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CLOSING THE GAP IN DIABETIC RETINOPATHY:

Data From the Latest Studies

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CONTENT SOURCE

This continuing medical education (CME) activity captures content from a roundtable discussion.

ACTIVITY DESCRIPTION

The following program brings together thought leaders in university-based and private-practice settings to discuss this landscape and consider ways for improvement. Panelists discuss best practices in screening and imaging, the timing of follow-up exams, and how recent data can inform management strategies and current treatments.

TARGET AUDIENCE

This certified CME activity is designed for ophthalmologists and retina specialists involved in the treatment and management of patients with retinal disorders.

LEARNING OBJECTIVES

Upon completion of this activity, the participant should be able to:

- **Discuss** the increasing prevalence of diabetes and diabetic retinopathy (DR).
- **Discuss** the clinical findings and classification of DR using existing scales.
- **Determine** the effect of anti-VEGF treatment on the progression of DR.
- **Evaluate** the use of advanced imaging technologies to confirm diagnosis/treatment regimens for those with nonproliferative DR.

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PRETEST QUESTIONS

Please complete prior to accessing the material and submit with Posttest/Activity Evaluation.

1. **PLEASE RATE YOUR CONFIDENCE IN YOUR ABILITY TO APPLY UPDATES IN THE TREATMENT OF DIABETIC RETINOPATHY (DR) AND DIABETIC MACULAR EDEMA (DME) IN THE CLINIC. (BASED ON A SCALE OF 1 TO 5, WITH 1 BEING NOT AT ALL CONFIDENT AND 5 BEING EXTREMELY CONFIDENT).**
   a. 1
   b. 2
   c. 3
   d. 4
   e. 5

2. **PLEASE RATE HOW OFTEN YOU INTEND TO APPLY ADVANCES IN THE MANAGEMENT OF DR AND DME IN THE CLINIC. (BASED ON A SCALE OF 1 TO 5, WITH 1 BEING NEVER AND 5 BEING ALWAYS).**
   a. 1
   b. 2
   c. 3
   d. 4
   e. 5

3. **WHICH PATIENT POPULATION WITH DIABETES IS MOST AT RISK OF PRESENTING WITH SEVERE, UNCONTROLLED SYSTEMIC DISEASE?**
   a. Type 2 diabetics with previously high A1c levels
   b. Type 2 diabetics who have been referred by a primary care physician
   c. Type 1 diabetics who are still in childhood
   d. Type 1 diabetics in their mid- to late-20s

4. **IN 2016, THE WORLD HEALTH ORGANIZATION ESTIMATED THAT THE PREVALENCE OF DIABETES IN ADULTS WORLDWIDE WAS:**
   a. One in 1,000
   b. One in 100
   c. One in 12
   d. One in 4

5. **A PHAKIC PATIENT WITH DR COMPLAINING OF BLURRY VISION HAS NUMEROUS DOT BLOT HEMORRHAGES, CENTER-INVOLVING DME, AND NO NEOVASCULARIZATION. THE PATIENT IS REQUESTING TREATMENT WITH THE BEST VISUAL OUTCOMES. WHAT IS THE MOST APPROPRIATE THERAPY?**
   a. Focal laser photocoagulation
   b. Intravitreal anti-VEGF therapy
   c. Panretinal photocoagulation (PRP)
   d. Observation

6. **THE PANORAMA STUDY EVALUATED PATIENTS WITH MODERATELY SEVERE TO SEVERE NONPROLIFERATIVE DR WHO WERE TREATED WITH AFLIBERCEPT OR SHAM TO ASSESS THE TWO-STEP IMPROVEMENT RATE ON THE DIABETIC RETINOPATHY SEVERITY SCALE. AT 6 MONTHS, WHAT PERCENTAGE OF EYES TREATED WITH AFLIBERCEPT SHOWED A TWO-STEP IMPROVEMENT?**
   a. 6%
   b. 21%
   c. 34%
   d. 58%

7. **_____ IS THE PRIMARY WELL-DESIGNED PHASE 3 PROSPECTIVE TRIAL THAT WE HAVE FOR REFERENCE AMONG TREATMENT-NAÏVE EYES WITH PROLIFERATIVE DR.**
   a. Protocol I
   b. Protocol S
   c. RIDE/RISE
   d. PANORAMA

8. **ACCORDING TO PANORAMA DATA, WHAT PERCENTAGE OF PATIENTS WITH NONPROLIFERATIVE DR DEVELOPED CENTER-INVOLVED DME WITHIN 6 MONTHS?**
   a. 20%
   b. 25%
   c. 30%
   d. 45%

9. **MRS. JONES, A 55-YEAR-OLD WOMAN WITH TYPE 2 DIABETES THAT IS FAIRLY WELL CONTROLLED, PRESENTS IN YOUR CLINIC FOR THE FIRST TIME. AN ANGIOGRAM SHOWS SUBSTANTIAL ISCHEMIA AND PERFUSE LEAKAGE, BUT NO FIBROSIS OR TRACTION. HER VA IS 20/30, AND THERE ARE SIGNS OF CENTER-INVOLVED DME. WHAT WOULD THE PANEL RECOMMEND YOU DO?**
   a. Treat with an anti-VEGF
   b. Treat with PRP
   c. Treat with both an anti-VEGF and PRP within the next month
   d. Observe since her VA is good

10. **REVIEWING A PATIENT'S HISTORICAL A1c DATA CAN INFORM RETINA SPECIALISTS ON ALL BUT _____.**
    a. Patient adherence to treatment
    b. Concern for early worsening of DR if a rapid drop is seen in A1c
    c. Stage of DR
    d. B and C

Closing the Gap in Diabetic Retinopathy:
Data From the Latest Studies

As the incidence of diabetes in the United States increases, so too are cases of diabetic retinopathy (DR) and diabetic macular edema (DME). Because DR is typically asymptomatic until late stage, it is critical that patients with diabetes are properly screened to minimize the risk of disease progression and eventual blindness.[1] Population-based studies indicate that there are an estimated 93 million people with DR, 17 million with proliferative DR (PDR), 21 million with DME, and 28 million with vision-threatening DR,[1] making DR a mammoth, worldwide public health challenge. Treatment—and screening—is often an uphill battle for patients and physicians alike because it often requires frequent, repeated clinical visits. Injection burden, noncompliance, and loss to follow-up continue to be significant challenges in the management of this potentially blinding disease.

The following roundtable brings together thought leaders in university-based and private-practice settings to discuss this landscape and consider ways for improvement. Panelists discuss best practices in screening and imaging, the timing of follow-up exams, and how recent data can inform management strategies and current treatments.

—Charles C. Wykoff, MD, PhD, Moderator

BEST PRACTICES IN SCREENING

Q | CHARLES C. WYKOFF, MD, PHD: In 2016, the World Health Organization estimated that 1 in 12 adults worldwide have diabetes.[2] Given the increasing prevalence of diabetes in the United States and around the world, is the burden of DR and DME increasing?

GEETA A. LALWANI, MD: My practice is located in Colorado, where the prevalence of diabetes is significantly lower than the rest of the country. However, even considering this, I have personally seen an increase of the prevalence of DR in the state over the past 5 years. There are multiple reasons that allow for this observation—not only is the prevalence increasing, but there has been a fairly large population influx into Colorado, and there is increased access to care for the previously underinsured via the Affordable Care Act.

ALEKSANDRA RACHITSKAYA, MD: The other issue is noncompliance in this patient population. They can be noncompliant with their diabetic treatment and noncompliant with their ophthalmology follow-up and ophthalmologic treatment.

YOSHIHIRO YONEKAWA, MD: Primary care physicians have improved their practice of referring their patients with diabetes to ophthalmologists now. Electronic health records (EHRs) often provide physicians with a reminder, and this also ties in with meeting Merit-based Incentive Payment System benchmarks. As part of an integrated health care system, we are seeing earlier direct referrals of patients with diabetes in our practice, likely due to the efforts of primary care.

DEREK KUNIMOTO, MD, JD: In the Phoenix, Arizona, area where I practice, we have a large Hispanic and Native American population. I am seeing more patients with DR at both ends of the disease-severity spectrum. I am seeing more patients with early-stage disease, as well as the patients with severe disease. I agree with Dr. Yonekawa; primary care physicians are pushing their diabetic patients to have a yearly ophthalmology exam to screen for DR. EHRs also make it easier for primary care physicians to identify patients with diabetes who need an eye exam.

