Anti–Vascular Endothelial Growth Factor Therapy for Diabetic Retinopathy: Consequences of Inadvertent Treatment Interruptions

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• PURPOSE: To illustrate that patients with diabetic retinopathy who are treated exclusively with anti–vascular endothelial growth factor (VEGF) therapy and have an interruption in treatment may experience marked progression of disease with potentially devastating visual consequences.

• DESIGN: Retrospective, multicenter, case series.

• METHODS: Retrospective review of patients treated exclusively with anti-VEGF therapy for proliferative diabetic retinopathy (PDR) or nonproliferative diabetic retinopathy (NPDR), with or without diabetic macular edema (DME), and temporarily lost to follow-up. Baseline disease characteristics, cause and duration of the treatment interruption, and resulting disease progression, complications, and outcomes were assessed.

• RESULTS: Thirteen eyes of 12 patients with type 2 diabetes were identified. The mean age was 57 ± 10 years, and 50% were women. Anti-VEGF therapy was indicated for PDR with DME in 7 (54%) eyes, PDR without DME in 3 (23%) eyes, and moderate to severe NPDR with DME in 3 (23%) eyes. Eight eyes had visual acuity (VA) of 20/80 or better before treatment interruption. The median duration of treatment hiatus was 12 months. Reasons for treatment interruption included intercurrent illness (31%), noncompliance (31%), and financial issues (15%). Complications upon follow-up included vitreous hemorrhage (9 eyes), neovascular glaucoma (5 eyes), and traction retinal detachment (4 eyes). Despite treatment of these complications, 77% of eyes lost ≥3 lines of VA, with 46% of eyes having a final VA of hand motion or worse.

• CONCLUSIONS: Diabetic patients are subject to significant lapses in follow-up because of illness, financial hardship, or noncompliance. In patients with diabetic retinopathy, especially PDR, who are managed with anti-VEGF therapy alone, unintentional treatment interruptions can result in irreversible blindness. (Am J Ophthalmol 2019;204:13–18. © 2019 Elsevier Inc. All rights reserved.)

PROLIFERATIVE DIABETIC RETINOPATHY (PDR) IS TYPICALLY a progressive disease, and affected eyes may develop visually devastating consequences, such as traction retinal detachment (TRD) and neovascular glaucoma (NVG), unless permanent regression is achieved or temporary regression is renewed and maintained with ongoing treatment.[1–3] Panretinal photocoagulation (PRP) has been the standard treatment to achieve this regression since the Diabetic Retinopathy Study in the 1970s, and this intervention has proven to be highly durable.[1]

Long-term follow-up studies and decades of clinical experience have shown that once achieved, PRP-induced PDR regression typically lasts indefinitely. For example, Vander and associates[4] showed that visual outcome did not vary with length of follow-up after PRP-induced PDR regression. Similarly, several reports have shown that PRP provides good anatomic and visual outcomes for ≥10 years.[5–7] Blankenship[8] reported that PRP resulted in stable PDR regression for ≥15 years, with only 4% of patients requiring additional laser treatment. Notably, once PDR is stabilized with complete PRP, late complications are typically related to the tractional effects of vitreoretinal separation, which may produce vitreous hemorrhage rather than the progressive growth of neovascular tissue.[4,8]

There has been increased interest in using intravitreal anti–vascular endothelial growth factor (VEGF) therapy in the treatment of PDR since it was shown to be noninferior to PRP.[3,9] Moreover, studies have shown that anti-VEGF therapy may also prevent diabetic retinopathy (DR) progression and even lead to improvement in retinopathy severity scores.[10,11] However, these clinical outcomes were obtained in the tightly controlled setting of randomized clinical trials, and the durability of the observed improvements in DR severity with anti-VEGF therapy alone remains uncertain.

