CME MONOGRAPH

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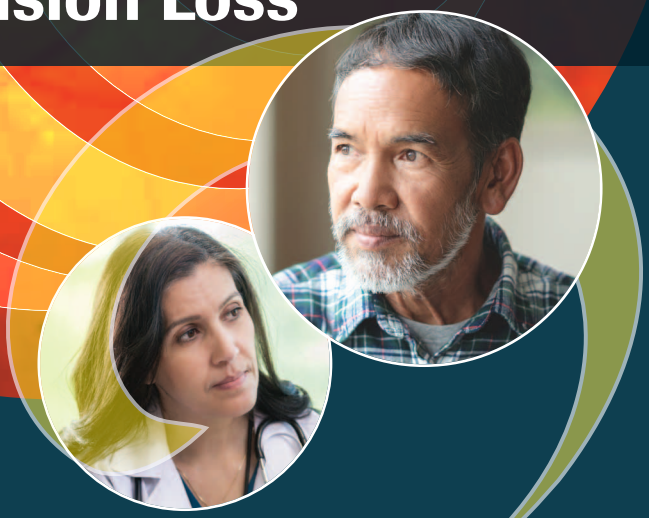
EVOLVING
Diabetic Retinopathy Management Strategies
to Prevent Vision Loss



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This continuing medical education activity is jointly provided by **New York Eye and Ear Infirmary of Mount Sinai** and MedEdicus LLC, in collaboration with Women in Retina, a section of ASRS.

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This continuing medical education activity is supported through an unrestricted educational grant from Regeneron Pharmaceuticals, Inc.

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ACTIVITY DESCRIPTION

After 25 years living with diabetes, up to 83% of people with nonproliferative diabetic retinopathy will progress to proliferative diabetic retinopathy, which is vision threatening. Nonproliferative diabetic retinopathy can also progress to vision-threatening, center-involved diabetic macular edema. Until recently, treatment options for nonproliferative diabetic retinopathy were limited to laser photocoagulation or ranibizumab anti–vascular endothelial growth factor injection if diabetic macular edema was also present. Ranibizumab and, as of recently, aflibercept are now approved to treat all forms of diabetic retinopathy, with or without diabetic macular edema. Accumulating evidence shows that approximately 40% of patients with untreated nonproliferative diabetic retinopathy will develop proliferative diabetic retinopathy or center-involved diabetic macular edema within 1 year, but treatment at this stage of disease can drastically reduce the risk. Whether patients benefit more from laser or from anti–vascular endothelial growth factor treatment depends on factors unique to individuals, and communication of modifiable risk factors and discussion of individual patient needs is critical for sight preservation. The desired results of this activity are for retina specialists to gain the knowledge and competence needed to help patients with nonproliferative diabetic retinopathy prevent loss of vision from proliferative diabetic retinopathy and diabetic macular edema.

TARGET AUDIENCE

This educational activity is intended for retina specialists and other ophthalmologists caring for patients with diabetic retinopathy.

LEARNING OBJECTIVES

Upon completion of this activity, participants will be better able to:

- Analyze the evidence supporting treatment for preventing vision-threatening outcomes in diabetic retinopathy
- Examine clinical trial data supporting treatment of nonproliferative diabetic retinopathy to prevent diabetic retinopathy progression and diabetic macular edema
- Design treatment plans for diabetic retinopathy that consider individual patient factors
- Identify information that should be shared with patients with diabetic retinopathy to help them prevent vision loss

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EVOLVING

Diabetic Retinopathy Management Strategies

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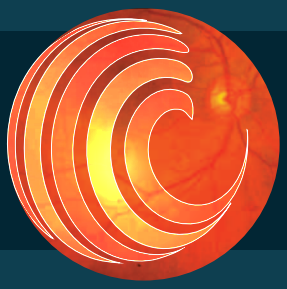

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INTRODUCTION

The rapidly rising incidence of diabetes in the United States has reached epidemic proportions. As of 2015, an estimated 30.3 million people in the United States are living with diabetes, of which 7.2 million are undiagnosed.[1] Another 84.1 million people—including 48.3% of adults aged ≥ 65 years—have an elevated fasting glucose or HbA1c, putting them at high risk of developing diabetes.[1] By 2030, the prevalence of diabetes in the United States is expected to reach approximately 42 million.[2] Ocular complications that can result from uncontrolled diabetes are the leading cause of blindness among working-age adults; by 2030, it is estimated that more than 6 million people with diabetes will have some degree of visual impairment.[2,3] Diabetic retinopathy (DR), a precursor to more severe, vision-threatening manifestations of diabetic eye disease, is estimated to affect approximately one-third of adults with diabetes aged > 40 years in the United States, predominantly blacks and Hispanics.[3]

Identifying patients at high risk of vision loss is a pressing public health issue. After living with diabetes for 25 years, > 80% of patients will develop DR.[4] Many of these patients are at high risk of progression to sight-threatening proliferative DR (PDR) or center-involving diabetic macular edema (CI-DME). An often-unappreciated consequence of vision loss is reduced quality of life. For patients who are still working or caring for others, loss of vision can be devastating. In a recent cross-sectional study conducted by the Centers for Disease Control and Prevention, visual impairment was associated with life dissatisfaction (odds ratio [OR] 2.06; 95% confidence interval, 1.80-2.35), mentally unhealthy days (OR 1.84; 95% confidence interval, 1.66-2.05), and activity limitation days (OR 1.94; 95% confidence interval, 1.71-2.20).[5] Until recently, the only treatment option for patients with DR was laser photocoagulation, but several clinical trials have resulted in the approval of both aflibercept and ranibizumab anti–vascular endothelial growth factor (VEGF) intravitreal injections for all forms of DR in the presence or absence of DME. Aflibercept has also recently been evaluated for its ability to prevent progression to PDR and CI-DME.

—NANCY M. HOLEKAMP, MD

NATURAL HISTORY OF DIABETIC RETINOPATHY

Recent studies have confirmed earlier observations of inevitable progression of DR in a subset of eyes. In the 1991 Early Treatment Diabetic Retinopathy Study (ETDRS), 26% of patients with moderately severe nonproliferative DR (NPDR) and 52% of patients with severe NPDR at baseline progressed to PDR within 1 year **(Figure 1)**.[6] At the recent Angiogenesis, Exudation, and Degeneration 2019 meeting, Charles C. Wykoff, MD, PhD, presented the 52-week results from the PANORAMA trial, the first prospective trial to investigate if anti-VEGF therapy can prevent PDR or CI-DME in patients with moderately severe or severe NPDR. The 1-year data from PANORAMA showed a similar trend to ETDRS in the sham arm.[7] In PANORAMA, 26% of participants with moderately severe to severe NPDR at baseline who were randomized to sham developed PDR or CI-DME within 24 weeks.[8] At 52 weeks, this incidence increased to 41%.[7]

PANEL DISCUSSION: REAL-WORLD PROGRESSION OF DIABETIC RETINOPATHY

Dr Holekamp: Do the results of ETDRS and the PANORAMA natural history arm align with what you have seen in your practices?

Dr Lim: Yes, they do. The results also beg the question: Should we treat everyone with moderately severe or severe NPDR within the first 6 months or the first year?

Dr Kovach: Yes, and there are modifiable lifestyle risk factors that can affect the rate of progression, including blood sugar, blood pressure, and body mass index. The option to

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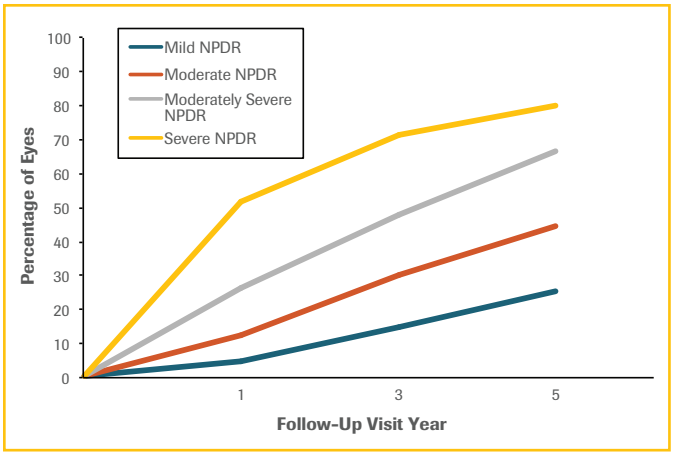

Figure 1. Progression of diabetic retinopathy by severity in the Early Treatment Diabetic Retinopathy Study[6]
Abbreviation: NPDR, nonproliferative diabetic retinopathy.

treat patients with DR earlier in the disease process and thereby prevent progression and associated vision loss would be life changing for these working-age patients.

