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Seeing Eye to Eye: Case Series on Treatment Strategies for Diabetic Retinopathy Mod/Severe NPDR

Announcer: This activity is provided in partnership with the National Eye Institute, of the National Institutes of Health, of the US Department of Health and Human Services. The National Eye Health Education Program of the NEI is acknowledged for its important contributions to this initiative.

Dr. Do: The treatment of nonproliferative diabetic retinopathy in the presence of diabetic macular edema is well established, but what about those patients with severe nonproliferative diabetic retinopathy who do not have macular edema? To find out, we're going to take a look at some new data from the PANORAMA Study, and its treatment implications as part of the Assert-D Strategy to protect our patients' vision. This is CME on Reach MD. I'm Dr. Diana Do from Stanford University, and I'm joined today by two great colleagues, Dr. Peter Kaiser from Cole Eye Institute, and Dr. Charles Wykoff from Retina Houston Consultants. Thank you both for joining me.

Dr. Kaiser: Happy to be here.

Dr. Wykoff: Great to be here with you, Peter.

Dr. Do: Starting with you, Dr. Kaiser, can you share with us the current management of patients with severe nonproliferative diabetic retinopathy and how that has evolved?

Dr. Kaiser: Over the years, how we treat patients with severe nonproliferative diabetic retinopathy has actually changed. In the beginning, we actually had no treatment for it and so we have studies that show what happens when nothing is done to these patients. The largest of these studies was WESDR; in that study, we saw that patients with severe nonproliferative diabetic retinopathy progressed to proliferative diabetic retinopathy in about 12 to 18 months. In fact, when you looked at it, a six-step change in the diabetic retinopathy severity score occurred in almost 60% of patients. So this is of a very large number of patients progressing very rapidly. But to understand what I really just said, you need to understand the scale that we use. And this scale is called a Diabetic Retinopathy Severity Scale, and it goes from mild nonproliferative disease all the way up to proliferative disease. The scale is based on a numerical scale that was used in the early treatment of diabetic retinopathy study. So a patient who has a 10, for instance, has no diabetic retinopathy; somebody who has a #60, has proliferative diabetic retinopathy, and the scale goes in between. Now the scale isn't an exact number scale, so for instance, 35 is mild nonproliferative disease, so that's a 25-number difference, but that's only considered a one-step change. So a two-step change would be taking someone from moderate to none, or severe down to mild. And it's important to understand what that means to understand the studies that have been looked at. Now the early treatment diabetic retinopathy study looked at the use of panretinal photocoagulation for these patients, and it works very well to prevent proliferative disease and eliminate the neovascularization. The problem is, panretinal photocoagulation leads to side effects, including decreased contrast sensitivity, dark adaptation problems, color vision problems, visual field defects. And because of that, the ETDRS only recommends the use of PRP in patients with high-risk proliferative disease, so this is much further beyond severe nonproliferative disease. Well, recently a study was done in the DRCR looking at the use of an anti-VEGF agent versus panretinal photocoagulation in patients with proliferative disease. And, in fact, the results using anti-VEGF injections were better than the use of panretinal photocoagulation in terms of vision, as well as side effects. And we have other studies were we used anti-VEGF agents; in particular, RISE and RIDE studies, the VIVID and VISTA studies. All these studies use anti-VEGF agents in the presence of diabetic macular edema. But one of the secondary outcomes that came out of both these studies showed an improvement in diabetic retinopathy severity scores, which allows us to consider using an

anti-VEGF agent to get this two-step or more improvement in the scale.

Dr. Do: Now it appears that in the presence of diabetic retinopathy, patients who are treated for diabetic macular edema with anti-VEGF therapy that their retinopathy regresses with treatment. Dr. Wykoff, what happens to patients who do not have diabetic macular edema, but who receive anti-VEGF therapy for nonproliferative diabetic retinopathy? What happens there?

