost to follow up than those with higher income levels.¹¹

Although it has been shown that lapses in regular anti-VEGF treatment can produce poor visual outcomes,¹⁰ few studies have examined the anatomic changes that occur as a result of this loss to follow-up and the reversibility of these changes on resumption of regular treatment. The objective of this study was to analyze the anatomic and VA changes seen in DME patients who experience at least a 3-month unintended lapse in treatment with anti-VEGF, as well as to characterize changes that occur following reinitiation of anti-VEGF treatment and subsequent follow-up.

METHODS

THIS RETROSPECTIVE STUDY WAS PERFORMED AT COLE EYE Institute, Cleveland, Ohio, after receiving approval from the Cleveland Clinic Investigational Review Board. Because of the retrospective nature of the study, written informed consent was not required. ICD-9 and ICD-10 codes for the diagnoses of DME, DR, and retinal edema were used to filter potential patients for the study. The study included men and women at least 18 years of age, foveal-involving retinal edema secondary to DME based on investigator review of clinical examination and spectral-domain optical coherence tomography (OCT), with initiation of anti-VEGF treatment for DME, and unintended treatment lapse for at least 3 months. Patients who experienced a lapse of 3 months or greater per provider recommendation, such as those being treated with treat and extend or pro-re-nata protocols, were excluded from the study cohort. Only 1 eye was included per eligible patient, and the first eye diagnosed with DME as noted in the patient chart was included in cases of bilateral unintended treatment lapse. For patients who exhibited multiple lapses in treatment in the study eye, the first lapse was used. Patients who had other retinal diseases or any cause of macular edema not related to diabetes, including pathologic myopia (spherical equivalent of -8 diopters or more negative, or axial length of 25 mm or more), ocular histoplasmosis syndrome, choroidal neovascularization, age-related macular degeneration or multifocal choroiditis in the study eye were excluded.

A comprehensive chart review was performed to assess ophthalmic data in eligible patients who experienced a treatment lapse of at least 3 months (lapse group) and patients without a treatment lapse (control group). The variables collected for both groups included baseline demographics (age, sex, race), duration of diabetes, diagnosis date of DME, and glycated hemoglobin (HbA_{1c}) within 3 months of last appointment before treatment lapse. For the lapse group, the following additional variables were collected: OCT values (central subfield thickness [CST], cube volume [CV], and cube average thickness [CAT]), anti-VEGF injection, and VA at last appointment before treatment lapse

(baseline), first appointment after treatment lapse (post-lapse), and 3, 6, and 12 months after treatment lapse. For the control group, we collected the following additional variables: OCT values, anti-VEGF injection, and VA for 7 appointments during treatment period (baseline, 3 months, 6 months, 12 months, 15 months, 18 months, and 24 months). Baseline VA and the time period between first injection and baseline appointment was controlled between the lapse group and control group.

To accurately compare the patients from the lapse and control groups, patients in the lapse and control groups were individually matched (greedy matching) based on time between first injection and baseline (maximum difference of 3.5 months) and baseline VA (maximum difference of 15 Early Treatment Diabetic Retinopathy Study [ETDRS] letters). Intervals between appointments in the lapse group were used to choose corresponding appointments in the control group. Patients with lapses longer than 24 months, and more than 13 months between first injection and lapse were removed, to ensure adequate matching to a corresponding control patient. Twelve-month post-lapse appointments were removed from analysis because of insufficient data. The resulting matched data set consisted of 82 control patients and 82 lapse patients.

The primary endpoint was the effect of an unintended treatment lapse on CST at 6 months following lapse in comparison to those patients without lapse of anti-VEGF treatment in DME. Secondary endpoints included average length of period without treatment, changes in CV and CAT, and changes in VA at post-lapse, 3 months, and 6 months after lapse.