Unfortunately, in the real-world setting, diabetic patients underuse eye care services and are prone to

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significant losses to follow-up.[12,13] The purpose of this report is to show that patients with DR who are treated exclusively with anti-VEGF therapy and have an interruption in treatment may experience marked progression of disease with potentially devastating and irreversible visual consequences. Only 1 other study to date has examined outcomes in such eyes after a prolonged treatment hiatus.[14]

METHODS

THIS IS A RETROSPECTIVE, MULTICENTER, CASE SERIES OF patients treated exclusively with anti-VEGF therapy for PDR or nonproliferative diabetic retinopathy (NPDR), with or without diabetic macular edema (DME), and who were temporarily lost to follow-up. Patients were identified between April 10, 2017 and April 10, 2018 by recollection of the investigators. The institutional review board of the University of Michigan Medical School, Ann Arbor, Michigan waived oversight because the study involved only coded private information that could not be linked to a specific individual by the investigators. All procedures conformed to the tenets set forth by the Declaration of Helsinki and all federal and state laws. Baseline disease characteristics, cause and duration of the treatment hiatus, and resulting disease progression, complications, and outcomes were assessed.

High-risk PDR was defined as previously described by the Diabetic Retinopathy Study Research Group.[1] Non–high-risk PDR was any proliferative disease that did not meet the high-risk characteristics. Advanced PDR was defined as any amount of tractional retinal detachment. Beyond these definitions, the method by which DR was categorized (fundus photos, fundus examination, fluorescein angiography, or a combination of these) for each respective eye was at the discretion of the individual investigator who contributed the case.

Data were analyzed with GraphPad Prism (GraphPad Software, La Jolla, CA, USA), and unpaired *t* tests were used to compare mean values. For the purpose of statistical analyses, logarithm of minimal angle of resolution (logMAR) visual acuities (VAs) were used, and count fingers (CF), hand motion (HM), light perception (LP), and no light perception (NLP) VAs were assigned the following values based on a previously used scale: 2.00, 2.30, 2.60, and 2.90, respectively.[15]

RESULTS

INVESTIGATORS AT 6 CENTERS IDENTIFIED 12 PATIENTS (13 eyes) that were treated solely with anti-VEGF therapy for DR and were subsequently lost to follow-up for a period of time. The average age of these patients was 56.6 ± 10.4 years and half were women (Table 1). All of the patients had type II diabetes mellitus, with a median disease duration of 19 years and a mean hemoglobin A1c of 9.5% ± 2.5%. Ten of the 13 eyes (77%) in this series were treated exclusively with anti-VEGF therapy for some degree of PDR with or without DME, while the remaining eyes were treated for DME complicating moderate to severe NPDR (Table 1). Before treatment interruption, the patients in this cohort had been treated for an average of 16.8 ± 21.7 months with a mean of 7.1 ± 6.4 injections (Table 1). Ten of the 13 eyes (77%) were receiving bevacizumab. The mean VA before the treatment hiatus was 0.61 ± 0.41 (logMAR; Table 2), and most eyes (8/13, 62%) had a Snellen VA of ≥20/80.

The most common reasons for treatment interruption included intercurrent illness (31%), noncompliance

TABLE 1. Demographic and Clinical Features of Patients Treated Exclusively with Anti–Vascular Endothelial Growth Factor Therapy

Feature	Number
Age (y),[a] mean ± SD (range)	56.6 ± 10.4 (30-71)
Sex, n (%)	
Male	6 (50)
Female	6 (50)
Race, n (%)	
Caucasian	5 (42)
Black	3 (25)
Hispanic	4 (33)
Diabetes type, n (%)	
Type 2	12 (100)
Diabetes duration (y), mean ± SD (median)	18.6 ± 3.3 (19)
Hemoglobin A1c,[a] mean ± SD	9.5 ± 2.5
Diabetic Retinopathy Severity,[b] n (%)	
Moderate NPDR	2 (15)
Severe NPDR	1 (8)
Non–high-risk PDR	6 (46)
High-risk PDR	3 (23)
Advanced PDR	1 (8)
Indication for anti-VEGF therapy, n (%)	
NPDR plus DME	3 (23)
PDR plus DME	7 (54)
PDR	3 (23)
Injections before treatment hiatus, mean ± SD (range)	7.1 ± 6.4 (1-20)
Anti-VEGF therapy, n (%)	
Bevacizumab	10 (77)
Aflibercept	2 (15)
Ranibizumab	1 (8)
Treatment length before hiatus, months, mean ± SD (range)	16.8 ± 21.7 (1-62)

