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What You Need to Know About Strategies for Treating NPDR

Announcer:
Welcome to CME on ReachMD. This activity is part of a special series titled "The Mission Continues: Saving Sight Through Early Referral, Diagnosis and Treatment for DR/DME." and is provided in partnership with the National Eye Institute of the National Institutes of Health, of the U.S. Department of Health and Human Services, along with Prova Education. It's supported by an independent educational grant from Regeneron Pharmaceuticals. To view this activity or others in the series, please visit EyeHealthAcademy.org/SaveSight

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Dr. Khurana:
There's been a lot of talk in the retina community about the results from Protocol W and the PANORAMA clinical trials. But what do these data really mean for our patients with nonproliferative diabetic retinopathy [NPDR], and how should we be interpreting these results in relation to proliferative diabetic retinopathy [PDR]?

This is CME on ReachMD. I am Dr. Rahul Khurana, and joining me today for today's discussion is Dr. Jennifer Sun. Welcome to the program.

Dr. Sun:
Thank you so much, Rahul. It's great to be here.

Dr. Khurana:
Well, Jennifer, first let's quickly review the main findings from Protocol W and PANORAMA. Jennifer, can you remind us or summarize the data there?

Dr. Sun:
Absolutely. So both PANORAMA and Protocol W enrolled patients that had moderate to severe nonproliferative diabetic retinopathy, so none of these patients had retinal neovascularization at the start of the study. And both these studies randomized patients to either treatment with aflibercept or to sham injection. And both these studies – I think the results were quite consistent with each other. They both showed decreases in the rates of vision-threatening complications, such as proliferative diabetic retinopathy or center-involved DME, over the course of 2 years. In Protocol W, we saw approximately 3 times higher risk of developing PDR or center-involved DME in the sham versus the aflibercept-treated eyes, and in PANORAMA, the results were very similar. I think the other thing that we saw in these studies, and in fact, with the primary outcome in PANORAMA, was the fact that DR severity seemed to improve to greater extent in patients treated with aflibercept versus those treated with sham.

So I'll stop and just ask the audience, based on these data, how would you respond to the following question?

Dr. Khurana:
Ideally, we want to stop diabetic retinopathy [DR] from progressing to vision-threating proliferative diabetic retinopathy. A recent

retrospective analysis of the IRIS [Intelligent Research in Sight] Clinical Registry, performed by Dr. Charlie Wykoff, myself, Quan Nguyen, and others, looked at patients who were newly diagnosed with diabetes with good visual acuity and looked at which one of these patients actually developed sustained vision loss. This was defined as visual acuity worse than 20/200 over a period of 3 months, and this analysis involved over 50,000 patients. And what we found was that patients with moderate and severe nonproliferative diabetic retinopathy had a nearly two- to threefold higher rate of developing sustained vision loss.

Well, it really begs the question, though, will the treatment of moderate to severe nonproliferative diabetic retinopathy with anti-VEGF [vascular endothelial growth factor] therapy, specifically, improve patient outcomes in the real world? What do you think, Jennifer?

Dr. Sun:
I think this is a fabulous question, Rahul, and this is really the crux of the matter, I think, for us as clinicians and for our patients. Does early treatment with anti-VEGF improve longer-term visual outcomes or patient outcomes for them? So I think there are a few things to think about in assessing the sort of risk-benefit ratio of early treatment. We've already talked about the fact that clearly there are some advantages with early anti-VEGF treatment. We see fewer rates of development of advanced vision-threatening complications. We see regression of diabetic retinopathy in ways that are very gratifying when you look at the fundus photographs. But I think there are a few other considerations. Most importantly, I think we need to understand, does early anti-VEGF treatment for nonproliferative retinopathy give our patients better long-term visual outcomes? This is something that has been difficult to answer at this time.

Two other things that I think are important to understand are what is the burden of treatment when you start treating early versus potential improvements in quality of life? The numbers of injections may be slightly fewer if you start early, but not very, very different from what we're seeing if you just start once these complications develop. And I think what we also need to know is, can we stop these injections over the long term? The quality of life study is important and really lacking. We have quality of life studies that show that if you treat diabetic macular edema [DME], certainly people's quality of life improves, and that's wonderful, but we don't have good studies in this patient population of nonproliferative retinopathy without DME at this time.