DR. RACHITSKAYA: Are you usually the first person to see those patients or did they go through general ophthalmology and optometry?

DR. KUNIMOTO: In the past, I have had mostly referrals from optometrists and other ophthalmologists. But over the last several years, I have seen more direct referrals from primary care physicians and endocrinologists. There has also been an increase in health care insurance companies referring patients and providing incentives to those patients for obtaining diabetic eye exams.

DR. WYKOFF: Dr. Sridhar, you practice at the University of Miami in Florida. Are you directly involved with primary care and endocrinologists' education?

JAYANTH SRIDHAR, MD: The University of Miami has made a big push to identify patients with diabetes who need ophthalmologic screening. We have a very large endocrinology department within the Diabetes Research Institute which now utilizes both a pilot teleretinal screening system as well as automatic referral to ophthalmology or optometry within the EHR. The patient may go straight from a primary care physician or endocrinologist to a retina specialist, such as myself, rather than to one of our comprehensive ophthalmologists or optometrists.

"Many patients in my practice are still seen by a general ophthalmologist or optometrist. However, the call center has a protocol that states that, when a referring physician or patient mentions they have diabetes, the patient is automatically scheduled with a retina specialist. What I favor about the system is that with integrated EHRs, I can always communicate back to the referring doctor. Many times, the primary care physician will acknowledge they received my report, which is helpful. A patient may have well-controlled diabetes, but they may still have very pronounced disease. Therefore, that communication with the primary care physician or endocrinologist is important."

— Aleksandra Rachitskaya, MD

We are seeing more DR because patients are developing type 2 or noninsulin dependent diabetes at a younger age, so the complications of that systemic disorder are presenting earlier. Anecdotally, I have noticed that younger patients who are working fulltime tend to be less likely to come in for DR screening and less likely to pay attention to their health.

DR. KUNIMOTO: Our education initiatives are more focused around direct referral sources such as ophthalmologists and optometrists.

DR. WYKOFF: Dr. Rachitskaya, you practice in a unified health care system. Is diabetic screening a good use of a retina specialist's time? Or do you think the system will evolve to having a general ophthalmologist or optometrist conduct the screenings, so the retina specialist can focus on more detailed management decisions?

DR. RACHITSKAYA: Many patients in my practice are still seen by a general ophthalmologist or optometrist. However, the call center has a protocol that states that, when a referring physician or patient mentions they have diabetes, the patient is automatically scheduled with a retina specialist. What I favor about the system is that with integrated EHRs, I can always communicate back to the referring doctor. Many times, the primary care physician will acknowledge they received my report, which is helpful. A patient may have well-controlled diabetes, but they may still have very pronounced disease. Therefore, that communication with the primary care physician or endocrinologist is important.

DR. LALWANI: When the referring physician receives your feedback, they are much more inclined to directly send you patients in the future, as opposed to sending patients to optometrists first. I do not think the concept of using optometrists and ophthalmologists for screening exams is well-understood.

DR. WYKOFF: Let us consider you are screening a patient with diabetes and they have no DR. Will you continue to follow that patient, or will you refer them to someone else for continued screening?

DR. SRIDHAR: Many patients are resistant to changing providers once I have examined them once. I generally try my best to get them to a primary care optometrist or ophthalmologist for follow-up visits, but at the request of some patients, I will do their annual screening.

DR. RACHITSKAYA: It depends on their needs. Many of my patients with diabetes have no visual complaints, but they do use glasses and contacts, which is not my area of expertise. I explain to patients that I am happy to continue to see them, but that they would be better served seeing a general ophthalmologist or optometrist. The general ophthalmologist can refer them back to me if they notice any issues that require my expertise. That approach works well.

DR. YONEKAWA: I have a similar approach for patients without retinopathy with normal retinas, where I will refer them to comprehensive ophthalmology.

DR. WYKOFF: If you tell a patient that their retina is normal, how do you also communicate that they are at a very real risk of developing a problem in the future?

DR. YONEKAWA: It is definitely a great opportunity for us to educate our patients on the risks associated with DR. For new patients, I usually document the baseline examination with a fundus photograph. I show patients the photograph and the retinal vasculature to explain the pathophysiology of DR and the stages of progression if their diabetes is not well-controlled. We also discuss the importance of yearly dilated fundus exams.

DR. SRIDHAR: I use it as an opportunity for positive reinforcement, too. If I have a patient without DR who has a good A1c or whose good sugar control has been documented, I use that as an opportunity to praise them for taking care of their disease. I explain that they need to continue so their vision stays on track.

DR. WYKOFF: Does anyone routinely mention the word "blindness" or regularly discuss the risk of becoming blind due to DR?

DR. KUNIMOTO: I tend to focus on the positive with my patients. However, if I have a patient with high A1c, I do explain that if left untreated, there is a significant chance they could go blind unless they can improve their disease.[1] There are some subpopulations that I end up treating differently.

DR. RACHITSKAYA: I agree. I look at their hemoglobin A1c (HbA1c) and how well they have controlled it in the past. You may have a patient who is well-controlled now, but who was at an A1c level of 14% before. I explain to those patients that this disease is relentless, and those sugars from 5 years ago can come back and haunt them. Therefore, we need to keep an eye on it, and they need to maintain low A1c levels. Many patients think that once they have achieved a low A1c goal, they are safe from DR progression. But, unfortunately, that is not the case.

DR. SRIDHAR: Unfortunately, there seems to almost be a point of no return with DR. Sometimes patients are confused because they do not understand why they need continued DR treatment if their blood sugar levels are controlled. I explain that the ball is already rolling downhill at that point and the retinopathy still requires ongoing treatment. For people with high A1c, who come in with no retinopathy, I tell them that they do not want to get to that point of no return.

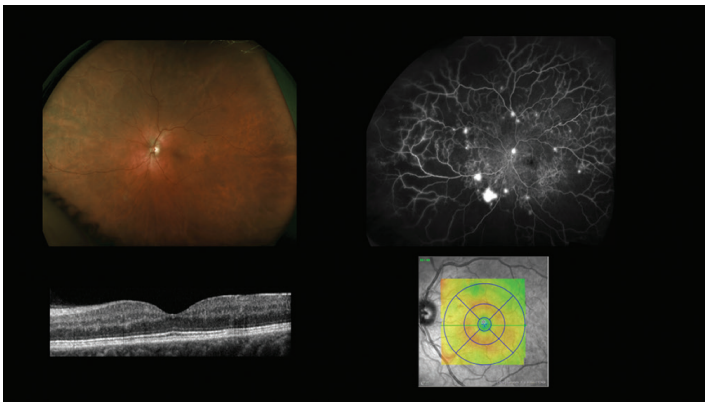
DR. YONEKAWA: The subgroup of patients where this is especially important to stress is for patients with type 1 diabetes. I work in a children's hospital, so I see many of these children relatively early. I explain to them and their parents that they will develop retinopathy—it is just a matter of when and how severe. Establishing this partnership early to help prevent vision loss is key.

DR. KUNIMOTO: Do you find there is a difference between the type 1 and type 2 diabetics in terms of how quickly they develop retinopathy?

DR. YONEKAWA: It is highly variable in the younger population. Children who are diagnosed and plugged into the system early with good support can have great control, but we all have our toughest DR cases of young adults who present with tractional retinal detachment (TRD) on their first visit.

DR. RACHITSKAYA: Many young adults feel invincible. Their disease is well-controlled while they are living with their parents, but then they go to college or leave home and lose track of diabetes control. Then they suddenly come in with severe disease at age 25.

DR. SRIDHAR: There is a financial component, too. In Florida, juvenile diabetic patients can be on their parents' insurance or Medicaid will cover them until age 18. Then these patients go to college or go off their parents' insurance and do not take care of their disease and attend recommended follow-up appointments. They return to us when they have matured in their mid- to late-20s after years without treatment, and, unfortunately, many have advanced retinopathy.



Courtesy of Charles C. Wykoff, MD, PhD.

Figure 1. A 40-year old asymptomatic female with type 1 diabetes mellitus and HbA1c of 8.9%. Fundus photograph shows few scattered intraretinal hemorrhages. SD-OCT foveal cross sectional and associated macular thickness map shows no evidence of DME. Ultrawide-field FA shows relative preservation of retinal perfusion of posterior pole in combination with large, prominent areas of retinal nonperfusion in the mid and far periphery with multifocal zones of neovascularization including neovascularization of the disc and neovascularization elsewhere.