Dr Lad: The findings from ETDRS and PANORAMA on progression of DR are indeed consistent with what I see in my academic practice. They have reinforced my belief that early intervention, either via aggressive blood glucose control and anti-VEGF injections or both, is key in managing moderate-to-severe DR.

Dr Holekamp: It is interesting to see that despite a time gap of nearly 30 years, the PANORAMA study echoes the results of ETDRS regarding progression of disease at various levels of DR; the results of the 2 studies are amazingly consistent.

EVOLUTION IN THE TREATMENT OF DIABETIC RETINOPATHY

Treatment of DR has evolved substantially over the past half century **(Figure 2)**.[9-16] Prior to the advent of laser photocoagulation for DR, the only recourse for severely affected eyes was pituitary ablation or surgical enucleation. Laser photocoagulation revolutionized treatment of DR, enabling prevention of vision loss for many patients. Laser treatment is not a perfect solution, however, because it is inherently destructive. Frequent complications include new or worsening macular edema, visual field loss, loss of color vision or night vision, reduction in contrast sensitivity, or choroidal complications for some patients.[9] Pharmacologic intervention in the angiogenic process underlying diabetic eye disease has been extensively studied in the last 13 years. Bevacizumab, an anti-VEGF monoclonal antibody, was first used in 2006 to regress retinal neovascularization and improve visual acuity (VA) in patients with PDR.[10] Subsequently, the RISE/RIDE and VIVID/VISTA trials formed the basis for US Food and Drug Administration (FDA) approval of ranibizumab and aflibercept for the treatment of DME, respectively.[11-13] The Diabetic Retinopathy Clinical Research Network (DRCRnet) Protocol S study provided direct evidence for treatment to regress DR with or without DME, resulting in the approval of ranibizumab to treat all forms of DR in 2017.[14,15] Recently, aflibercept was approved to treat all forms of DR with or without DME according to results from the PANORAMA trial.[16]

The DRCRnet Protocol T study provides additional rationale for treating DR with anti-VEGF intravitreal injections. The primary end point of Protocol T was change in VA among patients with DME at baseline, but many of the participants also had DR, which enabled analysis of the relative efficacy of aflibercept, bevacizumab, and ranibizumab to halt or reverse DR.[17,18] In a preplanned secondary analysis, improvement in DR severity was seen at the 1- and 2-year visits among eyes treated with aflibercept, bevacizumab, or ranibizumab, with significant treatment group differences observed at both timepoints **(Table 1)**.[18]

The rate of DR worsening with treatment was $< 5\%$ in all treatment groups with NPDR at baseline at the 1-year visit.[18] At 2 years, this rate had increased only modestly, ranging from 7.1% to 10.2%, with no significant treatment group differences. In eyes with PDR at baseline, however, the rate of DR worsening more than doubled, ranging from 17.2% to 26.4% among treatment groups. This result suggests that for maximal prevention of progression, treatment should begin when patients have NPDR, rather than waiting until PDR develops. The ongoing PANORAMA and Protocol W trials are assessing treatment of moderately severe and severe NPDR in the absence of DME, but with aflibercept as the study treatment and with slightly different end points that will shed light on best practices for preventing vision loss.[7,19]

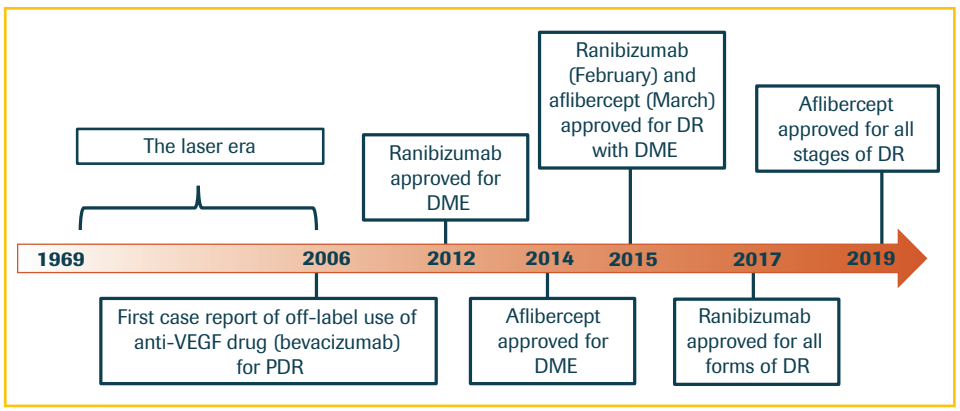

Figure 2. Evolution of treatment for DR and DME[9-16]
Abbreviations: DME, diabetic macular edema; DR, diabetic retinopathy; PDR, proliferative diabetic retinopathy; VEGF, vascular endothelial growth factor.

PANEL DISCUSSION: CURRENT PRACTICES FOR TREATING DIABETIC RETINOPATHY

Dr Holekamp: The aforementioned studies provide compelling evidence for earlier treatment of DR, yet in the latest Preferences and Trends survey of retina specialists, many respondents reported that they have not changed their practices according to the results of Protocol S, and few treat PDR with anti-VEGF therapy alone to regress retinopathy and prevent progression.[20]

How do you currently treat NPDR and PDR?

Dr Lad: For me, the choice of treatment depends on the patient's VA. For a patient with PDR but 20/20 vision, I would recommend panretinal photocoagulation (PRP) because injections carry a small risk of endophthalmitis, which can permanently affect VA. For patients with worse vision, I recommend combination treatment of PRP and anti-VEGF injections. I have also noticed that some patients with type 1 diabetes are more sensitive to PRP owing to photosensitivity and pain. For these patients, I recommend combination treatment to minimize the number of PRP sessions. Cost and insurance coverage are also important considerations that factor

Table 1. Eyes With a ≥ 2-Step Improvement in DR in the Diabetic Retinopathy Clinical Research Network Protocol T Study[18]

	Eyes With NPDR at Baseline			Eyes With PDR at Baseline		
	n*	Improvement at 1 Year (95% CI), %	Improvement at 2 Years (95% CI), %	n*	Improvement at 1 Year (95% CI), %	Improvement at 2 Years (95% CI), %
Aflibercept	167	31.2 (23.7-39.5)	24.8 (17.7-33.0)	30	75.9 (56.5-89.7)	70.4 (49.8-86.2)
Bevacizumab	147	22.1(15.4-30.2)	22.1 (14.9-30.9)	38	31.4 (16.9-49.3)	30.3 (15.6-48.7)
Ranibizumab	163	37.7 (30.0-46.0)	31.0 (23.2-39.7)	32	55.2 (35.7-73.6)	37.5 (18.8-59.4)
Pairwise treatment group comparison (adjusted 95% CI)†						
Aflibercept vs bevacizumab		11.7 (2.9-20.6) ***P* = .004**	3.1 (-3.3 to 9.5) *P* = .85		50.4 (26.8-74.0) ***P* < .001**	35.9 (6.1-65.6) ***P* = .01**
Aflibercept vs ranibizumab		2.9 (-5.7 to 11.4) *P* = .51	0.7 (-6.4 to 7.7) *P* = .85		30.0 (4.4-55.6) ***P* = .02**	31.4 (-0.6 to 63.4) *P* = .06
Ranibizumab vs bevacizumab		8.9 (1.7-16.1) ***P* = .01**	2.4 (-4.0 to 8.7) *P* = .85		20.4 (-3.1 to 44.0) ***P* = .09**	4.5 (-20.5 to 29.4) *P* = .73

Abbreviations: CI, confidence interval; DR, diabetic retinopathy; NPDR, nonproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy.

* Eyes that were evaluable for improvement at baseline (ie, excluding eyes with baseline DR severity level ≤ 20 or level 60).

† Difference in percentage with improvement. Pairwise comparisons were performed using binomial regression, with adjustment for categorical baseline DR severity and multiple treatment group comparisons. Eyes with NPDR were categorized into 2 subgroups: (1) mild or moderate NPDR (level 35 or 43); or (2) moderately severe or very severe NPDR (level 47 or 53). Eyes with PDR were categorized into 3 subgroups: (1) mild (level 61), (2) moderate (level 65), or (3) high risk (level 71 or 75). Reported *P* values and 95% CIs were adjusted using the Hochberg method to account for an overall type 1 error of .05.

into each patient's decision. I follow patients with moderate-to-severe NPDR without DME closely, and recommend an anti-VEGF injection for patients who might have difficulty with adherence to follow-up or who have other disease-specific factors, such as peripheral retinal ischemia. For patients with PDR, I begin the treatment course with anti-VEGF therapy if there is a vitreous hemorrhage or preretinal hemorrhage, then follow with PRP.