• **STATISTICAL ANALYSIS:** Continuous variables were summarized with mean (standard deviation), and categorical variables were summarized with frequency (%). Differences between groups were analyzed at each appointment, using paired *t*-tests for the continuous variables, and McNemar test and Bowker test for the categorical variables. The analysis was then expanded to include a mixed effect model regression to examine VA, CST, CAT, and CV after the lapse period. The mixed model regression analysis was done in SAS (v9.04, SAS Institute Inc, Cary, North Carolina, USA). Predicting variables included in the regression analysis were the following: age, sex, race, HbA_{1c}, duration of diabetes mellitus, duration of DME, and appointment and lapse group interaction. Stratification by significant CST change (defined as a 20- μ m difference) was done to further assess CST changes over the lapse time period among the lapse and control patients.

RESULTS

A TOTAL OF 164 EYES WERE EVALUATED IN THE STUDY, WITH 82 eyes in the lapse group and 82 eyes in the control group.

TABLE 1. Baseline (Last Appointment Before Lapse) Analysis

Factor	Overall (N=164)			Control Group (n=82)	Lapse Group (n=82)	P Value
	n	Statistics				
Age	164	64.7 ± 10.4		65.5 ± 9.8	63.8 ± 11.1	.294 ^a
HbA _{1c} (%)	118	7.6 ± 1.8		7.3 ± 1.2	7.9 ± 2.1	.047^a
Diabetes duration (y)	161	13.5 ± 9.1		12.2 ± 9.1	14.8 ± 9.0	.074 ^a
DME duration (y)	163	1.00 ± 0.87		0.94 ± 0.60	1.07 ± 1.07	.310 ^a
ETDRS (letters)	164	70.9 ± 11.5		71.2 ± 11.6	70.6 ± 11.4	.136 ^a
CST (μm)	153	337.9 ± 94.9		347.6 ± 95.5	327.3 ± 93.8	.268 ^a
CV (mm ³)	153	11.2 ± 1.5		11.2 ± 1.5	11.1 ± 1.6	.904 ^a
CAT (μm)	153	310.3 ± 41.6		311.1 ± 40.0	309.5 ± 43.4	.946 ^a
Race, n (%)	164					.001^b
White		115 (70.1)		69 (84.1)	46 (56.1)	
Black		40 (24.4)		12 (14.6)	28 (34.1)	
Other		9 (5.5)		1 (1.2)	8 (9.8)	
Anti-VEGF injections prior to baseline	163	5.4 ± 3.0		5.7 ± 3.0	5.0 ± 3.0	.177 ^a
Anti-VEGF drug, n (%)	164					.597 ^b
Bevacizumab		119 (72.6)		58 (70.7)	61 (74.4)	
Aflibercept		22 (13.4)		7 (8.5)	15 (18.3)	
Ranibizumab		17 (10.4)		12 (14.6)	5 (6.1)	
None		4 (2.4)		3 (0.0)	1 (0.0)	
Other ^c		2 (1.2)		2 (2.4)	0 (0.0)	

CAT = cube average thickness; CST = central subfield thickness; CV = cube volume; DME = diabetic macular edema; ETDRS = Early Treatment Diabetic Retinopathy Study; HbA_{1c} = glycated hemoglobin; VEGF = vascular endothelial growth factor.

Subset of population used: Appointment = "First." Unless otherwise noted, values are mean ± SD.

Bold represents statistically significant values.

^aPaired *t* test.

^bMcNemar test.

^cOther indicates that the patient received a corticosteroid injection at the given appointment rather than anti-VEGF.

The 12-month post-lapse data were removed from analysis because of insufficient data among the patient groups. Seventy-seven percent of the patients (127 patients) had complete follow-up data (until 6 months post-lapse) for VA and CST after the treatment lapse. Baseline demographics are shown in Table 1.