CLINICAL MANAGEMENT OF MILD DR

Q | **DR. WYKOFF:** What type of imaging do you routinely perform in patients with mild DR?

DR. YONEKAWA: In my practice, all patients with DR have baseline documentation with ultrawide-field retinal imaging and OCT on the first visit, regardless of the DR severity, so that any changes in the future can be easily detected.

DR. SRIDHAR: I examine first, and then anyone with retinopathy receives an OCT every visit. I may also obtain photos, but it depends on how the retinopathy is progressing.

DR. RACHITSKAYA: If this is a new patient, I also see them first unless I suspect they have pathology. If they have zero pathology and they refract to 20/20, I do not perform imaging. If I do observe some pathology, I am more likely to obtain an OCT than a fundus photo. I only obtain fundus photos if I need to follow something. I also obtain a fluorescein angiography (FA), but not on all new patients.

DR. LALWANI: I do not typically obtain a photo unless there is some degree of retinopathy present. When there is DR present, I have tended to perform wide-field angiography more often, because I have been surprised that what I am labeling "mild disease" is actually more severe than I previously thought. I also feel that baseline angiography helps to guide patient follow-up more appropriately as well as to educate the patient.

DR. KUNIMOTO: For new patients, I generally do not order testing prior to seeing them. Once the exam is complete, I will obtain imaging in the absence of obvious retinopathy in patients with either poorly controlled blood glucose levels or a long duration of diabetes even with good control. But, most often, I only order imaging if I see

retinopathy. For follow-up, I see them once a year for photos and/or fluorescein. If they are coming in more often than that, I obtain an OCT on every visit.

DR. WYKOFF: I usually examine such patients before obtaining any imaging. If I find no abnormalities, I typically do not obtain any imaging. However, if I find any abnormalities then I typically will obtain an OCT. I typically obtain fundus photographs at the same time as angiography, and I usually only obtain angiography on the patients who I think need treatment or are close to a treatment threshold.

For example, Figure 1 shows a collection of images I obtained on a 40-year-old asymptomatic female with type 1 diabetes mellitus and an HbA1c of 8.9%. The fundus photograph shows a few scattered intraretinal hemorrhages. Spectral domain OCT (SD-OCT) shows no evidence of DME. Ultrawide-field FA shows relative preservation of retinal perfusion of the posterior pole in combination with large, prominent areas of retinal nonperfusion in the mid and far periphery with multifocal zones of neovascularization including neovascularization of the disc and neovascularization elsewhere.

CASE EXAMPLE: ASYMPTOMATIC PATIENT WITH TYPE 2 DIABETES

Q | **DR. WYKOFF:** A 40-year-old female with type 2 diabetes presents in your office with blurry vision in their right eye (Figure 2). The patient has DME and 20/30 and 20/20 VA in their right and left eyes, respectively. You have only examined the patient without any imaging. Would you consider wide-field imaging for this patient?

DR. SRIDHAR: I like wide-field imaging in DR where the peripheral findings are especially important, but I do not obtain it in every patient. If I am concerned about proliferative disease after performing a dilated examination, I prefer to obtain a wide-field FA prior to initiating either panretinal laser or anti-VEGF therapy.

DR. WYKOFF: If the site where wide-field imaging is available is too far for the patient to travel, and you do not have access to wide-field imaging, does that limit what you can do?

DR. KUNIMOTO: Yes, it does in a practical sense. If a patient is 2 hours away from a clinic that does wide-field imaging, I generally will not bring them in for that. However, I can certainly see the merits of doing so. It has a patient-education value, and I have found patients tend to be more compliant after seeing their wide-field results. In a real-world setting, though, having a patient drive a significant distance to get a wide-field image is a significant barrier. I take what images I can get when they are there in front of me and will make my best estimate of their disease severity without having the wide-field testing. Of course, the ideal situation is having access to wide-field imaging in every office.

DR. SRIDHAR: The original grading for disease severity was based on standard color photographs, and, now, we receive much more information with the wide-field imaging. If we are seeing things that are more severe on the angiogram, such as more posterior areas of nonperfusion, does that mean that the disease is more severe in those grades? Or does it mean that those old fundus photographs did not capture that information? Are we over-calling some people's disease in today's practice or were we under-calling it back then? Our scales are not matched up. How do you implement that into your treatment and follow-up practices? Do you base treatment and follow-up on the angiogram?

DR. KUNIMOTO: Yes. We also have a new set of treatments for which we know dose and response. For example, experience tells us that if we give anti-VEGF injections, we are going to see regression of neovascular fronds in the periphery. You bring up a good point, but if I find that the main issue is neovascularization, then I am going to lean toward anti-VEGF therapy. And I will use as my treatment endpoint either regression of neovascularization by clinical observation or by angiography. With expanding indications for anti-VEGF in DR, we are currently in a brave, new world where we have a basic understanding of the mechanistic effects of anti-VEGF on a DR parameter, such as neovascularization regression, but no good consensus of what our clinical endpoints for treatment with anti-VEGF agents are, including when to slow down treatment or when to stop treatment. But our experience will teach us that.

DR. WYKOFF: When I order FA, neovascularization is the most important finding I am looking for. If I have an angiogram that shows PDR, that eye is at a substantially higher risk of vision loss than an eye with nonproliferative DR (NPDR), and I treat will them more aggressively because of that.

DR. LALWANI: What if you observe large areas of capillary dropout? Do you believe that there is a higher risk of the development of neovascularization?

DR. WYKOFF: Maybe. I agree that retinal nonperfusion is an important biomarker for disease severity, and I am fascinated by changes in nonperfusion over time both with and without treatment. But I think we need more prospective data to inform us about what these areas can tell us about risk and disease progression.

DR. LALWANI: I agree. I worry that these patients are at a higher risk for vision loss, and wide-field angiography can correctly identify these patients.

DR. WYKOFF: Certainly.

DR. SRIDHAR: We do not know the quantification of that risk yet. We do not have long-term follow-up data on these wide-field patients.

DR. WYKOFF: In this case, the wide-field photography shows

Courtesy of Charles C. Wykoff, MD, PhD.

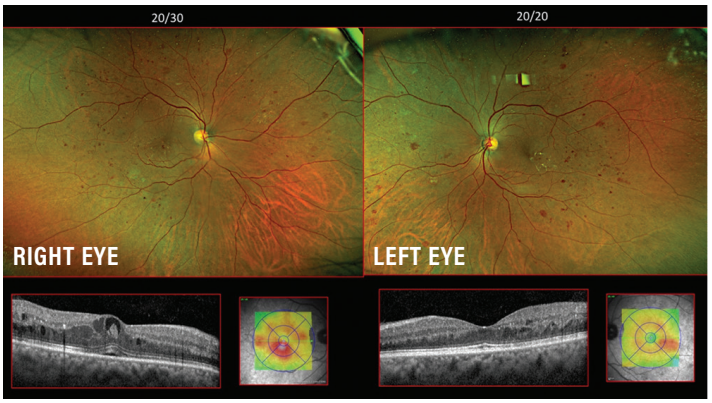


Figure 2. A 40-year-old female with type 2 diabetes notes blurry vision in her right eye for 2 months. VA is 20/30 and 20/20 in her right and left eyes, respectively. SD-OCT reveals center-involved DME in the right eye and noncenter involved DME in the left eye. While no neovascularization was obvious on fundus photography, ultrawide-field FA identified multifocal areas of neovascularization in both eyes.

no obvious proliferative disease, but there are many dot blot hemorrhages and vascular abnormalities, some of which I would call intraretinal microvascular abnormalities. There are no obvious fronds of neovascularization elsewhere or neovascularization at the disc, and there is certainly no preretinal hemorrhage. Since the patient has DME, you are probably going to treat them because they are symptomatic. Does an angiogram change your management approach for this patient?

DR. SRIDHAR: I probably would not obtain an angiogram for this patient yet. I say "yet" because I may choose to do it in the future if the clinical exam changes. But I would start anti-VEGF therapy for this patient in their right eye. I would then follow them clinically, and if an exam warrants suspicion for neovascularization, I would obtain a wide-field angiogram.