Dr Kovach: Individualized therapy is my treatment strategy, and factors such as anticipated visit adherence, cost, systemic health, and visit frequency all play a role in the decision-making process. I recently treated a patient with type 1 diabetes and PDR in the right eye with PRP. She was subsequently unhappy with the resulting peripheral visual field constriction, so when her left eye developed PDR, I treated her with bevacizumab instead of laser. She was able to follow up regularly and was happy with her visual outcome. I believe widespread adoption of anti-VEGF treatment for the purpose of preventing progression will follow longer-term studies that include robust functional vision outcomes. I usually treat PDR with combination therapy, using the laser before anti-VEGF treatment if I have concerns about adherence. If I administer anti-VEGF therapy first and see that the patient is doing well and is able to adhere to follow-up every 1 to 2 months, I might not use PRP at all. The PANORAMA data and subsequent FDA approval of aflibercept for all stages of DR will allow us to treat patients earlier in their disease course. Patients with moderately severe to severe NPDR would likely achieve the most benefit.

Dr Lim: Sharing the decision with the patient is crucial. I give patients—particularly those who are younger, not hospitalized often, and who do not have barriers to monthly visits—a choice of treatment strategies. I counsel them about the risk of endophthalmitis associated with anti-VEGF injections and, conversely, the risk of visual field loss and impaired night vision following laser treatment. I feel that younger patients are more bothered by visual field constriction and impaired night vision. For NPDR, I think that the available population data from Protocol S—and now from PANORAMA—are insufficient at this time for accurately estimating an individual's risk vs benefit. If a patient with NPDR is progressing rapidly, however, I would consider an anti-VEGF injection because the potential benefit likely outweighs the risk of infection. Longitudinal imaging is critical for following progression of DR and is also helpful as a patient education tool to motivate patients to make lifestyle adjustments and to get their blood glucose under control.

Dr Holekamp: For me, combination therapy using a combination of anti-VEGF therapy and laser is an option that, although off-label, allows for a gentler PRP that might not affect the peripheral vision as severely. I generally recommend this combination treatment for patients with high-risk PDR with or without vitreous hemorrhage, but who do not have traction retinal detachment.

CASE 1. "I SEE SOMETHING RED IN MY LEFT EYE"

FROM THE FILES OF ELEONORA LAD, MD, PhD

A 58-year-old black male was referred for a retinal evaluation. His VA was 20/40 OD (20/25 with a pinhole occluder) and 20/40 OS (20/20 with a pinhole occluder). His medical history was significant for hypertension, hyperlipidemia, and insulin-dependent type 2 diabetes mellitus. His HbA1c was 8.5%. On slit-lamp examination, scattered neovascularization of the iris was observed OU. Color fundus photography and fluorescein angiography revealed neovascularization of the disc (NVD) covering less than one-quarter of the disc area, multiple areas of neovascularization elsewhere (NVE), and a vitreous hemorrhage OS and NVD OD **(Figures 3A-3F)**. Optical coherence tomography revealed subclinical (not center-involving) DME, primarily focal OD and diffuse OS **(Figures 3G and 3H)**.

The patient was diagnosed with high-risk PDR with vitreous hemorrhage. Treatment of the left eye with anti-VEGF therapy was recommended to resolve the vitreous hemorrhage and prevent progression of DR and DME. Although ranibizumab and aflibercept are the only approved treatments for DR with or without DME, the patient was not eligible for Medicare and decided to proceed with a bevacizumab injection (used off label for DR/DME). In the Protocol T study, bevacizumab was compared with ranibizumab and aflibercept, and similar outcomes were observed for DR improvement among treatment groups at 2 years.[18] Thus, it is reasonable to try bevacizumab if the patient cannot access an on-label treatment. It should be noted, however, that use of bevacizumab is off-label, and its use to treat DR without DME is not directly supported by clinical trial data at this time.

In the next few months, PRP was completed OU over multiple sessions, and aggressive blood pressure, blood glucose, and lipid control were discussed with both the patient and his primary care physician. After PRP was completed, the patient was lost to follow-up for 2 months. During that time, a large vitreous hemorrhage

developed in the patient's opposite (right) eye. At follow-up, continued active neovascularization was observed in the left eye **(Figure 4)**.

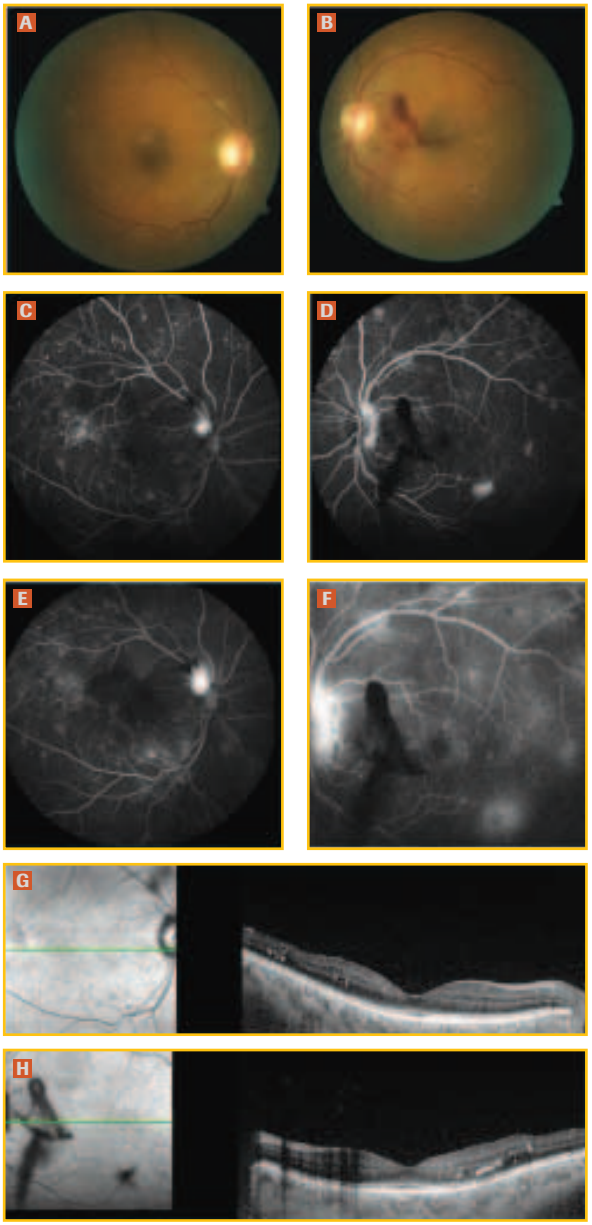

Figure 3. Color fundus photography (A and B), early (C and D) and late (E and F) fluorescein angiography, and optical coherence tomography (G and H) of the right and left eye, respectively, of the patient presented in Case 1

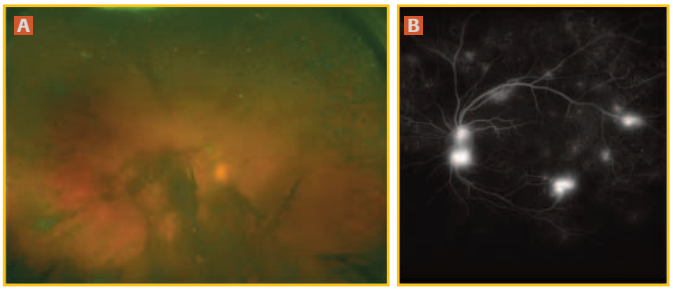

Figure 4. Color fundus photograph of the right eye (A) and fluorescein angiography of the left eye (B) for the patient presented in Case 1 after a 2-month loss to follow-up

The patient was again treated with bevacizumab OD to control the hemorrhage, followed by fill-in PRP OU to prevent further neovascularization. The patient continued to experience vitreous hemorrhage with rebleeds OD and needed 10 bevacizumab injections over 18 months to remain hemorrhage free. The left eye eventually began experiencing a similar series of events and had to be re-treated with bevacizumab 6 times over the next 18 months as the vitreous hemorrhage cleared. Despite the continued hemorrhages, the patient's vision remained minimally impaired. When the vitreous was clear enough, additional fill-in PRP was applied. The patient ultimately attained 20/20 vision, which was maintained over the next 2 years with periodic anti-VEGF injections, and only regressed NVE was observable on fluorescein angiography during the last visit **(Figure 5)**.