DME = diabetic macular edema; NPDR = nonproliferative diabetic retinopathy; PDR = proliferative diabetic retinopathy; SD = standard deviation; VEGF = vascular endothelial growth factor.
[a]At treatment onset.
[b]Thirteen eyes of 12 patients.

TABLE 2. Treatment Hiatus and Resulting Complications in Patients Treated Exclusively with Anti–Vascular Endothelial Growth Factor Therapy

Feature	Number
VA before hiatus (logMAR),[a] mean ± SD	0.61 ± 0.41
Reason for treatment interruption, n (%)	
Intercurrent illness	4 (31)
Noncompliance	4 (31)
Financial issues	2 (15)
Other	3 (23)
Lost to follow-up length (months), mean ± SD (median)	13.3 ± 8.5 (12)
Complication on return visit, n (%)	
Vitreous hemorrhage	9 (69)
Neovascular glaucoma	5 (38)
Tractional retinal detachment	4 (31)
VA at final visit (logMAR), mean ± SD	1.53 ± 1.02

LogMAR = logarithm of minimal angle of resolution; SD = standard deviation; VA = visual acuity.
[a]At last examination before hiatus.

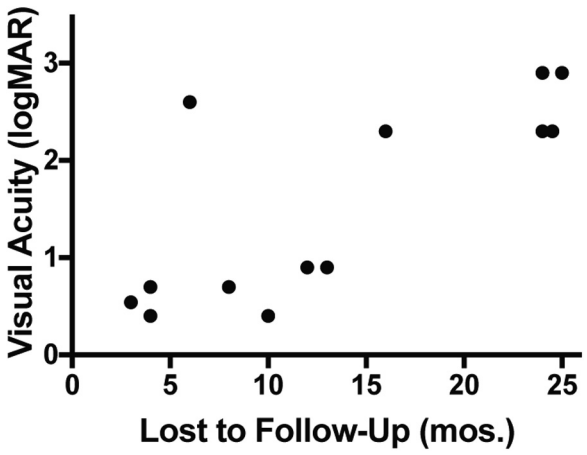

FIGURE. Visual acuity at last visit versus lost to follow-up time. Visual acuity at last visit worsened with increasing lost to follow-up time ($P = .002$).

(31%), and financial issues (15%), and the median length of the hiatus was 12 months (range 3-25 months; Table 2). Upon re-evaluation after the treatment lapse, 9 of 13 eyes (69%) had new vitreous hemorrhage, 5 eyes (38%) had developed NVG, and 4 eyes (31%) had new TRD (Table 2). Four of 5 eyes that developed NVG were lost to follow-up for ≥2 years, and all the eyes that presented with TRD underwent vitrectomy. Despite treatment of these complications, 10 eyes (77%) lost ≥3 lines of VA, with 46% of eyes having a final VA of HM or worse (including 2 eyes with NLP). The mean VA at the final visit (Snellen 20/678) was significantly worse than that before treatment interruption (Snellen 20/80; 1.53 ± 1.02 vs. 0.61 ± 0.41; logMAR; $P = .013$). In addition, VA at last visit worsened with increasing length of treatment interruption ($P = .002$; Figure). There was no statistically significant difference in mean VA at the final visit between eyes that received <3 injections (n = 5) and those that received ≥3 injections (n = 8) before treatment hiatus (1.16 ± 1.00 vs. 1.76 ± 1.02; logMAR; $P = .65$), despite a similar lost to follow-up length (median 12 months for both groups). All 3 eyes that were being treated with anti-VEGF therapy for NPDR with DME had a VA of ≥20/40 before treatment interruption, and all had VA of HM or worse at the final visit because of NVG (2 eyes) or vitreous hemorrhage (1 eye).