DR. WYKOFF: What if you were only able to see neovascularization by obtaining an angiogram, as it was not obvious on examination or photography? Would they, therefore, be at a higher risk at baseline in your mind if you obtained the angiogram and confirmed the presence of proliferative disease? Because if you treat them, you may not see neovascularization on a subsequent angiogram.

DR. SRIDHAR: I will obtain the angiogram if there is a suspicion of neovascularization before I start therapy because I need to know their baseline. In my experience, some patients will stay quiet if you inject an anti-VEGF, and then have a flare up with the return of neovascularization when you stop therapy. It would be nice to know where they are before you start treatment.

DR. WYKOFF: Who would obtain an angiogram in a case like this, in which you are going to treat anyway?

DR. RACHITSKAYA: Since this patient is a 40-year-old type 2 diabetic, they do not have a high risk of rapid progression. If you suspect that there are some intraretinal microvascular abnormalities, I would probably obtain an angiography before I start treatment, because it might influence how often I treat them. Their edema is going to respond to anti-VEGF, and this patient might be 20/20 after a couple of injections.

Then there is the question of injection timing and frequency. I have had patients who were seen at a satellite office, and I inject them because they have active disease. If then I bring them to my main office to obtain FA, the injected eye often looks great. But it probably looks great because I treated it.

DR. SRIDHAR: I try not to give a patient therapy until I get the fluorescein—if I am opting for fluorescein—because you want to maximize the information you are getting from both eyes by doing the test. If you treat with anti-VEGF and then do the fluorescein 2 weeks later, the imaging findings will not be as dramatic as they would have been at baseline.

DR. YONEKAWA: For such patients with confirmed center-involving DME, if transportation is not an issue, I often have them undergo a wide-field FA on their way out and perform the injection 1 to 2 weeks after. This works well for clinic flow, and you have an informative treatment-naïve angiogram. If anything on the angiogram alters management, I call the patient to discuss the findings.

DR. WYKOFF: I did obtain FA on this person. What about the left eye? She is asymptomatic with perfect vision in that left eye, but is there anything on the angiogram that would make you want to treat that eye?

DR. SRIDHAR: It depends on where they are from a compliance standpoint. Is their sugar under control? Do they fully understand the importance of controlling their diabetes? Personally, I have a lower threshold to treat.

DR. YONEKAWA: Our treatment threshold is lower now, where we often do not recommend waiting and watching the low-risk PDR become high-risk. That being said, I do have a handful of patients with low-risk PDR who strongly prefer observation, which is a legitimate option. It does help immensely to show patients the angiogram to discuss the potential risks of progression, and most usually will realize the benefit of treatment. For patients who still decline treatment, we have an agreement that they will adhere to consistent follow-up.

DR. WYKOFF: In most cases of PDR, I recommend treatment. I typically do not wait for classic high-risk characteristics to develop before I recommend treatment. If I do observe an eye with PDR without treatment at the preference of the patient, I am meticulous in my documentation because these eyes can deteriorate quickly.

DR. LALWANI: How do you treat patients with mild

"Many young adults feel invincible. Their disease is well-controlled while they are living with their parents, but then they go to college or leave home and lose track of diabetes control. Then they suddenly come in with severe disease at age 25."

—Aleksandra Rachitskaya, MD

neovascularization? Do you consider monthly anti-VEGF therapy, or do you opt for panretinal photocoagulation (PRP)?

DR. SRIDHAR: To treat patients with mild neovascularization, it depends on two things: the patient's understanding of their disease and the degree of capillary dropout. If they have capillary dropout and everything peripheral to the major vascular arcades is ischemic, then I have a much lower threshold to start a conversation about PRP. But some patients prefer injections to laser treatment, and in those cases I will give them anti-VEGF therapy. When I do anti-VEGF, I do treatment monthly and then take a brief break before repeating the angiogram. If it does not look better and they have neovascularization again, I will revisit the conversation on PRP and strongly recommend it.

DR. WYKOFF: This patient had substantial retinal nonperfusion on angiography. The OCT map looks decent, but there is diffuse leakage and some zones of thickening. There is multifocal neovascularization in both eyes, but no fibrosis or traction. What do you recommend?

DR. KUNIMOTO: Given that the right eye is blurry, with 20/30 VA and center-involved DME, I would treat with anti-VEGF. I think, given the angiography, we need to treat the asymptomatic eye as well. Both eyes have been exposed to the same glycemic levels. The left eye is teetering on a cliff and could worsen at any time. For me, the fluorescein would be very helpful. It would help confirm that there is significant underlying DR, and it would help me educate and convince the patient to initiate injections or laser in both eyes.

DR. WYKOFF: We have discussed using historical data to guide management. I like the concept of considering the trajectory of a patient's A1c. Are there data to drive that? How do you implement this practice?

DR. SRIDHAR: I use past A1c data to explain to patients that even though their sugar is well-controlled now when it was not in the past, they still need treatment with at least anti-VEGF because the ball is already rolling downhill with the presence of proliferative disease. And, even if their sugar control is perfect going forward, they may need laser treatment anyway. However, if they are trending in the right direction, I am more likely to consider a strategy of anti-VEGF injections serially. I will follow them, have the conversation about laser, and then revisit that conversation if their disease does not fully respond after anti-VEGF therapy.

Most of my patients who have proliferative disease do end up receiving laser therapy. I think that is also a consequence of proliferative disease often being the result of poor sugar control, noncompliance, and poor follow-up.

DR. RACHITSKAYA: HbA1c gives me two points of information. One is how compliant the patient is. Second, it tells me if there was a sudden drop in a short time span. I am always careful about patients, especially type 1 diabetics, who have poor control and then were put on a pump or had a dramatic change in management where they go, for example, from an A1c of 13% to 6% in a short period of time.[3] I have seen those patients progress rapidly, and a flat area of neovascularization can become a TRD.

DR. LALWANI: Even though we have more treatments than ever for DR, an individualized assessment of a patient's understanding of the disease is still incredibly important. Do they fully understand their disease and the risk of vision loss? I find it ironic that we are seeing more patients than ever and have less time to spend discussing their management. The decisions we make with them are much more crucial than they have been in the past.

PROTOCOL S DATA

Q | **DR. WYKOFF:** The Diabetic Retinopathy Clinical Research Network's (DRCR.net's) Protocol S study randomized patients with PDR (including patients with either low or high risk) with or without DME to PRP (n = 203) or ranibizumab 0.5 mg (n = 191).[4,5] DRCR.net's phase 3 Protocol S is the main well-designed prospective trial that we have for reference among treatment-naïve eyes with PDR. Protocol S was an elegant trial for many reasons. PRP was given to patients randomized to the laser arm at baseline, and then additional PRP was given if the size or amount of neovascularization increased. If a patient had persistent neovascularization that did not increase, they did not receive additional laser.

The ranibizumab arm was treated fairly aggressively. Patients had monthly dosing through the first 6 months, but treatment could be deferred at the last two visits (weeks 16 and 20) if the neovascularization was resolved. Most patients received six monthly doses, which may not have been necessary. We have learned a lot about this disease process and its responsiveness to anti-VEGF therapy since Protocol S was designed. After the 6-month interval, patients continued to receive monthly injections if the neovascularization improved or worsened, and they stopped

receiving treatment if the neovascularization resolved or was stable following two treatments.

At 2 years, ranibizumab was noninferior to PRP with a mean gain of +2.8 letters compared with +0.2 letters in the PRP arm.[5] While there was a VA benefit to anti-VEGF dosing compared to PRP through 2 years, this benefit was lost by 5 years. Similarly, while there was a marked visual field benefit associated with anti-VEGF dosing compared to PRP through 2 years, much of this benefit was lost by the end of the 5th year. Severe vision loss was uncommon, at 6% in both arms, and at the 5-year final visit average vision was very good in both treatment arms.[4] Finally, there were significant compliance challenges through 5 years in Protocol S data with about 35% of living patients being lost to follow-up.[4]

CLARITY also compared anti-VEGF and PRP treatment, but in this smaller phase 2 trial, the anti-VEGF agent was aflibercept 2 mg (Eylea, Regeneron Pharmaceuticals, Inc.) and 47% of enrolled patients already had prior PRP.[6] Like Protocol S, CLARITY demonstrated that anti-VEGF therapy can be an excellent treatment for PDR.

How can these trials inform our management of PDR patients? How do you use anti-VEGF injections in PDR patients who you are not planning to laser?