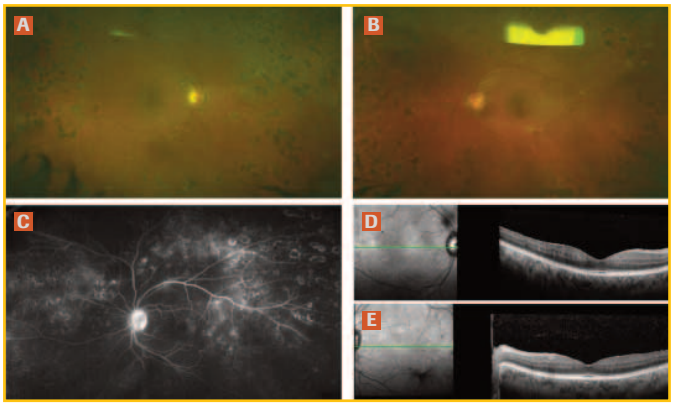

Figure 5. Color fundus photograph of the right eye (A) and of the left eye (B), fluorescein angiography (C) of the left eye showing regressed neovascularization elsewhere, and optical coherence tomography images of the right eye (D) and of the left eye (E), respectively, for the patient presented in Case 1 at the last visit

Commentary

Dr Lad: This case illustrates the importance of considering the more severely affected eye when designing preventive treatment strategies for the fellow eye. In my experience, the fellow eye will usually follow a similar disease trajectory unless proactively treated.

Dr Holekamp: What was your rationale for treating this patient's PDR with frequent anti-VEGF injections vs laser alone?

Dr Lad: The rationale for using anti-VEGF therapy to treat PDR in the absence of clinically significant DME was based on the DRCRnet Protocol S study comparing intravitreal ranibizumab with PRP.[14] In this noninferiority study, eyes with PDR with or without DME were randomized to receive either 1 to 3 sessions of PRP (n = 203) or 0.5 mg of intravitreal ranibizumab alone (n = 191) at baseline and every 4 weeks through 12 weeks, with retreatment after 12 weeks based on investigator assessment. Eyes with DME in either group received ranibizumab. At 2 years, the ranibizumab group gained more letters than did the PRP group (mean change in letter score, 2.8 vs 0.2, respectively; $P = .11$ and $P < .001$ for the mean area under the curve for letter score).[14,21] The difference in mean letter change between the groups largely disappeared by 5 years of study (3.1 vs 3.0 letters, respectively), possibly because more

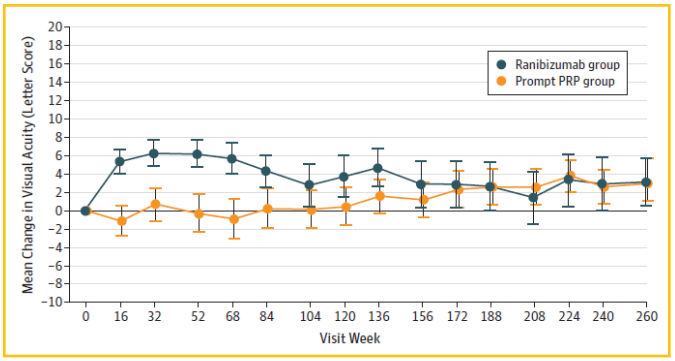

Figure 6. Mean change in visual acuity over 5 years in the Protocol S study[21]

Abbreviation: PRP, panretinal photocoagulation.

than half of the eyes in the PRP group were treated with ranibizumab for DME over the course of the study **(Figure 6)**.[21] At 2 years, DR score improved by ≥ 2 steps in 48% of eyes treated with ranibizumab. At 5 years, 46% of ranibizumab-treated eyes had improvement by at least 2 steps, with 10% experiencing complete resolution of DR.

The PRP group had more visual field loss and higher rates of both DME development and vitrectomy than did the ranibizumab group.[21] At 2 years among 242 eyes without baseline DME, the cumulative probability of vision-impairing DME development was 9% vs 28% for the ranibizumab and PRP groups, respectively ($P < .001$).[14]

Fill-in PRP takes a while to take effect. To avoid unwanted consequences between PRP treatments, I added anti-VEGF therapy to this patient's treatment regimen. The use of combination therapy is supported by the recently published European PROTEUS study, wherein patients with high-risk PDR were randomized to receive either ranibizumab plus PRP (n = 41) or PRP alone (n = 46).[22] Ranibizumab injections were given monthly for the first 3 months, whereas PRP was given in 1 to 3 sessions, 2 ± 1 weeks after the ranibizumab injection. Retreatment was at investigator discretion based on neovascularization. At 1 year, 92.7% of the combination group had reduced total neovascularization vs 70.5% of the PRP monotherapy group ($P = .009$). Mean best-corrected VA was comparable between the groups.

Another important aspect of treatment for patients with NPDR or PDR is education on modifiable risks. Several health and lifestyle interventions have been associated with a reduced risk of DR progression. **Table 2** summarizes findings from selected large randomized trials.[4,23-29]

Table 2. Modifiable Risk Factors for DR Progression

Risk Factor	Study	Findings
Hyperglycemia	DCCT/EDIC	Intensive glycemic control reduced risk of DR progression by 71% at 4 years, 51% at 10 years, and 46% at 18 years[23]
	UKPDS	Relative risk of 2-step progression increased with rising HbA1c[24]
	ACCORD	Rate of progression was 7.3% with intensive control vs 10.4% with standard therapy[25,26]
Systemic hypertension	UKPDS	Risk of 2-step progression was reduced by 34%[27]
Elevated lipids	ACCORD	Rate of progression was 6.5% with fenofibrate vs 10.2% with placebo[25,26]
	FIELD	Rate of progression was 3.1% with fenofibrate vs 14.6% with placebo[28]
Smoking	EURODIAB IDDM Complications Study	Smoking was associated with early development of microvascular complications[29]
Body mass index	WESDR	Body mass index (per 4 kg/m^2) was associated with progression of DR (hazard ratio 1.16; 95% confidence interval, 1.07-1.26; $P < .001$)[4]

Abbreviations: ACCORD, Action to Control Cardiovascular Risk in Diabetes; DCCT, Diabetes Control and Complications Trial; DR, diabetic retinopathy; EDIC, Epidemiology of Diabetes Interventions and Complications; FIELD, Fenofibrate Intervention and Event Lowering in Diabetes; IDDM, insulin-dependent diabetes mellitus; UKPDS, United Kingdom Prospective Diabetes Study; WESDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy.

On the basis of the strength of evidence for the association between glycemic index, blood pressure, and serum lipids and DR progression, the American Academy of Ophthalmology and the American Diabetes Association both recommend educating patients on the importance of controlling these systemic risk factors to prevent further progression of DR.[30,31] Obstructive sleep apnea might also affect the progression of DR, and should be discussed with patients during initial and follow-up appointments.[32]

Dr Lim: Having a close one-on-one conversation with patients about their glucose control can be very powerful. At every appointment, I ask my patients what their HbA1c is, understanding that recent holidays or illnesses might cause temporary setbacks, and try to motivate them to do better. The effects of retina specialists counseling patients about diabetes control has been studied by the DRCRnet; regrettably, it did not find an effect.[33] In practice, however, I have found that approximately one-quarter of my patients respond to our discussions and are able to significantly reduce their HbA1c.

Dr Kovach: Also, including the patient's family in counseling can help the entire family move toward a healthier lifestyle. Reviewing images with the patient is helpful as well. Good communication among the retina specialist, endocrinologist, and primary care physician is important. Giving educational seminars in the community can also raise awareness of the importance of glycemic control for prevention of vision impairment at both the patient and primary care levels.

Dr Holekamp: I completely agree, but I think it is also important to note that counseling does not change our treatment plan. For all forms of DR, we are treating damage caused by hyperglycemia that started 5 to 10 years ago; thus, I often motivate my patients by encouraging them to get their HbA1c under control so I do not have to treat their retinopathy 5 or 10 years into the future.