Dr. Wykoff: Diana, that's a great question. And Peter outlined where we are in the field excellently. And there's two trials that are now bringing us forward, looking specifically at this group of high-risk NPDR eyes without DME, and they are DRCR protocol W and PANORAMA. Both of these trials are enrolling a similar population of patients. So eyes with levels 47 to 53 on the ETDRS, DRSS that Peter described quite well. And these are high risk nonproliferative diabetic retinopathy eyes that we know with natural history have a substantial and very clinically real possibility of progressing to proliferative disease over the next one to three years. In both PANORAMA and DRCR-W, patients did not have center-involved DME at baseline and therefore, these eyes, by and large, had excellent baseline visual acuity. PANORAMA is a two-year trial, and DRCR-W is ultimately going to be a four-year trial. Both of the trials are actually ongoing, but we have data from PANORAMA at this point through the one-year primary endpoint. Looking specifically at PANORAMA, this was a three-arm trial, in which 402 patients were randomized equally to either sham treatments or two different doses of repeated intravitreal anti-VEGF therapy; the anti-VEGF agent in both of these trials being aflibercept. And the two aflibercept arms in PANORAMA were either every 8-week dosing, or every 16-week dosing following five and four loading doses, respectively. There were actually three primary endpoints in PANORAMA; one of them at month six, and then two primary endpoints at the one-year point. And at one year, the sham arm, 15% had improved two or more steps on the DRSS, whereas with repeated intravitreal aflibercept injections, the percentage was 65% and 80% of eyes in the q16 and q8 arms improving two or more steps on the DRSS, showing highly statistically significant improvements in anatomic outcomes through one year with aflibercept dosing compared to sham.

Dr. Do: And just as a quick follow-up to that, Dr. Wykoff, did patients do well with anti-VEGF therapy? How did they respond?

Dr. Wykoff: Yeah, it's a great question, Diana. You know, really at the end of the day, our patients, as well as us as physicians, at some level, don't really care what the diabetic retinopathy severity scale is, because that scale is really based on primarily the number of hemorrhages or aneurysms or for the appearance of blood vessels in the back of the eye. What our patients really care about is their visual function and their risk of vision loss over time. And in this trial, as we have seen in all the trials that Peter beautifully described, we've seen elegant improvements in anatomy with anti-VEGF dosing, right? The numbers of hemorrhages and abnormal blood vessels all improved in the majority of eyes that are repeatedly treated with anti-VEGF injections. Again, that percentage being 65-80%; the large majority of eyes in PANORAMA demonstrating robust and meaningful anatomic improvements. But then what patients and physicians do care about is visual function over time. And what we saw in PANORAMA is, first of all, there was really no significant change in visual acuity over time. The aflibercept arms improved one and a half letters through one year, but we didn't expect much improvement in visual acuity, because again they had excellent baseline visual acuity. But what we did see a significant improvement on in the anti-VEGF treatment arms in PANORAMA, was the development of clinically meaningful adverse outcomes; meaning, proliferative diabetic retinopathy and center-involved DME. In the sham treated patients, about 41% of eyes developed either PDR or center-involved DME compared to a relative reduction with aflibercept dosing of about 75% down to about 10% with aflibercept dosing through one year. So a meaningful reduction in the clinically-relevant endpoints of the proliferative disease and DME with anti-VEGF dosing in these high-risk, well-cited NPDR eyes.

Dr. Do: It appears that both dosing schedules worked in the treatment of diabetic retinopathy. Were there other effects that were seen, Dr. Wykoff?

Dr. Wykoff: Yeah, that's a good question. There are really two ways to think about adverse outcomes in this trial. First of all, from an intravitreal injection perspective, there's always a risk with any procedure we do in the human body, and those risks overall are very small with repeated intravitreal injections. In this case, there were no serious adverse events from the injection procedure itself, and there were no unexpected systemic adverse outcomes in this trial. The biggest safety outcome that was highly clinically relevant was what we just discussed, which is the development of proliferative diabetic retinopathy and center-involved DME that was highly significantly reduced with repeated aflibercept injections through both six months and one year. And the second year outcomes of PANORAMA will be enlightening, because the question is: What happens to these eyes that don't convert in the sham arm through one year? Sixty percent of eyes in the sham arm did not develop proliferative disease and center-involved DME. And likely through the second-year PANORAMA, we'll see that a meaningful portion of those go on to develop these clinically-meaningful endpoints. Again, driving the point that potentially earlier intervention can lead to better outcomes and a lower risk of vision loss over time.

