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Viewpoints on Managing DR: Addressing Moderate-to-Severe NPDR

Dr. Brown: As the prevalence of diabetes continues to rise on a global scale, we as eye care professionals have an important role in actively screening, referring, and treating patients with diabetic eye disease. And as the science continues to evolve, we're finding more ways to help these patients. So what are the latest data surrounding nonproliferative diabetic retinopathy and how should affect our practice as ophthalmologists.

This is CME on ReachMD and I'm Dr. David Brown.

Dr. Singh: And I'm Dr. Rishi Singh at the Cleveland Clinic in Cleveland, Ohio. And I'm here today to talk to you, David, about diabetic retinopathy and the growing epidemic we're seeing. Can you tell us about how you monitor patients with diabetic retinopathy and how it sort of forms over time?

Dr. Brown: Sure. We know that hyperglycemia or high blood sugars hurt the small blood vessels all over the body and the eye is sort of the canary in the coal mine. It's the first place that really most patients see end-organ damage. And, over time, you see from very faint changes like intraretinal hemorrhages and dilated vessels to more worrisome signs like proliferative diabetic retinopathy and diabetic macular edema. There are, you know, when you look at NPDR, we kind of look at a progression, and, years ago, they figured out that if you have hemorrhages in four quadrants, the 4-2-1 rule, or venous beading, which means kind of sausage-like enlargement of the veins in over two quadrants, or intraretinal microvascular abnormalities which are the very beginning buds of neovascularization in any quadrant, you're really at high-risk to going on to PDR, which was the main cause of blindness for years with diabetic retinopathy. Before the ETDRS used the criteria for the use of PRP to where you had to have quite a significant amount of neovascularization, either over a third of the disc area or multiple areas of a disc around the peripheral retina associated with vitreus hemorrhage before you do pan retina photocoagulation. The reticence to do pan retina photocoagulation early is that laser causes damage. The reason it's working, is those areas of retina have decreased blood supply and it's that hungry blood supply that's saying I'm hungry, I want more blood supply. So, the way to have an effective laser is to kill off that peripheral retina. You're actually giving up some peripheral visual field though and patients really notice that as you progress on with more severe laser. Fortunately, We're able to attack directly that I'm hungry factor. The main one, which is VEGF, with pharmacologic agents which are injected into the eye.

Dr. Brown: Rishi, what's our initial data about the success of anti-VEGF and NPDR? In other words, Rise Ride was for diabetic macular edema and that's what is was approved for, but what did those data show us about potential progression of NPDR to either PDR or regression of NPDR to a less risky stage?

Dr. Singh: Dave, the studies you mentioned are probably the most pivotal trials for our understanding about how anti-VEGF therapy can go and treat diabetic retinopathy and that wasn't the intention initially, as you mentioned, it was to treat diabetic macular edema. But in RISE and RIDE, they enrolled patients who had moderate to severe retinopathy and even some patients had proliferative disease and treated them with Ranibizumab for the treatment of diabetic macular edema and found a variety of secondary end-points related to their diabetic retinopathy progression. The first and foremost thing is they found a significant number of patients not going on to develop vision-threatening complications from diabetic retinopathy, including vitrectomy and vitreous hemorrhages and other sort of visual loss issues related to these conditions. One of the other interesting end points that they have found from the RISE and RIDE trials, was

there was a significant number of patients, 30-35% of patients, who developed a two-step retinopathy improvement across the board regardless of their baseline retinopathy scoring and those in the highest category of severe non-proliferative disease actually had a very significant rate of two-step retinopathy improvement of about 60-75% of patients achieving a two-step retinopathy scoring. So, this study was the first trial we've sort of had as a pivotal study to show us that not only are we treating the diabetic macular edema but we're also treating diabetic retinopathy as a result of that. We then went on to the VIVID/VISTA trials, which used Aflibercept for the treatment of diabetic macular edema and, in this study, they were a little bit stricter about enrolling patients with just severe, moderate to severe non-proliferative disease and they were able to then also show very similar end points with regards to the same efficacy with first reducing visual-threatening retinopathy complication events like vitreous hemorrhage and going on to developing proliferative disease and neovascular glaucoma and, additionally, showing a significant percentage of patients who had a two-step retinopathy scoring over the period of time they received Aflibercept in this pivotal study.

Dr. Brown: So Rishi, data RISE and RIDE and VIVID/VISTA show us that anti-VEGF agents can be helpful in the prevention or progression of no proliferative diabetic retinopathy. However there's a new study PANORAMA which is interesting in that it tests these agents in the absence of diabetic macular edema. Can you tell us about the PANORAMA trial?

Dr. Singh: Dave, the PANORAMA study was a critical understanding of how these patients that are most at risk of developing a proliferative disease were treated and affected by anti-VEGF therapy. In PANORAMA, patients were randomized to either sham treatment or two different frequencies of Aflibercept over a 52-week period where the primary end point was determined. And that primary end point was actually the proportion of patients who achieved a two-step retinopathy improvement over the course of the study. This study went on to week 100 and we know the data from the week 52 results which have shown a significant improvement in two-step retinopathy scoring in those patients with either the Aflibercept versus sham treatment. You saw almost a 79% rate of two-step retinopathy scoring in those patients who received Aflibercept every eight weeks versus those patients who were in the q16 week group or quarterly dosed Aflibercept group who achieved almost a 65.2% rate of two-step retinopathy score improvement. So, the study overall has really shown some true benefits in patients developing two-step retinopathy improvements and decreased rates of these visual-threatening retinopathy complications we see normally with the development of proliferative diabetes over time.