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"Having a close one-on-one conversation with patients about their glucose control can be very powerful. At every appointment, I ask my patients what their HbA1c is, understanding that recent holidays or illnesses might cause temporary setbacks, and try to motivate them to do better."

—JENNIFER I. LIM, MD

Take-Home Points

- Patients with high-risk PDR, with or without vitreous hemorrhage, benefit most from combination therapy of anti-VEGF injections and PRP
- It is important to remember and to remind our patients that both eyes are likely to follow a similar fate. Thus, preventive treatment in the less-involved eye should be started earlier rather than later.
- Motivate your patients to get their blood glucose under control and educate them on modifiable risk factors. A team approach that includes the patient's family, his/her community, primary care physician, and other medical specialists prevents worsening of the retinopathy ≥ 5 years into the future

CASE 2: SEVERE NONPROLIFERATIVE DIABETIC RETINOPATHY — TO TREAT OR NOT TO TREAT?

FROM THE FILES OF JACLYN L. KOVACH, MD

A 62-year-old female with type 2 diabetes mellitus presented with decreased vision OU. Her HbA1c was 7.5%, and her medical history was significant for hypertension. Her VA was 20/150 OD and 20/25 OS. Her right eye had PDR, with a relatively dense vitreous hemorrhage. Her left eye showed severe NPDR, no neovascularization of the iris, and normal pressure **(Figure 7)**. Optical coherence tomography showed no CI-DME.

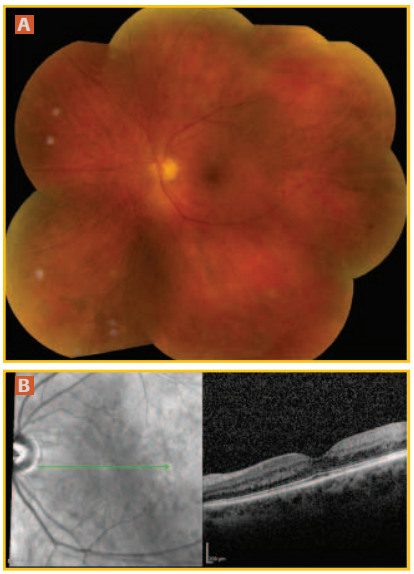

Figure 7. Imaging of the left eye of the patient presented in Case 2. (A) Color fundus photograph showing numerous hemorrhages scattered throughout the retina and cotton wool spots. (B) Spectral domain optical coherence tomography shows no center-involving diabetic macular edema.

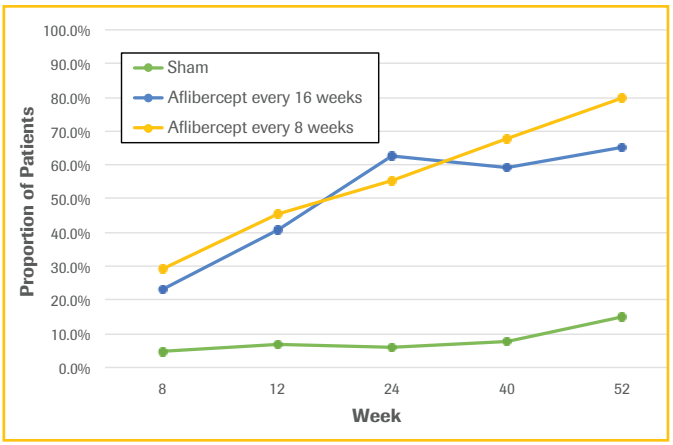

Figure 8. Proportion of patients with a ≥ 2-step improvement in their Diabetic Retinopathy Severity Scale score over time in the PANORAMA study[7]

Commentary

Dr Kovach: Should we be treating patients with severe NPDR such as that in the left eye in this case? Over the past 6 to 7 years, a wealth of information has been accumulating that supports treatment with anti-VEGF therapy to regress DR. Data from the VIVID/VISTA, RISE/RIDE, and DRCRnet Protocol S, T, and I studies show that approximately 25% to 50% of eyes treated with aflibercept or ranibizumab had at least a 2-step improvement in DR severity.[11,13,14,18,34] A post hoc analysis of the VIVID and VISTA trials found that improvement was greatest among eyes with a Diabetic Retinopathy Severity Scale score of 47 or 53 at baseline.[35] A similar analysis of the RISE and RIDE trials found that the greatest improvement was observed among eyes with moderately severe or severe NPDR at baseline.[36]

PANORAMA is the first large prospective randomized trial since ETDRS to study treatment of moderately severe to severe NPDR specifically without CI-DME. The 52-week results were presented at the Angiogenesis, Exudation, and Degeneration 2019 meeting.[7] In this ongoing phase 3 trial, participants were randomized to receive either sham injection (n = 133), 2 mg of intravitreal aflibercept every 16 weeks (n = 135), or 2 mg of intravitreal aflibercept every 8 weeks (n = 134). Patients receiving aflibercept every 16 weeks had 6 planned injections in the first year, whereas those receiving aflibercept every 8 weeks had 9 planned injections. The primary end point was met, with 79.9%, 65.2%, and 15.0% of patients receiving aflibercept every 8 weeks, aflibercept every 16 weeks, and sham, respectively, achieving a ≥ 2-step improvement in their Diabetic Retinopathy Severity Scale score at week 52 ($P < .0001$ for both treatment groups vs sham) **(Figure 8)**.[7] Key secondary end points included the proportion of patients developing PDR or anterior segment neovascularization (ASNV) and the proportion of patients developing CI-DME. Significantly more patients in the sham group developed PDR/ASNV or CI-DME than in the aflibercept-treated groups (40.6% vs 9.6% for aflibercept every 16 weeks and 11.2% for aflibercept every 8 weeks; $P < .0003$ for both comparisons).

According to this analysis, the number needed to treat is 3 to prevent 1 prespecified PDR/ASNV or CI-DME event.[7] Participants will be followed through 100 weeks. The most common adverse events observed in patients receiving aflibercept every 16 weeks and every 8 weeks were conjunctival hemorrhage (11.9% and 17.2%, respectively), vitreous floaters (4.4% and 9.0%, respectively), and eye pain (7.4% and 3.7%, respectively).

Dr Lim: A number needed to treat of 3 is actually good. This is comparable to what we see for the treatment of age-related macular degeneration and vein occlusion with anti-VEGF therapy.[16] In this case, however, we are preventing the development of PDR as opposed to treating a patient with visual loss. It is important to remember that these patients are asymptomatic, and if NPDR progresses to PDR, we can usually successfully treat them with anti-VEGF therapy or PRP.

Dr Holekamp: Throughout all of medicine, a number needed to treat of 3 is considered very reasonable. The PANORAMA study gives us unique data regarding both regression of DR and failure to progress to vision-threatening complications. Does the treatment burden have any effect on your interpretation of the applicability of these results?

Dr Kovach: What is the optimal number of injections? I think this is based on what the patient's goals are and what he/she is willing to tolerate.

Dr Lim: That is a very good point. The patients in this study had good vision at baseline, so you are proposing risking infection at least 6 to 9 times over the course of a year without any VA gain.

Dr Lad: What if we could get the DR to regress by 2 stages and then go back to observation only? This might alleviate the treatment burden and associated risk.

Dr Kovach: The treatment burden will also likely depend on the patient's glycemic control and on our clinics' ability to accommodate an increased patient load. Further study will be needed to determine the exact best practices for treating NPDR in the real world. In this vein, the DRCRnet Protocol W study is assessing outcomes of prompt treatment of severe NPDR (without CI-DME) with aflibercept vs observation only.[19] Enrollment is complete at 328 participants, and the planned study completion is 2022.[37] Synthesizing the data that we have discussed, there are several pros and cons for treatment of NPDR without CI-DME, as summarized in **Table 3**.[7,16,17,38]

Table 3. Comparison of Pros and Cons Associated With Treatment of NPDR Without CI-DME

Pros	Cons
• Potential regression and modulation of disease course • Young, working patient population would greatly benefit from vision loss prevention	• 59% of sham-treated patients in PANORAMA did not develop PDR or CI-DME at 1 year[7] • Intravitreal injections carry risks, including[16,17,38]: – Endophthalmitis – Retinal detachment – Increased intraocular pressure • Lack of data demonstrating functional outcomes with treatment

Abbreviations: CI-DME, center-involving diabetic macular edema; NPDR, nonproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy.