DR. YONEKAWA: We all differ in our approaches to PDR. We know anti-VEGF works beautifully thanks to these studies, but at the moment, we have not identified the optimal dosing and follow-up paradigm yet. Protocol S is a little more aggressive than what we can accomplish in the real world. Many of my PDR patients are not able to come in every month for injections. I have had success with having patients come in every 6 to 8 weeks and then quarterly after that if they have a good response. I repeat the fluorescein after 1 year to see where we stand; I may mix in photocoagulation depending on the response and the patient's ability to keep appointments.

DR. SRIDHAR: Protocol S is the only well-designed treatment-naïve head-to-head trial of anti-VEGF and PRP. Because of that, I tell patients that we are going to do monthly injections for at least 6 months, and then we are going to treat on an as-needed basis. If we are going to repeat the angiogram, it has to be at least 8 weeks since their last injection. I want to minimize the impact of the most recent injection to get a sense of where they are. I agree that every 6 to 8 weeks is probably more practical for most patients, followed by quarterly injections. But if we are going to go this route, I try to stick to the study protocol as much as possible. That being said, I treat a very small percentage of my patients with proliferative disease with anti-VEGF monotherapy.

DR. LALWANI: If a patient decides to use anti-VEGF therapy to control their PDR after an informed discussion, I typically start monthly for 3 to 4 months and slowly extend to 6 weeks and then to 8 weeks. I usually repeat the angiogram before extending to the 8-week interval. I have a very low threshold to perform PRP in these patients if neovascularization persists. Similar to Dr. Sridhar, I treat a very small percentage of patients with PDR with anti-VEGF monotherapy.

DR. KUNIMOTO: Our understanding of anti-VEGF therapy with PDR is much more limited than with DME; we simply have more experience treating DME with anti-VEGF injections. With PDR patients, I start the conversation with lessons learned from DME patients. I explain that the disease will take a long time to treat, and they may not see any changes at first. I set them up with the expectation that this could be a 2-year-long process. They may not receive monthly injections for that entire duration, but we will be monitoring their disease.

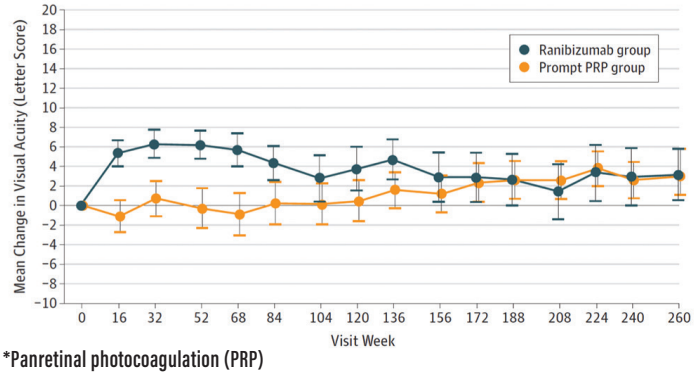
With PDR patients, in the up-front months, I am aggressive about treatment. I start with monthly injections at least for the first 3 months. If the patient has a good response, I will use treat-and-extend therapy to see if that neovascularization returns. As Dr. Sridhar points out, I think it is a good idea to let that anti-VEGF wear off before you capture that angiogram to obtain a good understanding of the true anti-VEGF requirement.

I do want to caution that Protocol S was not really a head-to-head trial of anti-VEGF versus laser because the laser arm also had anti-VEGF treatment if there was DME at presentation, which was 25% of the trial population.[4,5,7] My conclusions are less formed about the laser than they are for anti-VEGF therapy based on this study. In my opinion, there is certainly still a role for PRP in the treatment of PDR. As time goes on, we are going to have a much better understanding of how to treat patients with PDR with anti-VEGF, when to get testing, and when to treat with PRP, but we just do not have that experience and knowledge right now for this patient population.

DR. SRIDHAR: There are some data comparing the visual outcomes of patients who had PRP versus anti-VEGF.[5,8,9] There is some benefit in giving up-front anti-VEGF even if you perform the laser. I struggle with just doing extensions because we do not know what that means for PDR. You could watch them and see when the neovascularization returns, but is the extension for PDR going to be the same as it is for DME? How do I know that when I extend from 6 weeks to 8 weeks that they are not going to end up with a PDR-related complication in that window? Where is the safe zone? We just do not know at this point.

DR. RACHITSKAYA: I am actually very cautious in my selection of patients who I treat with anti-VEGF alone. The majority of patients who I treat with anti-VEGF also have DME. I feel much more comfortable because I am following them pretty closely for their DME, and as I am treating them for DME, I am addressing the PDR with anti-VEGF and laser. The two populations that I usually treat with anti-VEGF alone are patients who have isolated neovascularization of the disc and the periphery looks pretty good, as well as patients who have extremely posterior disease.

We do not know much about this, but I think there are two populations of DR: those with very posterior disease and those with pronounced peripheral disease. Sometimes you get these patients who



*Panretinal photocoagulation (PRP)

Figure 3. Mean Change in VA from baseline over time for the overall cohort in Protocol S.[4]

have great perfusion peripherally, but right by the arcades they have areas of neovascularization. It does not quite make sense to me to ablate the entire retina for the sake of very posterior disease.

DR. WYKOFF: If you are going to use anti-VEGF treatment for PDR, and leave PRP out of the management plan, how do you implement?

DR. RACHITSKAYA: I tend to use treat-and-extend therapy.

DR. WYKOFF: Looking at mean change in VA in Protocol S, much has been made of the curves through the first 2 years (Figure 3). The blue line above the orange line represents that patients treated with anti-VEGF monotherapy; these patients did better visually than patients treated with PRP. But by the end of 5 years, these lines are superimposable. Further, the visual field was stable in the anti-VEGF arm for the first 2 years,[5] whereas the visual field declined substantially among patients treated with PRP. By the end of 5 years, however, the difference between the arms is less dramatic. With the anti-VEGF injections, are we damaging the nerve fiber layer with these repeated treatments over time; or, are we observing the natural course of DR and its impact on visual field? I do not know. How do you interpret the VA and the visual field findings across Protocol S? Does it shift how you manage this disease?

DR. RACHITSKAYA: I am pretty impressed with the VA outcomes. Most protocol S patients are 20/20 and 20/25.[4] Now, we know that VA measurements are not necessarily representative of the vision the patient experiences. Someone with dense PRP and 20/25 VA does not see as well as a patient with no pathology and VA 20/25.

DR. SRIDHAR: My biggest question from the 5-year data is what percent of patients got to 5 years? Only two-thirds of the completing patients were available for follow-up after 5 years,[4] which is shocking because patients who enroll in clinical trials tend to be more compliant, and you have the resources available, such as coordinators, to encourage these patients to follow-up. What happened? What does the other third that were lost to follow-up look like?

In regard to vision, I agree it is impressive. The vision in both groups is really good, which is probably a reflection of including patients who chose to follow-up. As for the visual field, it is possible that it reflects the progressive nature of PDR. Maybe patients are losing field from peripheral ischemia over time regardless of our therapies. Or maybe the anti-VEGF is less effective over time in protecting patients from peripheral nonperfusion. We do not know; we do not have those data.

DR. WYKOFF: I echo both of your points strongly. Having been active in Protocol S as a recruiting physician, the coordinating center for this trial was excellent and relentless. We spent a tremendous amount of effort reaching out to patients including certified letters and even physically going to these patients' homes. Loss to follow-up is a real problem. Imagine what the loss to follow-up would have been if the DRCR.net's efforts to reach these patients were less aggressive.

DR. SRIDHAR: This is the ultimate issue. We have a disease that is associated with either not having access to medical care or not seeking medical care even if it is available.

DR. KUNIMOTO: And a noncompliant population.

DR. RACHITSKAYA: There is a stigma associated with noncompliance.

DR. WYKOFF: I agree. There is a strong stigma. It implies that the patient is at fault, when in many situations, that is not the case as the patient may not be able to return for a visit due to circumstances out of their direct control such as being hospitalized.

DR. SRIDHAR: In medical school, the term we used was nonadherent. For some reason, these patients are not able to adhere to treatment recommendations. Many of these patients are sick. In my practice, some of these patients disappear because they get admitted to the hospital. They need dialysis or they have kidney transplants. These are all real issues in this patient population.

DR. LALWANI: Part of the problem is these patients do not fully understand their disease and its risk of progression. When they have very good vision, they do not understand why they still need to be treated with anti-VEGF injections and followed closely.