And then finally, the last question I'd raise is this sort of question about underlying disease modification. That is, what's the future risk of retinopathy worsening in these eyes, particularly if you stop anti-VEGF treatment? We definitely see that the ETDRS [Early Treatment Diabetic Retinopathy Study] DR severity levels improve in many of these patients, and so the hemorrhage and microaneurysms improve. The IRMA [intraretinal microvascular abnormalities] look better. We think right now that anti-VEGF treatment may slow the worsening nonperfusion but may not necessarily bring back vessels that have already been compromised. And I think that's going to be an important issue for us as we look in future studies to understand, again, what the long-term potential is for being able to get patients off these medications.

Dr. Khurana:
Let's put this new information into context and consider a couple patient cases. The first case I want to present to you, Jennifer, is a 64-year-old gentleman with type 2 diabetes for approximately 10 years and a history of hypertension who's got a hemoglobin A1C of 8.6 and a visual acuity of 20/20 in both eyes. Dilated fundoscopic exam of the right eye shows a presence of intraretinal hemorrhages present in all 4 quadrants, the presence of numerous cotton wool spots seen superiorly. Dilated fundoscopic exam of the left eye also shows a fair amount of retinal hemorrhages scattered throughout the periphery and some cotton wool spots seen nasally. Fluorescein angiography shows a presence of nonperfusion in many areas but the absence of any neovascularization with many leaking microaneurysms in the periphery, while the fluorescein angiography of the left eye also shows a presence of numerous microaneurysms in the periphery with areas of nonperfusion with the absence of any neovascularization.

So in the context for this patient, Jennifer, how would you manage this patient, and would you consider treatment with anti-VEGF therapy?

Dr. Sun:
Thanks so much, Rahul. So this is a great case to start with. I think it's important to first recognize that the foundation of management for all our diabetic patients is really the importance of systemic control, and so sitting down with the patient, really talking to him about the importance of trying to get the blood sugars better. He's at an A1C of 8.6, and typically we'd like to see our patients at an A1C of less than 7%. Also managing any high blood pressure and high cholesterol – all these things are going to be really important in optimizing his long-term visual outcomes.

But let's talk about the eye itself. So both of these eyes, with severe nonproliferative disease, I think there are 3 options for management. You could certainly go with anti-VEGF or panretinal photocoagulation [PRP], or you could observe the eye. When we talk about anti-VEGF, we've talked about the Protocol W and the PANORAMA data that clearly show that early treatment in eyes like this will reduce the longer-term rates of proliferative retinopathy and center-involved DME. He is at high risk of – about 50% chance, I think – of developing proliferative retinopathy within the next 1 to 2 years. The early treatment diabetic retinopathy study also suggests

there may be long-term visual benefits, particularly in patients with type 2 diabetes with severe nonproliferative retinopathy, when you treat them early with panretinal photocoagulation. But actually, I think, my probably most likely management at this point would really just be to observe him and follow him closely. Now, I do think there is a very important lesson to make sure that you talk to the patient about – in terms of coming back and being compliant with visits and monitoring him closely to make sure that he doesn't develop more advanced disease that requires treatment down the road.

And so I'll just say that assessing the severity of diabetic retinopathy, especially quickly in a clinic, can be difficult. So to test your skills, please visit the diagnostic activity at EyeHealthAcademy.org/SaveSight to see how your skills measure up.

Dr. Khurana:
Thanks, Jennifer. For those just tuning in, this is CME on ReachMD. I am Dr. Rahul Khurana, and today, Dr. Jennifer Sun and I are discussing the recent data from Protocol W and the PANORAMA clinical trials and what they mean for the clinical management of diabetic retinopathy.

I wanted to present another case. And this is a 44-year-old lady with type 1 diabetes who has a little bit more of a complicated medical history. She's had a history of an amputation done, and she has a more complicated ophthalmic history in the sense that in her left eye, she developed proliferative diabetic retinopathy and a tractional retinal detachment that ultimately required a vitrectomy for repair. And her visual acuity in that left eye is about 20/70, while in her right eye it's 20/20. And we can see from the dilated exam in the right eye, there's intraretinal hemorrhages scattered in all 4 quadrants, and there's some cotton wool spots seen superiorly. There's no macular edema involving the center of the macula. And dilated fundoscopic exam of the left eye shows extensive PRP present, some fibrotic neovascularization scars on the disc and along the superior arcade, and an attached retina.

So in this situation, where you have a patient who's had a complication from PDR in one eye but is seeing well in the other eye, how would you manage this patient? Would you consider anti-VEGF therapy for the right eye?