The average treatment lapse was 6.2 ± 3.5 months (range 3-24 months). Mean ages in the control and lapse groups were 65.5 ± 9.8 and 63.8 ± 11.1 years, respectively (*P* = .294). Baseline CST was 347.6 ± 95.5 μm in the control group and 327.3 ± 93.8 μm in the lapse group (*P* = .268) (Figure 1). Baseline VA in the control group was 71.2 ± 11.6 (Snellen 20/40) and 70.6 ± 11.4 (Snellen 20/40) in the lapse group (*P* = .136) (Figure 2). There were 22 patients in the lapse group and 28 patients in the control group who had an ETDRS of 80 or higher (Snellen 20/25 or better). The lapse group had a significantly higher baseline HbA_{1c} (7.9% ± 2.1) compared with the control group (7.3% ± 1.2%) (*P* < .05). African Americans were found to comprise a larger proportion in the lapse group (28 [34.1%]) compared with the control group (12 [14.6%]) (*P* < .05). The types of baseline anti-VEGF injections were similar between both groups (*P* = .373), with the majority of patients across the entire cohort receiving bevacizumab (72.6%). The lapse group

received a similar amount of anti-VEGF injections in the time they were treated prior to their baseline appointment (5.0 ± 3.0) compared with the control group (5.7 ± 3.0) (*P* = .177), with an overall average of 5.4 ± 3.0 injections received prior to baseline. Examination of the most common reasons for treatment lapses revealed that patients experienced lapses in treatment due to hospitalization or illness of the patient or family (6% of lapse patients), refusal of or missed care (4%), financial or accessibility issues (6%), prolonged travel period without treatment (4%), or unspecified reasons (80%).

Comparison of data between lapse and control groups at the post-lapse appointment (Table 2) yielded no significant differences in CST (359.9 ± 108.3 μm and 335.4 ± 94.6 μm, respectively, *P* = .066) or in VA (66.5 ± 14.3 and 68.9 ± 14.5, respectively, *P* = .136) (Figures 1 and 2). CV and CAT were statistically higher in the lapse group (11.6 ± 2.0 mm³ and 321.6 ± 53.1 μm, respectively) compared with the control group (11.0 ± 1.4 mm³ and 307.0 ± 39.6 μm, respectively) (*P* < .05). Stratification by significant CST change (defined as a 20-μm difference) yielded significant differences. A significantly higher amount of lapse patients experienced >20-μm increases in CST after lapse (36; 50.7%)

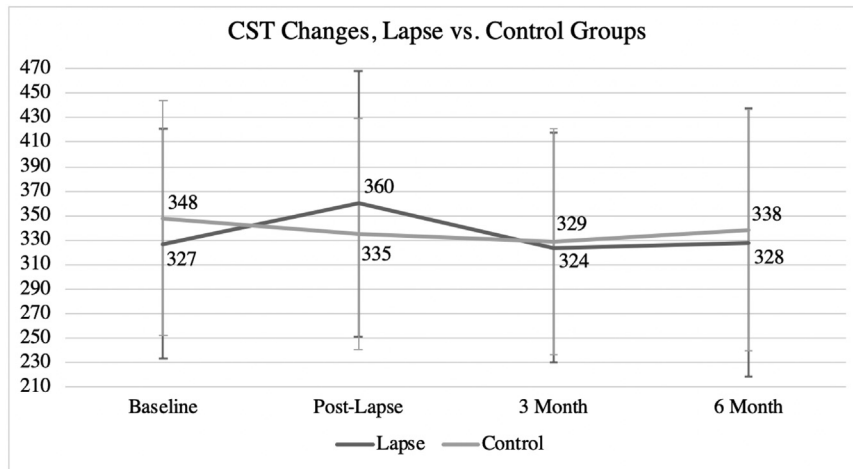


FIGURE 1. Analysis of average central subfield thickness (CST) in lapse and control groups across study period. $P > .05$ between groups at all time points.