DR. WYKOFF: Protocol S also gives us insight into the durability of PRP. I find it fascinating that one common interpretation of the data is that PRP was not that durable. My reading is the opposite, in that nearly half of the population (49%) required only one PRP treatment through 5 years. Approximately 15% of the PRP arm received additional PRP in years 3 through 5.[4] In comparison, 85% of patients in the anti-VEGF arm needed additional injections in years 3 through 5.[4] Now, as you all point out, 58% of the laser arm actually received anti-VEGF injections, so it is difficult to make a clean comparison.

Looking at the median number of visits, the PRP arm had 21 visits over 5 years versus 43 visits over 5 years in the anti-VEGF arm. We know PDR patients have difficulty coming in for appointments. How do you put these data in the context of patient care?

"Part of the problem is these patients do not fully understand their disease and its risk of progression. When they have very good vision, they do not understand why they still need to be treated with anti-VEGF injections and followed closely."

—Geeta A. Lalwani, MD

DR. SRIDHAR: The most interesting extrapolation from this is the "what if?" What if you have therapy that will last longer? If you have anti-VEGF or similar therapy that lasted 2 years, then that is a huge relief from the appointment burden. It is a huge issue. That is why, in the real-world, you have to have an up-front conversation about the long-term investment in their health. You have to explain to patients that this is something we are going to be treating for a long time without any obvious, tangible benefit to that patient for some time.

DR. KUNIMOTO: Based on our current knowledge, I look at PRP as an adjunctive therapy that reduces treatment burden. Just like we look to longer duration anti-VEGF agents to reduce treatment burden of injections, I think there is definitely a role for PRP in reducing injection treatment burden. This statement is also worth reflecting over, as we now view anti-VEGF as a first line therapy in the treatment of PDR, supplanting PRP. I think there is definitely a role for PRP in reducing burden. Long-term Protocol S data showed that you may have better vision with anti-VEGF up front for a few years, but in the end the disease is going to take its toll regardless. To me, the question is if the treatment burden decrease is worth those 2 or 3 years of better-quality vision. That is a discussion we should have with the patient because the treatment should be based on their personal preferences. What is more valuable to them? A few of years of better vision and more frequent visits or stable vision with less frequent visits and treatment?

DR. LALWANI: I favor the Protocol S trial to the CLARITY study because it reflects our practical management of patients in the clinic-combination treatment versus PRP or anti-VEGF alone. The reality is these patients receive an individualized treatment regimen based on their specific clinical findings, history of diabetic control, and the physician's assessment of their treatment compliance.

CASE EXAMPLE REVISITED

Q | **DR. WYKOFF:** To return to our second case example, what do you do with the DME patient with blurry vision in their right eye but who is asymptomatic in their left eye? How are you going to tell this patient you are going to treat their asymptomatic eye?

DR. SRIDHAR: I would tell them that we have done the testing and the exam, and, added together, they are at a high risk for complications in the left eye even though it is currently asymptomatic with good vision. This patient has a few different options. First, I explain that ongoing blood sugar and blood pressure control will be critical. Second, we can do one of four things for their PDR: observation, anti-VEGF injections, PRP, and surgery.

Now, even though surgery is a last resort, I bring it up during this conversation because most patients do not want to have eye surgery. I want them to know it is on the horizon if we do not initiate therapy and they progress or if they become nonadherent with therapy and their disease progresses. That also gets the patient thinking about the other treatment options I have described.

My typical recommendation is up-front anti-VEGF and some form of minimal laser treatment. I would also consider doing PRP in both eyes. My final recommendation would be combination treatment in both eyes: anti-VEGF injections with a PRP in the right eye and up-front anti-VEGF followed by PRP for the left eye.

DR. RACHITSKAYA: We, as ophthalmologists, are lucky in that we have images to show patients that clearly illustrate their disease; physicians in other subspecialties are discussing disease states that patients cannot visualize. I often show patients what normal imaging looks like for easy comparison. OCT and FA allow the patient to easily see the differences between normal and diseased eyes and comprehend what we are dealing with.

For this case, I would also do combination therapy. I would not do PRP on the first visit. I would inject both eyes. I tell patients with PDR that this will be a long-term relationship because you want to get their buy-in. I tell them that we are going to become friends.

DR. YONEKAWA: Personally, for this particular patient I would start with anti-VEGF monotherapy in the right eye to treat both the DME and PDR. When I have established buy-in from the patient about the benefit of anti-VEGF treatment after one or two injections, I would move to bilateral injections. I would then follow-up with a fluorescein 1 year later and see where things stand.

DR. KUNIMOTO: In this case, I would treat both eyes with up-front anti-VEGF because I know what will happen to the left eye eventually. I would also plan on doing laser at some point in both eyes, but probably that would be 3 to 6 months down the road, after the injections are on board.

DR. YONEKAWA: What if at 6 months there is no neovascularization whatsoever?

DR. KUNIMOTO: In that case, I would be looking at compliance as the deciding factor. If I thought that they would dependably return

"To treat patients with mild neovascularization, it depends on two things: the patient's understanding of their disease and the degree of capillary dropout. If they have capillary dropout and everything peripheral to the major vascular arcades is ischemic, then I have a much lower threshold to start a conversation about PRP. But some patients prefer injections to laser treatment, and in those cases I will give them anti-VEGF therapy. When I do anti-VEGF, I do treatment monthly and then take a brief break before repeating the angiogram. If it doesn not look better and they have neovascularization again, I will revisit the conversation on PRP and strongly recommend it."

— Jayanth Sridhar, MD

for assessment with FA, then I would hold off on the PRP. My treatment plan for this patient would be staggered, starting with anti-VEGF monotherapy and adding in the laser later.

DR. LALWANI: I would not start treating the left eye yet either. This patient will most likely return for follow-up of the right eye. Therefore, you have the ability to follow the left eye at that time. Of course, there are other factors to consider as well, such as compliance and history of the diabetic control. Anti-VEGFs will cause disease regression. But, as we have all mentioned repeatedly, long-term compliance is crucial.

DR. WYKOFF: How do you handle issues such as "preauthorization?" In my area, many insurance providers are not allowing same-day treatment. In Houston, Texas, there are plans, such as Blue Cross Blue Shield, that have up to a 2-week window where patients cannot get coverage for pharmaceutical treatment. However, you can laser the patient immediately. Would anyone offer laser treatment to this patient on the first day because medication is not available due to insurance coverage?

DR. SRIDHAR: This patient is not an emergency. The disease has been going on for a long time and has resulted in years of accumulated damage. There is no rush to do laser today, so I would wait for the preauthorization to come in and then perform anti-VEGF. I usually stagger treatment. I would probably perform the laser 2 weeks after the first or second injection.

DR. LALWANI: In this case, the presence of DME in the right eye is impacting their vision. This patient is likely to come back. However, if both eyes were asymptomatic, the patient would be less likely to return for treatment. In that case, I would document the evidence to perform laser and explain to the patient the high risk of blindness with poor follow-up.

MANAGING NPDR WITHOUT DME

Q | **DR. WYKOFF:** Let us discuss patients with NPDR without DME. We know eyes that are level 47 and 53 on the Diabetic Retinopathy Severity Scale (DRSS) cumulatively have a substantial rate of progression to PDR.[10,11] They also are at a high risk of developing DME. But these patients are often asymptomatic with good vision. How do you address and treat this population?

DR. LALWANI: This is the population that is standing at the cliff, and you actually have an opportunity to pull them away from the ledge with anti-VEGF therapy. I would treat, but you first must make sure these patients understand the disease process. The risk of progression from severe NDR to PDR is very high. Numerous clinical trials including the retrospective analysis of RIDE/RISE as well as PANORAMA have demonstrated a high percentage of two-step regression with anti VEGF therapy. However, as has been mentioned, patient understanding is crucial.[11]

DR. SRIDHAR: This population is tricky because if you are going to treat them, you have to have a conversation about that investment in the long term, just as you would have with a PDR patient. These patients are asymptomatic, and many of them will have a negative experience with injections because they are uncomfortable. They may decide that they do not want additional injections and will not return until they start to have complications.

DR. LALWANI: I agree with you. I would not treat these patients at the first visit. I would wait to treat until I have developed a relationship with them, which will help with compliance. After the first appointment, I would want them back in 3 months, but I would get them thinking about anti-VEGF treatment. I would treat a patient with NPDR without DME, but I would want their buy-in first.