Several unanswered questions regarding treatment of NPDR without CI-DME also exist, including the following:

- Should all patients with moderately severe or severe NPDR be treated? How often?
- Do all anti-VEGF agents provide similar efficacy for DR regression and vision loss prevention?
- How can we best communicate the benefits of vision loss prevention to our patients?

Dr Holekamp: I think that communication of the benefits of vision loss prevention will be the toughest aspect of treating NPDR without CI-DME. It is so hard for patients to appreciate what they have not yet lost.

Dr Kovach: We know that effective communication improves treatment adherence, but there are many barriers to effective communication. Patient demographics, functional health literacy, and even depression all can affect the quality of communication[39] and should be considered when tailoring an educational approach. I think our ongoing challenge is to keep educating our patients by showing them their retinal images and by reinforcing what they have to lose by allowing their vision to deteriorate.

Dr Lim: Patients will develop their own evaluation of the risk-benefit ratio. Some will choose to accept the risks, and some will decide not to. This case provides an example of such shared decision making in action.

Take-Home Points

- With the treatment of advanced NPDR, the ability to provide disease modulation and regression would minimize or completely avert the severe, often irreversible, effects on vision in a patient population for which there are currently no approved or generally accepted therapies
- Future studies will hopefully provide guidance regarding patient selection and timing of treatment and also data that include functional vision outcomes
- The key to maximizing visual outcomes in patients with diabetes going forward will involve augmenting screening efforts, implementing earlier treatment strategies, and communicating effectively

CASE 3: PROLIFERATIVE DIABETIC RETINOPATHY – BALANCING TREATMENT AND OBSERVATION

FROM THE FILES OF JENNIFER I. LIM, MD

A 53-year-old female with a 15-year history of diabetes presented in 2016 with fluctuating vision OU. She was taking insulin until her diabetologist placed her on liraglutide instead of insulin following achievement of reasonable glucose control. Relevant findings are as follows:

- HbA1c: 8.6%
- VA: 20/20 OU
- -3.75 + 1.00 × 165 OD; -3.50 + 1.25 × 10 OS
- Moderate NPDR
- No clinically significant DME OS

She was counseled to aim for an HbA1c of 7%, and instructed to follow up. She returned 10 months later complaining of mild visual changes. At that time, her vision was 20/25 OD and 20/20 OS, and refraction was comparable to that of her initial visit, with a 1+ nuclear sclerotic cataract OU. Her HbA1c was 8.3%. The DME had worsened but was still not affecting the center of the macula. Neovascularization was detected in the optic disc OU **(Figure 9)**.

Because the patient had developed PDR at this point, both laser and anti-VEGF treatment options were presented, along with their possible side effects. The patient chose to begin treatment with anti-VEGF injections OU. At her follow-up visit approximately 1 month later, the neovascularization and DME had completely resolved.

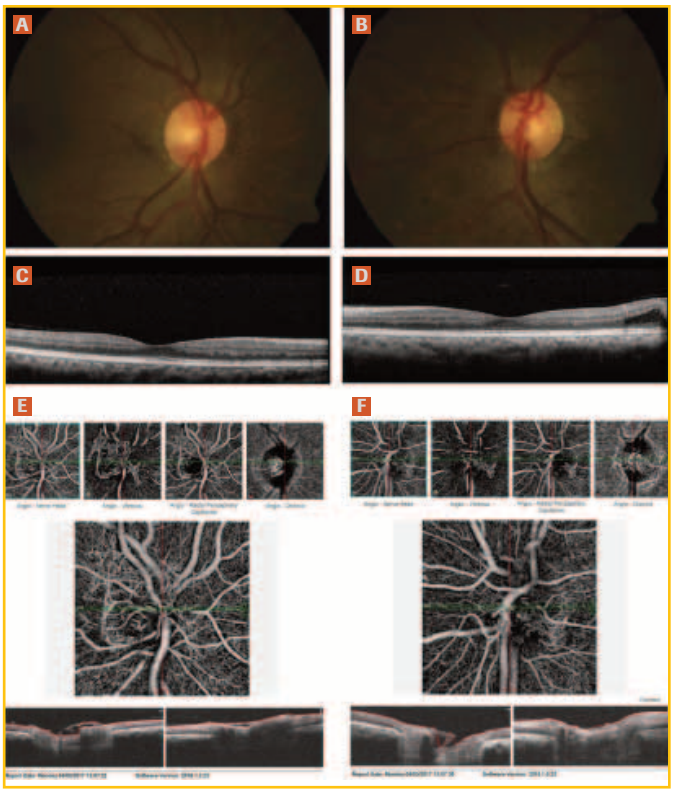

Figure 9. Color fundus photographs (A and B), optical coherence tomography images (C and D), and optical coherence tomography angiography images (E and F) of the right and left eye, respectively, of the patient presented in Case 3

Commentary

Dr Lim: What would you do now? Would you follow Protocol S and treat with a series of 3 monthly anti-VEGF injections?[14] Would you combine injections with PRP, or would you observe?

Dr Lad: I would observe this patient closely, given her excellent vision and lack of DME and neovascularization.

Dr Kovach: I would observe with close follow-up.

Dr Lim: I observed, and followed up 2 months later. In the interim, the patient was able to reduce her HbA1c to 7.4%; no edema or PDR was seen on that follow-up examination. I observed again, and asked her to return in another 8 weeks. She returned 12 weeks later, and in the intervening time, developed recurrent PDR OU despite having maintained her HbA1c at 7.5%. Visual acuity was 20/25 OD and 20/20 OS; it was 6 months after the first anti-VEGF injection had been given. At this visit, she received an anti-VEGF injection OU, but at the subsequent follow-up visit 4 weeks later, her PDR had not regressed as it had after her first set of injections. I therefore re-treated with anti-VEGF therapy (3 total in 7 months). She responded well, with regression of NVD within another month. Two months later, there was a tiny spot of NVD in the right eye. Three months later (6 months after her last anti-VEGF treatment), NVD had increased and was associated with mild vitreous hemorrhage OD despite her having a VA of 20/20 OU. She received an anti-VEGF injection OD (fourth received OD in 14 months). Over the next 6 months, I injected her with anti-VEGF therapy only when recurrent NVD was observed, at approximately 4 to 6 months. Although the patient might have benefitted from adjunctive laser therapy, she declined the treatment because she highly valued her peripheral vision. She returns at intervals of 3 months.

Dr Holekamp: I think you have done an excellent job of managing this patient rather than just managing the disease. You did not give her a series of injections just because Protocol S did. You learned that this patient has DR that recurs with a periodicity, but that she is motivated

to control her blood glucose and adhere to a follow-up schedule that she helped develop.

Dr Lim: Using anti-VEGF treatment alone for PDR has the advantage of avoiding the peripheral vision loss associated with laser treatment. In my practice, however, very few patients complain of visual field or VA loss after laser. Although this patient was very happy with anti-VEGF treatment alone, there are some downsides to this approach. When injections are missed, rapid progression can result, with vision-threatening vitreous hemorrhage or retinal detachment. Other considerations that should factor into a decision of whether to pursue anti-VEGF therapy for PDR include the following:

- Severity of diabetes (control of HbA1c)
- Transportation to the clinic
- Employment status
- Risk of endophthalmitis

Take-Home Points

- Anti-VEGF treatment results in regression of neovascularization in patients with diabetes and PDR
- Maintain careful follow-up while observing and during treatment of active disease
- Personalize your approach to determining the periodicity of the recurrent PDR
- Carefully coach the patient with regard to risk factors for diabetic control
- Consider adding laser treatment if issues of noncomplicance (due to illness or lack of follow-up) arise
- Optical coherence tomography angiography can be helpful in following the NVD and documenting regression or recurrence

CASE 4: A LESSON IN PERSEVERANCE

FROM THE FILES OF NANCY M. HOLEKAMP, MD

A 48-year-old black male with a 10-year history of poorly controlled diabetes presented with blurry vision that affected his ability to work. He also had a history of hypertension and high cholesterol. His HbA1c was 12.4% at presentation. His right eye was 20/30, with severe, high-risk PDR and extensive peripheral nonperfusion, NVD, NVE, and minimal DME **(Figure 10)**. His left eye was 20/125, with some macular edema. Given that it was 2013, prior to Protocol S, PRP was recommended for each eye. The patient received PRP in the right eye but failed to return for PRP in the left eye for 13 months.