DISCUSSION

THIS CASE SERIES SHOWS THE POTENTIALLY DEVASTATING visual consequences that may occur in a real-world setting when patients with DR are treated exclusively with anti-VEGF therapy and have an unanticipated interruption in treatment. Anti-VEGF therapy has proven to be noninferior to PRP in the treatment of PDR and has shown potential benefit for preventing DR progression or even causing its regression in the tightly controlled setting of a clinical trial where patients follow-up regularly.[3,9–11,16] However, in the real-world setting, diabetic patients underuse eye care services and are prone to significant losses to follow-up.[12,13] While the care team should play an active role in the treatment compliance of patients with diabetes mellitus, unanticipated events—such as intercurrent illness, which was observed in >30% of patients in this series—can affect even the most informed and reliable of patients. This issue is highlighted by the fact that >60% of patients originally enrolled in the Early Treatment Diabetic Retinopathy Study were deceased on long-term follow-up, with the majority of deaths resulting from comorbidities of diabetes.[7] Similarly, approximately 10 million diabetics are evaluated in the emergency department annually and nearly 6 million are hospitalized.[17] Coupled with these health issues is the concern for noncompliance, which was observed in >30% of patients in our cohort. The difficulty of this problem is further illustrated by the fact that despite considerable effort on the part of investigators and study personnel, only 67% of participants (excluding deceased patients) were retained through 5 years in the Diabetic Retinopathy Clinical Research Network Protocol S trial.[9] Therefore, the severe disease progression and visual loss seen in this cohort after anti-VEGF therapy treatment interruption, coupled with the results of a recent study showing significantly worse outcomes in eyes that were receiving anti-VEGF therapy compared with PRP before being lost to follow-up, should serve as a significant caveat for clinicians who are making initial treatment decisions.[14]

To our knowledge, only 1 other study has examined the outcomes of eyes with PDR that were treated exclusively with anti-VEGF therapy and subsequently lost to follow-up for an extended period of time.[14] As in our case series, Obeid and associates[14] showed that mean VA at the final visit was significantly worse than that before treatment interruption in eyes treated solely with anti-VEGF therapy, but not in eyes treated with PRP. Furthermore, Obeid and associates[14] observed significantly greater numbers of eyes with TRD and NVG or iris neovascularization in the anti-VEGF as compared with the PRP group after treatment interruption. Notably, no eyes in the PRP group developed NVG or iris neovascularization.[14] In our cohort, 31% of eyes developed TRD necessitating vitrectomy and 38% of eyes had NVG upon return after treatment hiatus. Despite treatment, all eyes with NVG had VA of HMs or worse at the final visit. Our findings and those of Obeid and associates,[14] combined with the Protocol S trial findings that the mean number of ranibizumab injections remained constant from years 2 through 5 and that 84% of ranibizumab-treated eyes needed reinjection after a period of treatment withholding, suggest that anti-VEGF therapy for PDR is an approach that requires ongoing, perpetual treatment in most eyes.[18] Otherwise, these patients are at risk for progressive growth of neovascular tissue and its severe adverse visual sequelae.

In contrast to the study by Obeid and associates,[14] our cohort included 3 eyes with NPDR and DME. All 3 eyes had severe vision loss after unanticipated treatment interruption, with 2 eyes developing NVG. One study of treatment adherence found that >40% of patients with DME had ≥1 interruption in treatment that lasted >100 days.[19] There is real concern for potentially disastrous visual consequences, including irreversible blindness, in patients with diabetic retinal ischemia who have an unplanned treatment hiatus, even patients without proliferative disease. Recent studies have demonstrated that ongoing anti-VEGF therapy may retard the progression of clinical manifestations of DR and even lead to improvement in DR severity scores.[10,11,20] Consequently, ranibizumab has been approved by the U.S. Food and Drug Administration for the treatment of DR with or without DME. However, >15% of eyes being treated with monthly anti-VEGF therapy still develop PDR, and progression to PDR is associated with baseline capillary nonperfusion.[10,11,21,22] Furthermore, Tadayoni and associates[23] recently showed that despite improvement in clinical features of DR on fundus photographs, the area of capillary nonperfusion remained unchanged or continued to worsen in eyes receiving monthly anti-VEGF injections. Therefore, the improvement in the clinical picture of DR seen with anti-VEGF therapy may give false reassurance, given the inability of such treatment to reverse retinal ischemia and to fully address the complex pathophysiology of DR.[24] When such reassurance leads to complacency and lack of close follow-up, severe and potentially permanent vision loss can result.