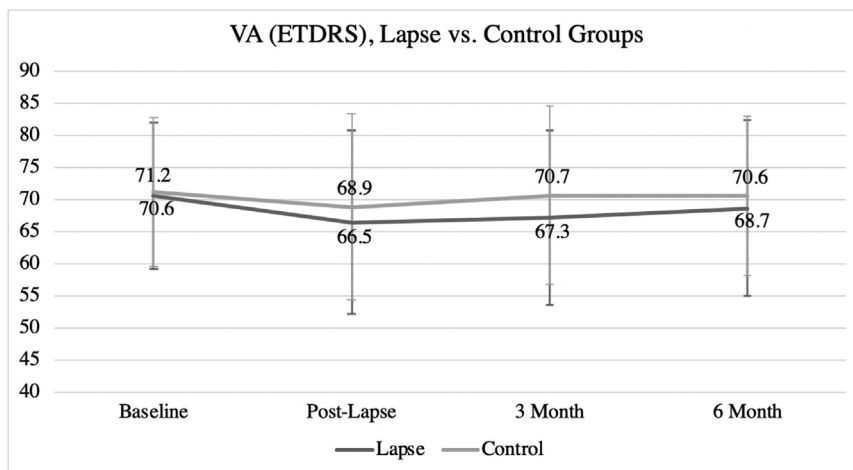


FIGURE 2. Analysis of average visual acuity (VA) in lapse and control groups across study period. $P > .05$ at all time points.

compared with the control patients (19; 24.4%) ($P < .05$). The number and type of anti-VEGF injections remained similar between both groups ($P = .99$).

At 3 and 6 months after lapse, no significant differences were found between the lapse and control groups. The number and type of anti-VEGF injection remained similar between both groups ($P = .99$).

Mixed model regression analysis results examined each variable individually without influence of confounding variables. The 6-month post-lapse time point was used as the reference point to which the other time points were compared. Model results for CST show that the lapse group exhibits a $39.46\text{-}\mu\text{m}$ increase in CST post-lapse compared with the control group ($P < .05$). However, there is no significant difference in CST at 3 months in the lapse vs con-

trol groups ($P = .720$) compared with 6 months after lapse. The model results also show that for each micrometer higher baseline CST in both lapse and control patients, there will be a $0.55\ \mu\text{m}$ higher CST ($P < .05$) at any appointment after baseline (post-lapse, 3 months, or 6 months). Thus, patients with more severe DME are likely to experience worse consequences over time regardless of lapses in treatment. Model results for CAT and CV show that the lapse group exhibits a $14.05\text{-}\mu\text{m}$ increase in CAT and 0.52-mm^3 increase in CV post-lapse compared with the control group ($P < .05$). However, there is no significant difference in CAT and CV at 3 months in the lapse vs control groups. Model results for VA showed no significant differences between lapse and control groups post-lapse or at 3 months ($P = .635$, $P = .838$).

TABLE 2. Post-lapse Analysis

Factor	Overall (N = 164)				P Value
	n	Statistics	Control Group (n = 82)	Lapse Group (n = 82)	
ETDRS	164	67.7 ± 14.4	68.9 ± 14.5	66.5 ± 14.3	.136 ^a
CST (µm)	158	347.5 ± 102.0	335.4 ± 94.6	359.9 ± 108.3	.066 ^a
CV (mm ³)	158	11.3 ± 1.7	11.0 ± 1.4	11.6 ± 2.0	.029^a
CAT (µm)	158	314.2 ± 47.2	307.0 ± 39.6	321.6 ± 53.1	.034^a
Anti-VEGF drug, n (%)	164				.99 ^b
Bevacizumab		56 (34.1)	28 (34.1)	28 (34.1)	
Aflibercept		22 (13.4)	11 (13.4)	11 (13.4)	
Ranibizumab		18 (11.0)	9 (11.0)	9 (11.0)	
No injection		64 (39.0)	32 (39.0)	32 (39.0)	
Other ^c		4 (2.4)	2 (2.4)	2 (2.4)	
Lapse length, n (%)	164				—
<6 mo		135 (82.3)	—	53 (64.6)	
>6 mo		29 (17.7)	—	29 (35.4)	
CST change baseline to postlapse, n (%)	149				< .001^b
≤20		94 (63.1)	59 (75.6)	35 (49.3)	
>20		55 (36.9)	19 (24.4)	36 (50.7)	

CAT = cube average thickness; CST = central subfield thickness; CV = cube volume; ETDRS = Early Treatment Diabetic Retinopathy Study; VEGF = vascular endothelial growth factor.

Subset of population used: Appointment = “First.” Unless otherwise noted, values are mean ± SD.

Bold represents statistically significant values.