Dr. Brown: Yeah, that's super exciting, especially to take a more preventative approach more like what we do in the prevention of heart attack and stroke with hyperlipidemia agents instead of our original paradigms where we wait until somebody is in trouble and then intervene. If we can keep them out of trouble, it makes sense that there'd be less morbidity and potentially better outcomes long-term. Let's look at the clinical implications with a patient case. Here we have a 54-year-old lady who presents with a diabetic retinopathy evaluation in May of 2017. Her hemoglobin A1c is a very south Texas 10.1, blood pressure is 150/97 our typical triad of hypertension, diabetes, and obesity, and she's got slightly elevated BUN and creatinine with protein in the urine. Past medical history might be as no surprise; she's got some coronary artery disease, hyperlipidemia and hypertension. She comes in with a visual acuity of 20/30 in the right eye and 20/40 in the left eye. Here are our pictures and, as you can see, you see a cotton wool spot just in the left eye. You see dot blot hemorrhages, you see venous beading. At this magnification, I'm not seeing neovascularization and here's her fluorescein angiogram showing capillary non-profusion, the dark areas, with a little bit of neovascularization of the optic nerve here, they're blooming, which is a high-risk criteria if it was just a little more. So, Rishi, describe to me, like in this type of patient, what are the options and, if you're following PANORAMA, how would you recommend treating this patient?

Dr. Singh: You can tell that this patient would qualify as a patient who either has moderate to severe nonproliferative disease certainly in the left eye but potentially pre-proliferative disease of non-high risk characteristics in the right eye. For me, this patient was illustrative of what we were able to show in PANORAMA. This patient was actually initiated on monthly anti-VEGF treatments and then we extended them over a period of time and, as we extended the period of time, we realized from PANORAMA, that we were able to go to even 16-week intervals and achieve a great amount of two-step retinopathy scoring in these patients and improvement in the retinopathy scoring as a result of going even longer treatment intervals. And that's exactly what we did with this patient. We treated this patient with bilateral anti-VEGF treatments over the course of this patient's treatment interval, and we saw a significant rate of improvement of the retinopathy as you can see here. Now, you mentioned the alternatives, and the alternatives were discussed with this patient. I mean we could just watch this patient and see if they progressed to proliferative disease over the next year or two. The chance of that happening is actually a pretty high rate; it's about 50% at two years. So, if we just waited for this patient to develop that vision-threatening complication that might mean significant morbidity for the patient with regards to their visual issues, it might mean time off of work, it might be the inability to drive, and so, rather than doing that, we decided to initiate anti-VEGF therapy in this patient to see what sort of outcome we could achieve with this patient over time.

Dr. Brown: That's a great outcome and a great learning lesson that the results of PANORAMA as it applies to a clinical patient. A lot of doctors are reticent to start anti-VEGF, but you see here, you really turned her around. So, in talking about our colleagues out there, like when should our patients with diabetic retinopathy be referred to a retina specialist?

Dr. Singh: Dave, I always talk to my referral colleagues about trying to get the patient in earlier. There are a couple of things that have really revolutionized our field. The first is obviously OCT and being able to see diabetic macular edema much more readily than biomicroscopic exams. The second is that we have ultra-widefield imaging and fluorescein angiography through that, and we've been able to see patients who have early proliferative disease much faster and more rapidly, I believe, than before because of these new modalities. And so, as a result, we're able to pick up patients in the early proliferative stage versus waiting for frank vitreous hemorrhage or tractional detachment to develop. And, lastly, the revolution of anti-VEGF therapy has improved our ability to achieve retinopathy improvements as a result of treating these patients over time and prevent some of these vision-threatening complications we discussed, including center involving diabetic macular edema or vitreous hemorrhage or proliferative disease requiring vitrectomy. So, for now, I recommend most patients with either mild to moderate to severe nonproliferative disease get referred to the retina specialist from the general ophthalmologist so we can at least take a look and evaluate with an angiogram and with other modalities if this patient's at risk for developing proliferative disease soon. That can help us sort of scale and determine if the patient needs to come back in a more rapid fashion and, if the patient has mild disease, we can certainly relegate them back to the ophthalmologist to follow but, if they have moderate to severe disease, we might discuss the use of anti-VEGF therapy in that patient because of the bigger bang for the buck you can get for the anti-VEGF treatment option in that patient because you have a significant number of patients who can develop a two-step improvement in retinopathy score. And, obviously, we want to weed out those who have proliferative disease, which I think is incredibly hard and certainly a lot easier to figure out now with the use of ultra-widefield angiography in these patients during their screening period.

Dr. Singh: I do discuss with the patients that obviously, as you mentioned, the canary in the coal mine sort of analogy works well. We're seeing the level of retinopathy in their eyes but this means that they have neuropathy and nephropathy that needs to be evaluated and managed. And, we know that retinopathy itself is an independent risk factor for cardiovascular risk and mortality. So, I do work with their primary care physician, their endocrinologist; I do inform them of their retinopathy progression rates, I do talk about the use of anti-VEGF with them so they are aware of the side effects and complications that can occur sometimes with these drugs, quite rare but, again, reported, and I certainly want to make sure that the primary care doctor is aware of them, and I work with them hand in hand to sort of treat the retinopathy while discussing the optimization of their systemic medications and management as you talked about before and getting their hemoglobin A1c to the target values we hope to achieve by the recommendations.

Dr. Brown: Rishi, thank you very much for joining me today

Dr. Singh: Thank you for having me.