Anti-VEGF therapy inarguably is an effective treatment modality for ischemic DR, especially PDR, so long as close monitoring and regular dosing are maintained. DRCR.net Protocol S results showed that in ranibizumab-treated eyes, mean change in VA at 2 years was comparable, DME status was improved, and there was better preservation of peripheral visual field compared to eyes treated with PRP.[3,9,18] At 5 years, the mean change in VA letter score was virtually identical between treatment groups and that visual field loss had progressed in the anti-VEGF treated eyes, diminishing the difference between the 2 groups.[9] Importantly, the potential short-term benefits of anti-VEGF therapy are attainable only with significantly greater cost and treatment burden.[18,25] On the other hand, PRP is highly durable, more cost effective, and provides better outcomes when diabetic patients are lost to follow-up.[4–6,8,14,25] Also, no differences in the majority of patient-reported outcomes have been identified between the 2 treatments.[26] While PRP is a destructive therapy that reduces quantitative measures of peripheral visual field, there were no significant differences between PRP and ranibizumab treatment in the peripheral vision subscale scores from the National Eye Institute Visual Function Questionnaire-25 or the University of Alabama Low Luminance Questionnaire.[26] So, while anti-VEGF therapy is effective, the uncertain long-term benefits of pharmacologic monotherapy over PRP as well as the increased cost and treatment burden may not be optimal for many diabetic patients. Rather, anti-VEGF therapy may be best used as a temporary adjunct to PRP, especially in light of the potentially blinding consequences of inadvertent treatment interruptions illustrated in our cohort and others.[14]

This study has several limitations, including its retrospective nature and small sample size. The limited size of our cohort may reflect in part the findings of the most recent American Society of Retinal Specialists Preferences and Trends Survey, where <13% of respondents indicated that they use anti-VEGF therapy alone for high-risk PDR.[27] In addition, the patients in this retrospective case series may have been predisposed to disease progression owing to the poorly controlled nature of their disease as evidenced by an average HbA1c >9% (Table 1). Equally, we cannot rule out a bias to recall those patients with the worst outcomes as our colleagues identified cases of anti-VEGF treatment interruption to contribute to this investigation. Because the patients were identified by investigator recall, our study design does not allow us to determine the overall percentage of patients that develop complications due to interrupted therapy. Finally, as a retrospective case series, our study has no control group or PRP-treated cohort for comparison. Even with these limitations, the sobering findings of this report should serve as a serious caveat to physicians who are treating PDR.

In conclusion, diabetic patients are subject to significant lapses in follow-up, despite the best efforts of the health care team, because of illness, noncompliance, financial hardship, and other issues. In patients with ischemic DR, especially PDR, who are managed with anti-VEGF monotherapy, unintentional treatment interruptions can result in visually disastrous consequences, including irreversible blindness, as observed in this retrospective case series. In contrast, PRP has a highly durable treatment effect as shown in numerous long-term follow-up studies, and evidence is emerging that anatomic and functional outcomes after losses to follow-up are significantly better in eyes receiving PRP compared with eyes receiving anti-VEGF monotherapy. While both anti-VEGF therapy and PRP are effective treatment modalities for PDR, the potentially severe consequences of interruptions in anti-VEGF therapy in these eyes should be carefully considered when making initial treatment decisions.

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