^aPaired *t* test.

^bMcNemar test.

^cOther indicates that the patient received a corticosteroid injection at the given appointment rather than anti-VEGF.

DISCUSSION

THE GOAL OF THIS STUDY WAS TO EVALUATE THE EFFECT OF unintended treatment lapses in patients receiving anti-VEGF injections for DME. There were no differences in CST or VA at any of the time points between the lapse and control groups, whereas CV and CAT significantly increased after lapse compared with the control group ($P < .05$). Mixed model regression analyses showed that 3- to 24-month treatment lapses result in increased CST. However, following a single anti-VEGF injection, this significance was no longer present. Treatment lapses did not adversely affect VA in this study at any timepoint or in the mixed model regression analysis. These findings indicate that treatment lapses of at least 3 months may result in reversible macular thickening following reinitiation of consistent anti-VEGF therapy for 6 months after lapse. Because there was insufficient 12-month data to include in the analysis, the long-term effect of treatment lapses beyond the 6-month post-lapse period is unknown.

Of note, there was a discernable trend upward in the CST in the lapse group from baseline to post-lapse compared with the control group. Similarly, there was a trend downward in VA in both the control and lapse groups from baseline to post-lapse. It can be postulated that the sample size of 82 eyes in each group ($n = 164$ total) may

have been slightly underpowered to find a significant difference in these trends between the lapse and control groups at the post-lapse visit.

The body of literature examining the effects of injection lapses in DME patients is exceedingly sparse. Weiss and associates found that VA decreased with multiple treatment lapses and that 60% of patients with DME who had a lapse experienced a decrease in VA.¹⁰ The sample size included only 63 patients who experienced lapses, but it was found that those with 1 treatment lapse on average showed no difference in VA during the study whereas those with more than 2 treatment lapses showed an average loss of 10 ETDRS letters.

In this study, 22 patients in the lapse group and 28 patients in the control group had a baseline ETDRS of 80 or higher. A previous study was conducted by Baker and associates of 702 patients with VA of 20/25 or better (ETDRS of 80 or higher), divided into 3 groups that received aflibercept every 4 weeks as needed, focal/grid laser, or observation. Aflibercept was given as a “rescue” treatment for patients in the laser or observation groups who experienced a decrease of at least 10 ETDRS letters at any visit or 5-9 ETDRS letters at 2 consecutive visits. At the 2-year point, Baker and associates found that 75% of patients in the laser group and approximately 66% of patients in the observation group did not need the aflibercept rescue treatment.¹²

In the context of these results, it is important to consider that patients with ETDRS scores of 80 or better may not be expected to experience significant negative consequences as a result of lapses in treatment.

The multicenter RISE and RIDE clinical trials enrolled 759 patients with center-involving DME and evaluated the efficacy of intravitreal ranibizumab with 24-month sham-controlled injection outcomes.¹³ Significant improvements in VA and reduction in CST were seen in the ranibizumab-treated group and maintained until the end of the 24-month period. A secondary analysis was conducted after the 24-month period in which the sham group received monthly ranibizumab injections for the next year. At month 36, there was no significant difference in OCT thickness among the sham/ranibizumab group and the ranibizumab group. At month 36 in RIDE, 36% to 40% of patients in the ranibizumab group gained at least 15 ETDRS letters from baseline, in contrast to 19% of patients in the sham/ranibizumab group. In RISE, 41% to 51% of patients in the ranibizumab group gained at least 15 ETDRS letters from baseline, in contrast to 22% of patients in the sham/ranibizumab group at month 36. When analyzing our study in the context of the secondary analysis of the RISE and RIDE trials, it is important to consider whether our patients remained stable because of a protective effect from receiving initial treatment with intravitreal anti-VEGF. In both RISE and RIDE, the group treated with ranibizumab continuously over the 3-year period exhibited improved VA compared with the group that had not started on ranibizumab until the third year. This suggests that timing for initiation of therapy is critical to visual gain in patients with DME. Although the average length of lapse in this study was approximately 6 months, with a 6-month follow-up after lapse, the RISE and RIDE trials examined patients over a much longer time period. This study found that VA or CST is not significantly affected by a short, unintended lapse in treatment. However, interpreting these results within the context of the longer-term RISE and RIDE trials, it is plausible that short treatment lapses in patients who have been previously treated with anti-VEGF for 13 months or less may not be detrimental, whereas longer lapses in treatment after DME becomes more advanced may lead to worsening consequences.