Dr. Do: Now that we know more about the PANORAMA clinical study and its results, let's look at its clinical invocations. Dr. Kaiser, can you share with us some patient cases?

Dr. Kaiser: So, Diana, we have two different patients here. And you can see from the color photographs that these patients have go

severe nonproliferative diabetic retinopathy and no macular edema. So this is the perfect case for what Charlie has been talking about. Both patients were treated with anti-VEGF agents. And you can see at follow-up a dramatic improvement in the number of hemorrhages, and this translates into a dramatic improvement in a nonproliferative disease. So they started with severe nonproliferative disease, and both these patients moved to the mild to moderate spectrum. So more than a two-step improvement in diabetic retinopathy illustrating the power of using anti-VEGF agents in these patients.

Dr. Do: So we should now be considering earlier intervention for patients with diabetic retinopathy. I think the PANORAMA study also provides us interesting information on the treatment of patients who have had diabetic macular edema or proliferative diabetic retinopathy, and now have regressed to nonproliferative disease.

Dr. Kaiser: So patients with moderately to severe NPDR, in the past we would wait until they developed proliferative disease and hemorrhages and high-risk characteristics. The recent findings from all our clinical studies, including the studies that were outlined by Charlie and myself, would indicate that using anti-VEGF agents in these patients actually can improve their diabetic retinopathy severity scores. Now, of course, this means follow-up. You need to follow these patients closely. But this gives us another avenue to treat patients with severe nonproliferative disease.

Dr. Wykoff: I think our management approaches to diabetic retinopathy have really evolved in the last 10 years. I think that many people used to think that diabetic macular edema asepisodic disease where you treat the eye when they're swelling, and you don't treat the eye when they're not swelling. My management approach is to eyes with DME and diabetic retinopathy more broadly have evolved to really consider this a long-term management approach. And so in an eye like this that used to have substantial DME and potentially proliferative disease, now that their DME is under control and they have nonproliferative diabetic retinopathy, these eyes I often will consider a continued ongoing long-term treatment. And I have a discussion with the patient; certainly we can stop at this point and observe. Many times, I'm choosing to treat these eyes every three or four months in an attempt to keep them stable long-term. I do also believe that the capillary nonprofusion story related to anti-VEGF therapy is important here. We have fairly strong data from both RIDE and RISE, as well as VISTA and VIVID to suggest that regular VEGF blockade can slow the progression of retinal nonprofusion that characterizes the pathophysiology of diabetic retinopathy. So will often continue to treat these eyes, albeit at a reduced frequency compared to when they have center-involved DME.

Dr. Kaiser: So, the PANORAMA results show that we don't have to use the treatments as frequently as we once thought. And I think this is a really large finding from the study. What we don't know is what would happen if we simply stop anti-VEGF agents at this point. And, in general, we probably want to continue to monitor them very closely, and certainly deliver additional anti-VEGF if there is any evidence of progression. But we don't really have good study guidelines to help us decide is it okay to stop the treatment after a certain point, or should we really just continue it over time. As we get better with this therapy, we will learn more in the future.

Dr. Do: Those are certainly topics that need further study. How should we be educating our patients with nonproliferative diabetic retinopathy?

Dr. Kaiser: So patients with nonproliferative diabetic retinopathy are at an increased risk of developing proliferative disease. In fact, when they developed severe nonproliferative disease, their risk is about 60%, and that's within 12 to 18 months. Proliferative diabetic retinopathy is a blinding disease, so it's very important they understand that, number one, they need to be followed very closely, so monitoring is very important. Number two, we have very good treatments to prevent this blindness, and these treatments need to be administered earlier to allow us to prevent this blinding disease.

Dr. Do: Thank you for that summary. As we wrap up today, I'd like to remind everyone about the actions we'd like to take on Assert-D to treat our patients with diabetic retinopathy. First, we should closely monitor patients with moderate nonproliferative diabetic retinopathy. Second, when they develop severe nonproliferative diabetic retinopathy, we should consider treatment with intravitreal anti-VEGF agents. And finally, we should be proactive in educating our diabetic patients about the importance of dilated eye exams, even in the absence of visual symptoms. Again, I'd like to thank Dr. Charlie Wykoff and Dr. Peter Kaiser for joining me today on Reach MD. And thank you very much for listening to our educational activities.