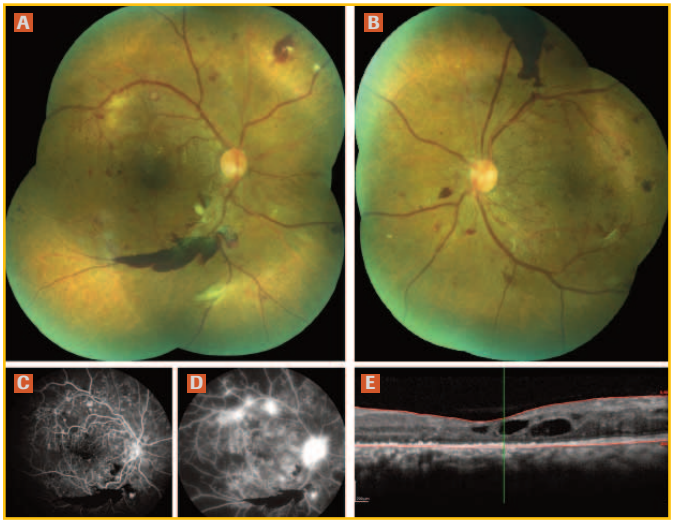

Figure 10. (A and B) Seven-field color fundus photographs of the right and left eye, respectively, of the patient described in Case 4. Early (C) and late (D) fluorescein angiograms of the right eye. (E) Optical coherence tomography of the left eye

Commentary

Dr Holekamp: Clearly, I failed to communicate the importance of treatment at the severe PDR stage. Maybe I should have talked to him more about his risk of progression and vision loss using numerical data. I did show him his retinal images, but it was just not enough. The fact that he presented to me so late in the disease course and with such a high HbA1c should have been red flags for possible nonadherence to follow-up.

Dr Lim: It is good that you did the PRP in 1 sitting. Many physicians prefer to spread PRP out among sessions because of the discomfort some patients experience with thermal laser. Newer laser systems use shorter pulse durations, which translates to less discomfort.[40,41] The DRCRnet also showed that there was no difference at 4 months postlaser in terms of macular edema or outcome when PRP was performed in 1 sitting or in more than 1 sitting.[42] I prefer to do the PRP in 1 sitting; that way I can be sure the treatment is complete and not have to worry about noncompliance for a follow-up visit to finish treatment.

Dr Holekamp: When he did return, this patient had severe, untreated neovascular glaucoma in the left eye and ended up permanently losing sight in that eye. We discussed treatment for his right eye, which had developed some fibrosis of the neovascular tissue because of the laser, yet he still had proliferative disease. To reinforce the seriousness of the situation, I asked him to cover his remaining eye and walk out of the room. This ended up being a pivotal moment for the patient. He subsequently became fully compliant with anti-VEGF injections—first with bevacizumab, and then with aflibercept. I prefer on-label injections for monocular patients. Frequent monthly injections were required to control small hemorrhages that would occur upon interval extension. He also received laser treatment. His VA remained at 20/25 until he passed away in early 2019.

Take-Home Points

- Patients with DR/DME are often challenged to adhere to lifestyle and treatment recommendations, which is why they have developed DR/DME
  - Acknowledge this challenge right up front and spend extra time at each visit building a physician-patient relationship that will lend itself to improved adherence
- Treat monocular patients with extra special care; consider using on-label, FDA–approved drugs for these patients
- Although frequent anti-VEGF injections are burdensome for patients, blindness will always be a far greater burden
  - Patients at risk for blindness will come back monthly if needed to prevent progression of disease

SUMMARY

- **Studies, including the ongoing PANORAMA study, show that patients with moderately severe and severe NPDR are at a high risk of developing PDR or CI-DME within 1 year if left untreated**
- **NPDR might respond better to anti-VEGF therapy than does PDR, and treatment at this stage might avert more vision-threatening complications**
- **Several studies, including PANORAMA and DRCRnet Protocol S, demonstrate that treatment of NPDR and PDR with anti-VEGF therapy can reverse DR and prevent development of vision-threatening complications**
- **Anti-VEGF intravitreal injection and PRP are both efficacious treatments for DR, but side effects such as infection risk (for anti-VEGF therapy) and loss of peripheral and night vision with the risk of developing DME (for PRP) should be discussed with patients as part of a shared decision-making approach**
- **Treatment selection for DR should be individualized, taking into account patient- and treatment-specific factors that might affect adherence, severity of disease, and the disease trajectory of the fellow eye**