On evaluating demographic characteristics, we found a significantly higher proportion of African Americans in our lapse group (34.1%) compared with our control group (14.6%) ($P < .05$), suggesting a possible predisposing demographic risk factor for lapses in treatment. A retrospective study of 2,302 patients with proliferative DR conducted by Obeid and associates revealed that among the 584 patients who experienced treatment lapses, there were higher proportions of patients aged 55 years and younger (28.1%); average adjusted gross incomes of \$44,000 or less (33.9%); African Americans (30.2%); and Hispanics, Native Americans, and Pacific Islanders (38.0%).¹⁴ Additional studies examining demographic factors, including socioeconomic

status, distance to clinic, and age may further delineate the populations most at risk for treatment lapses.

Although the vast majority of patients did not have a documented cause for lapse noted in the chart, those who were documented most commonly cited illness or hospitalization of the patient or a family member, financial difficulties, or accessibility issues as the cause. Further studies aimed at examining these underlying causes may help design approaches to decrease unintended treatment lapses in patients receiving regular anti-VEGF injections.

This study is limited by a relatively small sample size and retrospective nature, and only a single lapse was evaluated to determine anatomic and visual impact. The greedy matching process used to compare individual lapse patients with control patients may have introduced selection bias as the cohorts were narrowed. The sparse 12 months post-lapse data also limited the ability to examine more longitudinal effects of lapses in treatment. Additionally, other nonretinal ophthalmic comorbidities were not accounted for, including cataracts or glaucoma, which may have affected the patient's vision at some point during the course of the study. The type of diabetes (type 1 vs type 2) and its effect on treatment lapse could not be assessed in the context of this study because of a substantially higher proportion of type 2 patients in this cohort. The lack of patients with type 1 diabetes did not allow for appropriately powered statistical analysis. As a result, this is a hypothesis that would be better suited for a study with larger sample sizes, dedicated to investigating this research question. Another potential limitation is that patients with nephropathy may have experienced worsening of their DME because of the correlation of diabetic nephropathy with development of DME.¹⁵ It is hypothesized that the discrepancy between the raw data and mixed model regression analyses was due to confounding variables, such as gender, race, or HbA_{1c}. Certain races, gender, or varying HbA_{1c} values may have an independent effect on DME course with regards to VA and CST, which may have led to the insignificant changes seen in the raw data analysis and significant differences in the mixed model regression analysis.

In conclusion, a single, unintended, relatively short treatment lapse in anti-VEGF treatment in DME did not have significant anatomic or visual consequences on resumption of regular follow-up and treatment. In light of the current coronavirus pandemic (COVID-19), many patients are experiencing delays and lapses in treatment of their DME. This study is of particular relevance during this time, as the findings suggest that short treatment lapses of anti-VEGF therapy may not lead to significant or permanent anatomic or visual deterioration. The long-term consequences beyond 6 months of a lapse in treatment are unknown. Larger studies examining treatment lapses may be helpful to more clearly distinguish the short- and long-term consequences of treatment lapses. In addition, larger cohorts may help to delineate the predictors for lapse and create methods to improve overall compliance in this medically burdened patient population.

FUNDING/SUPPORT: NONE. FINANCIAL DISCLOSURES: AMY S. BABIUCH REPORTS GRANTS FROM REGENERON AND PERSONAL fees from vindico and MCME Global. Rishi P. Singh reports grants from Apellis and Graybug, and personal fees from Genentech/Roche, Alcon/Novartis, Zeiss, Bausch & Lomb, Ophthea, and Regeneron Pharmaceuticals, Inc. All other authors indicate no financial support or conflicts of interest. All authors attest that they meet the current ICMJE criteria for authorship.

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