DR. SRIDHAR: I would also want to get patient buy-in, but I would watch and wait to see how compliant they are with routine appointments before starting treatment. If they are coming back for their 3- or 4-month follow-up and they have early PDR or some neovascularization they did not have before, then I would start treatment. But either way, if they are noncompliant, they are noncompliant. One or two anti-VEGF injections will not give you a long-term durability effect.

DR. YONEKAWA: I would watch and wait but provide the option of treatment. I would show these patients their angiogram, which I would order in these cases, and discuss with them the severity of their disease. If the retinopathy is severe and there is diffuse leakage with broad areas of nonperfusion, I may consider PRP as well. I would like to get to know the patient before embarking on what is currently controversial treatment. I would have them return in 3 months and then discuss their treatment options and risks for progression again.

DR. SRIDHAR: Let us say they return in 4 months, and their disease looks exactly the same. You still want to treat them, they say no, and they return 4 months later, and you have the same conversation again. My point is, this is where the patient will reveal themselves. If they are not progressing in the time you are watching them, then why are you pushing the treatment, especially if we do not have long-acting therapy?

The DRSS is interesting, but I think it is all for future extrapolation. If we had long-acting therapy, then it would matter more.

DR. KUNIMOTO: The data to me are very compelling for the benefit of treatment at levels 47 and 53 of the DRSS,[10,11] but this is not only about medical evidence; it is about the psychology of the patient. I would not treat the vast majority of patients with NPDR without DME. Instead, I would have a conversation about their disease and follow them.

However, there is a subgroup of patients who I think could be motivated to receive treatment. Those patients tend to have had a major health issue in the past that they did not tend to, which turned out badly for them. It is interesting; we have medical treatment, but yet we have to convince the patient of its value. This is a new frontier for us, and that is part of the challenge that we have. Over time, we are going to improve at convincing patients that treatment is both needed and beneficial at these earlier stages of NPDR, but in 2018 we are not there yet.

DR. WYKOFF: PANORAMA is a phase 3 randomized, double-masked trial examining the safety and efficacy of intravitreal aflibercept in patients with moderately severe to severe NPDR in three treatment arms: sham (n = 133), aflibercept every 16 weeks after loading doses (n = 135), and aflibercept every 8 weeks after loading doses (n = 134).[11] There are two primary endpoints at 6 months and 1 year looking at the two-step improvement rate on the DRSS.

The two treatment arms through month 6 were equivalent, and there was no indication that one extra intravitreal injection made a difference. Fifty-eight percent of eyes improved two steps with aflibercept versus 6% with sham. A quarter of patients (43%) had a two-step improvement after just two treatments, which is fairly impressive if compared to outcomes from RIDE/RISE and VISTA/VIVID.[12-16]

These eyes are remarkably sensitive to the benefit of anti-VEGF dosing. A clinically meaningful percentage of these patients appear to not need aggressive monthly loading doses. What if you just started with quarterly dosing? I look forward to the development and refinement of algorithms that will be able to help prognosticate, based on imaging, which eyes may benefit from early anti-VEGF intervention.

DR. SRIDHAR: The algorithm is important, but what is our endpoint considering the drugs and the durability we have currently, the disease process, and the lifespan of our younger population? Further, what is our endpoint for stopping therapy? Maybe it is that you stop therapy and watch them and start therapy again if they progress.

DR. WYKOFF: What if our endpoint was just a change in DRSS score? We, as a field, are struggling for an endpoint because we do not have the equivalent to OCT-based changes observed with DME treatment. While change in DRSS score is the primary endpoint used in PANORAMA, we cannot measure DRSS score routinely or efficiently in clinic today, which is a problem. I look forward to software algorithms that can determine the DRSS score from a fundus photograph in real-time.

DR. SRIDHAR: In the future this will be helpful because we will be able to quantify DRSS better, and we are going to have drugs that last longer.

DR. WYKOFF: In PANORAMA,[11] one out of four sham-teated patients developed PDR or center-involved DME within 6 months. Is that clinically meaningful?

DR. YONEKAWA: It is going to be more at 1 year.

DR. LALWANI: What do you do with this severe NPDR and no DME?

DR. WYKOFF: These patients appear to be within a sweet spot to treat. This data are consistent with secondary analyses from RISE/RIDE where a substantially greater proportion of such eyes experienced two-step DRSS improvements compared to eyes with PDR.[16,17] Ideally, I want to treat these patients before they progress to PDR. But the panel is correct in that an asymptomatic 20/20 eye is challenging to treat. These injections are not without risk, and we need buy-in from patients.

DR. SRIDHAR: Then to manage these patients, you get fundus photos at baseline and at 6 months, so they can see the tangible difference. For me, the other question is what if they are monocular because their other eye went blind from diabetes? Do you treat the symptomatic eye, or do you not want to touch it because they are 20/20 currently and you are concerned about potential complications?

DR. LALWANI: The risk of endophthalmitis is roughly 1 in every 2,000 patients.[18] The risk of progression from severe NPDR to PDR is much higher than that. The question is, is there an impact on vision if we wait until the development of PDR. I do not think that we have enough data to determine this yet.

DR. SRIDHAR: We know that with DME, if you wait, the patient will lose some vision. But we do not have data showing that in this patient population. Now, obviously if you get a neovascular complication or a TRD, it is a different situation.

NOVEL THERAPIES IN THE PIPELINE

Q | **DR. WYKOFF:** There is exciting ongoing research in our field with great potential to improve treatment burden and outcomes. Modulation of the Tie-2 and Angiopoietin-2(Ang2) pathway appears promising. Faricimab (formerly RG7716, Genentech, Inc.), blocks both VEGF-A and Ang2 and is in phase 3 studies in DME; AKB-9778 (Aerpio Pharmaceuticals) is a medication in phase 2 given by subcutaneous injection that also serves to activate Tie-2. A next-generation anti-VEGF molecule, brolucizumab (Alcon) is now in a phase 3 DME trial. There are also novel drug delivery approaches, such the port delivery system for ranibizumab (Genentech, Inc.), and suprachoroidal delivery of steroids in combination with anti-VEGF intravitreal injections (Clearside Biomedical, Inc.) in phase 3 and 2 respectively.

What of these options do you think will make a difference? What will impact our field the most in the next 5 years?

DR. SRIDHAR: Drug delivery, whether it is a port system or an injectable, is the most important development from a global perspective because drug delivery hopefully brings sustained release. No matter what agent we think will work, we want it to last a long time.

DR. WYKOFF: Do you think patients are willing to undergo a surgical procedure to implant a sustained-release device?

DR. SRIDHAR: I do, but the ideal system would be something that does not require surgery. The ideal would be a sustained-release injectable or a pill that you take once and lasts a year. But, regardless, the development that would make the biggest difference is something that lasts a long time. All the data indicate that with persistent treatment, there is improvement on the DRSS score.

Otherwise, the Ang2 data look promising.[19] Having a different target and targeting different pathways will theoretically and practically be very helpful.

DR. LALWANI: It would be interesting to have a treatment that may act earlier in the DR cascade before capillary drop out and vascular changes.

DR. RACHITSKAYA: I would like to see more guidance for us in how to actually assess these patients with wide-field imaging and algorithms that help us establish the levels of nonperfusion and neovascularization. We are lacking a standardized protocol for wide-field imaging. I would also like to see less invasive testing. Patients do not like to repeat fluorescein. It is an invasive test that has potential risks.

DR. KUNIMOTO: As I consider what is on the horizon, whether it be next-generation anti-VEGF, dual-specific molecules, or drug-delivery systems that allow for sustained treatment, none of these treatments are cures. These are incremental improvements. Still, I think it is a promising time for the field in that there is so much research going on.

As these next therapies get approved, we will have more discussions about combination therapies with first- or second-generation anti-VEGF and a dual-specific molecule. How are we going to do that? Are we going to do that every 3 months? Are we going to use a loading dose? There is going to be so many permutations and variations on this that it will take many discussions just like this one to come to any conclusions. But, to me, it is an opportunity and it is promising.

DR. WYKOFF: I discuss things in the pipeline to my patients as I think it is valuable to give them hope. I explain that it may seem like a significant treatment burden now, but I believe that in the not too distant future, we are going to have options with improved durability and efficacy.