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REFERENCES

1. National Center for Chronic Disease Prevention and Health Promotion. *National Diabetes Statistics Report, 2017: Estimates of Diabetes and Its Burden in the United States*. Atlanta, GA: Centers for Disease Control and Prevention; 2017.
2. Rowley WR, Bezold C, Arikan Y, Byrne E, Krohe S. Diabetes 2030: insights from yesterday, today, and future trends. *Popul Health Manag*. 2017;20(1):6-12.
3. National Center for Chronic Disease Prevention and Health Promotion. Diabetic retinopathy. Centers for Disease Control and Prevention Web site. https://www.cdc.gov/visionhealth/pdf/factsheet.pdf. Accessed April 24, 2019.
4. Klein R, Knudtson MD, Lee KE, Gangnon R, Klein BE. The Wisconsin Epidemiologic Study of Diabetic Retinopathy XXII: the twenty-five-year progression of retinopathy in persons with type 1 diabetes. *Ophthalmology*. 2008;115(11):1859-1868.
5. Crews JE, Chou C-F, Zack MM, et al. The association of health-related quality of life with severity of visual impairment among people aged 40-64 years: findings from the 2006-2010 Behavioral Risk Factor Surveillance System. *Ophthalmic Epidemiol*. 2016;23(3):145-153.
6. Early Treatment Diabetic Retinopathy Study Research Group. Fundus photographic risk factors for progression of diabetic retinopathy. ETDRS report number 12. *Ophthalmology*. 1991;98(5)(suppl):823-833.
7. Wykoff CC. Intravitreal aflibercept for moderately severe to severe non-proliferative diabetic retinopathy (NPDR): the phase 3 PANORAMA study. Presented at: Angiogenesis, Exudation, and Degeneration 2019; February 9, 2019; Miami, FL.
8. Bankhead C. Benefits with early treatment of diabetic retinopathy. MedPage Today Web site. https://www.medpagetoday.com/meetingcoverage/asrs/74225. Published July 25, 2018. Accessed April 29, 2019.
9. Deschler EK, Sun JK, Silva PS. Side-effects and complications of laser treatment in diabetic retinal disease. *Semin Ophthalmol*. 2014;29(5-6):290-300.
10. Spaide RF, Fisher YL. Intravitreal bevacizumab (Avastin) treatment of proliferative diabetic retinopathy complicated by vitreous hemorrhage. *Retina*. 2006;26(3): 275-278.
11. Brown DM, Nguyen QD, Marcus DM, et al; RIDE and RISE Research Group. Long-term outcomes of ranibizumab therapy for diabetic macular edema: the 36-month results from two phase III trials: RISE and RIDE. *Ophthalmology*. 2013;120(10):2013-2022.
12. Korobelnik JF, Do DV, Schmidt-Erfurth U, et al. Intravitreal aflibercept for diabetic macular edema. *Ophthalmology*. 2014;121(11):2247-2254.
13. Brown DM, Schmidt-Erfurth U, Do DV, et al. Intravitreal aflibercept for diabetic macular edema: 100-week results from the VISTA and VIVID studies. *Ophthalmology*. 2015;122(10):2044-2052.
14. Gross JG, Glassman AR, Jampol LM, et al; Writing Committee for the Diabetic Retinopathy Clinical Research Network. Panretinal photocoagulation vs intravitreous ranibizumab for proliferative diabetic retinopathy: a randomized clinical trial. *JAMA*. 2015;314(20):2137-2146.
15. American Academy of Ophthalmology. FDA approves ranibizumab for all forms of diabetic retinopathy. https://www.aao.org/headline/fda-approves-ranibizumab-all-forms-of-diabetic-ret. Published April 18, 2017. Accessed April 29, 2019.
16. Eylea [package insert]. Tarrytown, NY: Regeneron Pharmaceuticals, Inc; 2019.
17. Wells JA, Glassman AR, Ayala AR, et al; Diabetic Retinopathy Clinical Research Network. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema: two-year results from a comparative effectiveness randomized clinical trial. *Ophthalmology*. 2016;123(6):1351-1359.
18. Bressler SB, Liu D, Glassman AR, et al; Diabetic Retinopathy Clinical Research Network. Change in diabetic retinopathy through 2 years: secondary analysis of a randomized clinical trial comparing aflibercept, bevacizumab, and ranibizumab. *JAMA Ophthalmol*. 2017;135(6):558-568.
19. Diabetic Retinopathy Clinical Research Network. Intravitreous anti-VEGF treatment for prevention of vision threatening diabetic retinopathy in eyes at high risk. Jaeb Center for Health Research Web site. https://public.jaeb.org/drcrnet/stdy/340. Accessed April 24, 2019.
20. Singh R, Stone T. *2018 Membership Survey: Preferences and Trends*. Chicago, IL: American Society of Retina Specialists; 2018.
21. Gross JG, Glassman AR, Liu D, et al; Diabetic Retinopathy Clinical Research Network. Five-year outcomes of panretinal photocoagulation vs intravitreous ranibizumab for proliferative diabetic retinopathy: a randomized clinical trial. *JAMA Ophthalmol*. 2018;136(10):1138-1148.
22. Figueira J, Fletcher E, Massin P, et al; EVICR.net Study Group. Ranibizumab plus panretinal photocoagulation versus panretinal photocoagulation alone for high-risk proliferative diabetic retinopathy (PROTEUS study). *Ophthalmology*. 2018; 125(5):691-700.
23. Lachin JM, White NH, Hainsworth DP, Sun W, Cleary PA, Nathan DM; Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) Research Group. Effect of intensive diabetes therapy on the progression of diabetic retinopathy in patients with type 1 diabetes: 18 years of follow-up in the DCCT/EDIC. *Diabetes*. 2015;64(2):631-642.
24. Stratton IM, Kohner EM, Aldington SJ, et al. UKPDS 50: risk factors for incidence and progression of retinopathy in type II diabetes over 6 years from diagnosis. *Diabetologia*. 2001;44(2):156-163.
25. Chew EY, Ambrosius WT, Davis MD, et al; ACCORD Study Group and ACCORD Eye Study Group. Effects of medical therapies on retinopathy progression in type 2 diabetes. *N Engl J Med*. 2010;363(3):233-244.
26. Chew EY, Davis MD, Danis RP, et al; Action to Control Cardiovascular Risk in Diabetes Eye Study Research Group. The effects of medical management on the progression of diabetic retinopathy in persons with type 2 diabetes: the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Eye Study. *Ophthalmology*. 2014;121(12):2443-2451.
27. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *BMJ*. 1998;317(7160):703-713.
28. Keech AC, Mitchell P, Summanen PA, et al; FIELD Study Investigators. Effect of fenofibrate on the need for laser treatment for diabetic retinopathy (FIELD study): a randomised controlled trial. *Lancet*. 2007;370(9600):1687-1697.
29. Karamanos B, Porta M, Songini M, et al. Different risk factors of microangiopathy in patients with type I diabetes mellitus of short versus long duration. The EURODIAB IDDM Complications Study. *Diabetologia*. 2000;43(3):348-355.
30. American Academy of Ophthalmology Retina/Vitreous Panel. *Preferred Practice Pattern® Guidelines. Diabetic Retinopathy*. San Francisco, CA: American Academy of Ophthalmology; 2017.
31. Solomon SD, Chew E, Duh EJ, et al. Diabetic retinopathy: a position statement by the American Diabetes Association. *Diabetes Care*. 2017;40(3):412-418.
32. Leong WB, Jadhakhan F, Taheri S, Chen YF, Adab P, Thomas GN. Effect of obstructive sleep apnoea on diabetic retinopathy and maculopathy: a systematic review and meta-analysis. *Diabet Med*. 2016;33(2):158-168.
33. Diabetic Retinopathy Clinical Research Network. Protocol M—Effect of diabetes education during retinal ophthalmology visits on diabetes control. Jaeb Center for Health Research Web site. http://publicfiles.jaeb.org/Protocol_M_Presentation_2_24_15_Final.pptx. Accessed April 24, 2019.
34. Bressler SB, Odia I, Glassman AR, et al. Changes in diabetic retinopathy severity when treating diabetic macular edema with ranibizumab: DRCR.net Protocol I 5-year report. *Retina*. 2018;38(10):1896-1904.
35. Staurenghi G, Feltgen N, Arnold JJ, et al; VIVID-DME and VISTA-DME Study Investigators. Impact of baseline Diabetic Retinopathy Severity Scale scores on visual outcomes in the VIVID-DME and VISTA-DME studies. *Br J Ophthalmol*. 2018;102(7):954-958.
36. Elman M, Hill L, Tarnowski K, Haskova Z, Stoilov I. To treat or not to treat: are we sacrificing treatment outcomes by allowing diabetic retinopathy (DR) to enter the proliferative stage? Abstract presented at: 36th Annual Meeting of the American Society of Retina Specialists; July 20-25, 2018; Vancouver, Canada.
37. Jaeb Center for Health Research. Anti-VEGF treatment for prevention of PDR/DME. ClinicalTrials.gov Web site. https://clinicaltrials.gov/ct2/show/NCT02634333. Updated August 24, 2018. Accessed April 29, 2019.
38. Lucentis [package insert]. South San Francisco, CA: Genentech, Inc; 2017.
39. Ratanawongsa N, Karter AJ, Parker MM, et al. Communication and medication refill adherence: the Diabetes Study of Northern California. *JAMA Intern Med*. 2013;173(3):210-218.
40. Mugit MM, Marcellino GR, Gray JC, et al. Pain responses of Pascal 20 ms multi-spot and 100 ms single-spot panretinal photocoagulation: Manchester Pascal Study, MAPASS report 2. *Br J Ophthalmol*. 2010;94(11):1493-1498.
41. Nagpal M, Marlecha S, Nagpal K. Comparison of laser photocoagulation for diabetic retinopathy using 532-nm standard laser versus multispot pattern scan laser. *Retina*. 2010;30(3):452-458.
42. Brucker AJ, Qin H, Antoszyk AN, et al; Diabetic Retinopathy Clinical Research Network. Observational study of the development of diabetic macular edema following panretinal (scatter) photocoagulation given in 1 or 4 sittings. *Arch Ophthalmol*. 2009;127(2):132-140.

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1. A 52-year-old patient with a 10-year history of type 2 diabetes mellitus presents with mild visual impairment. Relevant clinical findings are as follows:
   - HbA1c: 9.0%
   - VA: 20/25 OD, 20/20 OS
   - Non–high-risk NVD OD
   - Severe NPDR OS

   The patient is still working and is highly motivated to resolve ocular diabetes complications. According to the findings from Protocol S, what would be the best treatment for this patient to avoid development of DME and need for vitrectomy?
   a. Observation only
   b. Intensive glucose control
   c. Panretinal photocoagulation
   d. Anti-VEGF injection
   e. b and c
   f. b and d

2. A patient with moderately severe NPDR OD and severe NPDR OS without DME presents for follow-up. According to the findings of the PANORAMA study, what is the approximate probability that this patient will develop PDR or CI-DME in the next year without treatment?
   a. 20%
   b. 30%
   c. 40%
   d. 50%

3. Which of the following anti-VEGF agents has been shown to reduce the likelihood of developing CI-DME by approximately 30% after 1 year of treatment?
   a. Aflibercept
   b. Bevacizumab
   c. Ranibizumab

4. In which clinical scenario do data from the PROTEUS study support combination PRP/ranibizumab treatment over PRP monotherapy?
   a. Moderate NPDR OU
   b. Severe NPDR OD, moderately severe NPDR OS
   c. High-risk PDR OU
   d. Mild PDR OD, severe NPDR OS

5. Analysis of the VIVID and VISTA trials suggests that DR at the _____ stage responds the most robustly to treatment with anti-VEGF therapy.
   a. Mild NPDR
   b. Moderate NPDR
   c. Severe NPDR
   d. PDR

6. The American Academy of Ophthalmology and American Diabetes Association both recommend counseling patients on the following modifiable risk factors for progression of DR:
   a. Glycemic index, blood pressure, and serum lipids
   b. Body mass index, glycemic index, and smoking
   c. Blood pressure, serum lipids, and smoking
   d. Glycemic index, blood pressure, and sleep apnea

7. A 56-year-old truck driver with a 15-year history of type 2 diabetes mellitus whose HbA1c is 11.8% and who has moderate PDR OD and high-risk PDR OS would likely benefit most from treatment with:
   a. PRP monotherapy OU in 4 sittings
   b. Ranibizumab monotherapy OS
   c. Combination PRP/ranibizumab therapy