Dr. Sun:
Yeah, these are challenging patients, and this is a relatively young patient who, you know, hopefully has decades and decades of life ahead of her, and you want the visual function to be pristine throughout the course of those decades.

So this is a patient where I would probably be more aggressive and treat a little earlier than I would in the patient before this. You know, I think, looking at the images of her eyes, the surgeon did a fabulous job, and anatomically the left eye looks beautiful. But as you mentioned, the visual acuity is still down to about 20/70, which means that she's not able to drive, or if she only had the vision in that eye, she might not be able to drive at nighttime and it might limit some of her visual function otherwise. So for the right eye here, you know, you could observe and just wait for additional worsening disease in the right eye. Again, I think counseling about the importance of systemic control, and particularly for this patient, the importance of rigorous follow-up and making sure she's coming back into clinic. This is a patient that I really worry about if they disappear for, you know, 6 months or a year or longer, that they might come in with really advanced disease and irreversible vision loss that we can't treat. So for my younger type 1 patients, by the time I'm ready to treat them, I might often consider starting with anti-VEGF for the reason that it is a nondestructive agent. I think the other consideration would be panretinal photocoagulation, and that would be reasonable for her also. Particularly for somebody if you're at all concerned that there's going to be an issue of compliance, either because they're not coming in or because they can't come in. There are disadvantages to the PRP over anti-VEGF. You know, we see that there is worsening of the visual function in terms of peripheral visual fields over time, but many patients don't notice that in their daily lives, and they do very, very well. So I think that would be reasonable here as well.

Based on what you've just learned from the case discussions, how would you respond to the following question?

Dr. Khurana:
To put it mildly, patients do not like to get intravitreal injections. There's a lot of fear and anxiety around the procedure. My colleague Charlie Wykoff has created a video to share with patients to help them better understand intravitreal injections and what to expect if that's the path they're headed for. It can be found at EyeHealthAcademy.org/SaveSight.

I often tell my patients that the needle we use for the injections is often smaller than a hair. We give multiple levels of anesthesia, so all they feel is a little pressure/pinch, and I find that most of the time, once the procedure is done, they often feel a lot better about it. However, that pre-anxiety can be quite debilitating and very tough and challenging for our patients.

Jennifer, what are your go-to strategies for calming the patient fears regarding potential intravitreal injections?

Dr. Sun:
Oh, first, I just acknowledge the fact that it's very reasonable to feel anxious about injections. You know, I certainly would if I were

sitting in their place. And then, I think, for me, it's really a question of patients, making sure that I've really gone through a good, informed consent and given them the time to ask questions, and realistically, that includes a thorough discussion of potential risks of injections, which are very small but, you know, which are possible and known. I do make sure that they've gotten multiple rounds of numbing drops. I tend to use viscous lidocaine before the injection, particularly before the first one, when they're the most anxious. And then, mostly reassurance.

Dr. Khurana:
As we wrap up here, what are your key takeaways for our audience, Jennifer?

Dr. Sun:
So I think my take-home for patients that have nonproliferative diabetic retinopathy is that it's really important to talk to them about the importance of systemic control. Close follow-up and monitoring is also essential.

I think observation for many of these patients is very appropriate since we don't have clear evidence right now that there's visual acuity benefit from starting early treatment with anti-VEGF. But in selected cases, I think anti-VEGF or PRP both have their places, and I think it's wonderful that we've got these alternatives in management for these patients, particularly the ones that are likely to be at especially high risk for development of proliferative retinopathy or center-involved DME.

Dr. Khurana:
I would say my take-home message is that I think it's wonderful to have another treatment option for our management of nonproliferative and diabetic retinopathy with anti-VEGF therapy. However, there is an old saying: an ounce of prevention is worth a pound of cure. But here, with anti-VEGF therapy, the question is, is a pound of prevention worth a pound of cure, as often the treatments are the same. And I think, as Jennifer has really eloquently said, I think we really need the long-term outcomes, the 4-year results from Protocol W, to really see whether this early intervention with anti-VEGF therapy really leads to a change in visual acuity outcomes. But I do welcome the fact that we have another option, and I think it's important to give our patients those options and help individualize the therapy to them to see what really – we can get their best goals to have them seeing better for the long term.

Well, Jennifer, thank you so much for today's discussion in the management of nonproliferative diabetic retinopathy. It's been great having you here, and we always appreciate your wisdom on the topic.

Dr. Sun:
Oh, thank you so much. It's been my pleasure.

Announcer:
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