DR. SRIDHAR: Twenty years ago, your options were laser, steroids, and vitrectomy. Now we have so many more options, and it is only going to grow.

DR. LALWANI: Our field is becoming similar to the field of oncology with personalized medicine. Treatments are tailored to the patient based on predictable algorithm data.

DR. WYKOFF: Thank you all for your thoughts on the management of DR and DME. ■

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CLOSING THE GAP IN DIABETIC RETINOPATHY:
Data From the Latest Studies

Release Date: January 2019
Expiration Date: March 2020

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City _____ State _____ Zip _____

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DEMOGRAPHIC INFORMATION

Profession
___ MD/DO
___ NP
___ Nurse/APN
___ PA
___ Other

Years in Practice
___ > 20
___ 11-20
___ 6-10
___ 1-5
___ <1

Patients Seen Per Week (with the disease targeted in this educational activity)
___ 0
___ 1-20
___ 21-40
___ 41-55
___ 56-75
___ 75+

Region
___ Northeast
___ Northwest
___ Midwest
___ Southeast
___ Southwest

Setting
___ Solo Practice
___ Community Hospital
___ Government or VA
___ Group Practice
___ Other
___ I do not actively practice

Models of Care
___ Fee for Service
___ ACO
___ Patient-Centered Medical Home
___ Capitation
___ Bundled Payments
___ Other

LEARNING OBJECTIVES

DID THE PROGRAM MEET THE FOLLOWING EDUCATIONAL OBJECTIVES?	AGREE	NEUTRAL	DISAGREE
Discuss the increasing prevalence of diabetes and diabetic retinopathy (DR).	_____	_____	_____
Discuss the clinical findings and classification of DR using existing scales.	_____	_____	_____
Determine the effect of anti-VEGF treatment on the progression of DR.	_____	_____	_____
Evaluate the use of advanced imaging technologies to confirm diagnosis/treatment regimens for those with nonproliferative DR.	_____	_____	_____

POSTTEST QUESTIONS

1. **PLEASE RATE YOUR CONFIDENCE IN YOUR ABILITY TO APPLY UPDATES IN THE TREATMENT OF DIABETIC RETINOPATHY (DR) AND DIABETIC MACULAR EDEMA (DME) IN THE CLINIC BASED ON THIS ACTIVITY. (BASED ON A SCALE OF 1 TO 5, WITH 1 BEING NOT AT ALL CONFIDENT AND 5 BEING EXTREMELY CONFIDENT).**
   a. 1
   b. 2
   c. 3
   d. 4
   e. 5

2. **PLEASE RATE HOW OFTEN YOU INTEND TO APPLY ADVANCES IN THE MANAGEMENT OF DR AND DME IN THE CLINIC BASED ON THIS ACTIVITY. (BASED ON A SCALE OF 1 TO 5, WITH 1 BEING NEVER AND 5 BEING ALWAYS).**
   a. 1
   b. 2
   c. 3
   d. 4
   e. 5

3. **WHICH PATIENT POPULATION WITH DIABETES IS MOST AT RISK OF PRESENTING WITH SEVERE, UNCONTROLLED SYSTEMIC DISEASE?**
   a. Type 2 diabetics with previously high A1c levels
   b. Type 2 diabetics who have been referred by a primary care physician
   c. Type 1 diabetics who are still in childhood
   d. Type 1 diabetics in their mid- to late-20s

4. **IN 2016, THE WORLD HEALTH ORGANIZATION ESTIMATED THAT THE PREVALENCE OF DIABETES IN ADULTS WORLDWIDE WAS:**
   a. One in 1,000
   b. One in 100
   c. One in 12
   d. One in 4

5. **A PHAKIC PATIENT WITH DR COMPLAINING OF BLURRY VISION HAS NUMEROUS DOT BLOT HEMORRHAGES, CENTER-INVOLVING DME, AND NO NEOVASCULARIZATION. THE PATIENT IS REQUESTING TREATMENT WITH THE BEST VISUAL OUTCOMES. WHAT IS THE MOST APPROPRIATE THERAPY?**
   a. Focal laser photocoagulation
   b. Intravitreal anti-VEGF therapy
   c. Panretinal photocoagulation (PRP)
   d. Observation

6. **THE PANORAMA STUDY EVALUATED PATIENTS WITH MODERATELY SEVERE TO SEVERE NONPROLIFERATIVE DR WHO WERE TREATED WITH AFLIBERCEPT OR SHAM TO ASSESS THE TWO-STEP IMPROVEMENT RATE ON THE DIABETIC RETINOPATHY SEVERITY SCALE. AT 6 MONTHS, WHAT PERCENTAGE OF EYES TREATED WITH AFLIBERCEPT SHOWED A TWO-STEP IMPROVEMENT?**
   a. 6%
   b. 21%
   c. 34%
   d. 58%

7. **_____ IS THE PRIMARY WELL-DESIGNED PHASE 3 PROSPECTIVE TRIAL THAT WE HAVE FOR REFERENCE AMONG TREATMENT-NAÏVE EYES WITH PROLIFERATIVE DR.**
   a. Protocol I
   b. Protocol S
   c. RIDE/RISE
   d. PANORAMA

8. **ACCORDING TO PANORAMA DATA, WHAT PERCENTAGE OF PATIENTS WITH NONPROLIFERATIVE DR DEVELOPED CENTER-INVOLVED DME WITHIN 6 MONTHS?**
   a. 20%
   b. 25%
   c. 30%
   d. 45%

9. **MRS. JONES, A 55-YEAR-OLD WOMAN WITH TYPE 2 DIABETES THAT IS FAIRLY WELL CONTROLLED, PRESENTS IN YOUR CLINIC FOR THE FIRST TIME. AN ANGIOGRAM SHOWS SUBSTANTIAL ISCHEMIA AND PERFUSE LEAKAGE, BUT NO FIBROSIS OR TRACTION. HER VA IS 20/30, AND THERE ARE SIGNS OF CENTER-INVOLVED DME. WHAT WOULD THE PANEL RECOMMEND YOU DO?**
   a. Treat with an anti-VEGF
   b. Treat with PRP
   c. Treat with both an anti-VEGF and PRP within the next month
   d. Observe since her VA is good

10. **REVIEWING A PATIENT'S HISTORICAL A1c DATA CAN INFORM RETINA SPECIALISTS ON ALL BUT _____.**
    a. Patient adherence to treatment
    b. Concern for early worsening of DR if a rapid drop is seen in A1c
    c. Stage of DR
    d. B and C

ACTIVITY EVALUATION/SATISFACTION MEASURES

Your responses to the questions below will help us evaluate this continuing medical education (CME) activity. They will provide us with evidence that improvements were made in patient care as a result of this activity as required by the Accreditation Council for Continuing Medical Education (ACCME).

Rate your knowledge/skill level prior to participating in this course: 5 = High, 1 = Low _____

Rate your knowledge/skill level after participating in this course: 5 = High, 1 = Low _____

This activity improved my competence in managing patients with this disease/condition/symptom. _____ Yes _____ No

I plan to make changes to my practice based on this activity. _____ Yes _____ No

Please identify any barriers to change (check all that apply):

_____ Cost
_____ Lack of consensus or professional guidelines
_____ Lack of administrative support
_____ Lack of experience
_____ Lack of time to assess/counsel patients
_____ Lack of opportunity (patients)
_____ Reimbursement/insurance issues
_____ Lack of resources (equipment)
_____ Patient compliance issues
_____ No barriers
Other. Please specify: _____
_____
_____
_____

The design of the program was effective for the content conveyed. ___ Yes ___ No

The content supported the identified learning objectives. ___ Yes ___ No

The content was free of commercial bias. ___ Yes ___ No

The content was relative to your practice. ___ Yes ___ No

The faculty was effective. ___ Yes ___ No

You were satisfied overall with the activity. ___ Yes ___ No

Would you recommend this program to your colleagues? ___ Yes ___ No

Please check the Core Competencies (as defined by the Accreditation Council for Graduate Medical Education) that were enhanced through your participation in this activity:

_____ Patient Care

_____ Practice-Based Learning and Improvement

_____ Professionalism

_____ Medical Knowledge

_____ Interpersonal and Communication Skills

_____ System-Based Practice

Additional comments:

_____

_____ I certify that I have participated in this entire activity.

This information will help evaluate this CME activity; may we contact you by email in 3 months to see if you have made this change? If so, please provide your email address below.

_____


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