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### Viewpoints on Managing DR/DME: Implementing the Latest Treatment Strategies

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: Even though diabetic retinopathy is the leading causes of blindness in adults, it's important to remember that effective treatments are available. But as the evidence and treatment landscape continue to evolve, when should patients with diabetic eye disease be referred for treatment?

This is CME on ReachMD, and I am Dr. Diana Do calling in from Palo Alto, California.

Dr. Solomon: I am Dr. Sharon Solomon calling in from Baltimore, Maryland.

Dr. Do: We know that patients can acquire cumulative damage from their diabetes inside their eyes, and we would like to know as physicians when should we start implementing treatment if we see retinopathy. Can you first describe to us, Sharon, what are the different stages of diabetic retinopathy and what type of severity they indicate?

Dr. Solomon: Absolutely, Diana. I am happy to. As we know, there are two major stages of diabetic retinopathy. There is nonproliferative diabetic retinopathy, which means that no abnormal or aberrant blood vessels are growing on the surface of the retina. Then there is the more severe category, which is called proliferative diabetic retinopathy, and that is when you begin to have aberrant or irregular blood vessels called neovascular vessels growing on the surface of the retina. Going back to the milder category, the nonproliferative stage is broken into mild, moderate, and severe. Typically, if a patient has mild nonproliferative diabetic retinopathy, he should see his general ophthalmologist or retina specialist typically once a year, perhaps every 9 to 12 months. However, as someone has a step-up in his retinopathy, say to the moderate nonproliferative stage, typically patients should begin to be followed by a retina specialist and should be seen perhaps anywhere from six-to-eight month intervals, again for a dilated fundusoscopic examination. If someone has proliferative changes, which are the most severe changes, when we are talking about changes in the whole peripheral retina, not just the macula, those patients are typically followed every three to four months. Of course, if someone develops the leading cause of vision loss in patients with diabetes, which is diabetic macular edema, and that can be categorized into center-involved diabetic macular edema, which is what really causes acute reading loss or vision loss centrally, and non-center-involved diabetic macular edema, patients in that category are followed anywhere from every one to two months depending on the severity of the disease and how it affects vision.

Dr. Do: Sharon, you mentioned that patients can be seen by the general ophthalmologist or by the retina specialist. When should patients with nonproliferative diabetic retinopathy be referred to the retina specialist for consideration of anti-VEGF therapy?

Dr. Solomon: Diana, that is an important question, to touch on the guidelines, I would say in general if someone clearly has more than mild nonproliferative diabetic retinopathy, meaning that when you look into the retina, you can see microaneurysms in three or four quadrants, that person certainly, I think, should be followed by a retina specialist.

Dr. Do: Let us refocus again on those patients who have now progressed to the proliferative diabetic retinopathy stage that you

explained to us. Should these patients always be seen by the retina specialist, and should they be receiving treatment with these eye injections that inhibit VEGF?

Dr. Solomon: That is something that retina specialists are trying to decide right now amongst ourselves. You are familiar with Protocol S from the Diabetic Retinopathy Clinical Research Network, and in that clinical trial, patients who have proliferative diabetic retinopathy either underwent panretinal laser photocoagulation or treatment with intravitreal anti-vascular endothelial growth factor agents to manage the proliferative changes. We have five-year outcome data that show that treatment specifically with ranibizumab, which was the intravitreal anti-VEGF agent used in that clinical trial, showed non-inferiority in terms of management of the proliferative diabetic retinopathy changes, and a happy bonus was that patients who were prone to developing diabetic macular edema actually had less incidence and recurrence of their diabetic macular edema when they were at the proliferative diabetic retinopathy stage in patients who received ranibizumab compared to patients who received the gold standard panretinal laser photocoagulation therapy.

Dr. Do: That was indeed a very important clinical trial. You mentioned diabetic macular edema and how that can affect a patient's central vision. How often should patients with diabetic macular edema be followed, and does this disease get better or resolve with these eye injections that inhibit VEGF?

Dr. Solomon: Patients with diabetic macular edema typically once they have crossed the threshold and developed that sequela of having diabetes, typically they will come in at monthly intervals, and they may receive intravitreal anti-VEGF therapy. Again, there are different regimens to follow. If you look at the Protocol T data from the Diabetic Retinopathy Clinical Research Network, if patients have visual acuity that is better than 20/50, they will be starting intravitreal anti-VEGF therapy for their center-involved diabetic macular edema with any one of the three available anti-VEGF agents, bevacizumab, ranibizumab, or aflibercept. When we look at patients who meet the criteria from the very recent Protocol V in patients who have diabetic macular edema and better acuity, there we found that patients who had vision of 20/25 or better but had some level of diabetic macular edema actually did just as well as patients who received treatment with anti-VEGF or just had observation. It depends on the patient, and it depends on the patient's visual acuity.

Dr. Do: I agree. We really want to monitor these patients who have diabetic macular edema very closely. Let us look at a very brief case presentation discussion of an individual that I saw in my clinic. This is a 38-year-old woman with a history of type 1 diabetes who came in with occasional blurry vision. Her visual acuity on examination was 20/25, and I performed an exam, which showed mild nonproliferative disease. I also obtained an imaging study called OCT, optical coherence tomography. On that scan, we can appreciate there is very mild center-involved diabetic macular edema. What would you recommend for this individual, Sharon?

Dr. Solomon: If the vision as you are suggesting is only mildly affected and she is 20/25 or 20/20 and she is somebody who is prone to having good follow-up, you have spoken to her about her hemoglobin A1c control. We do not want to forget that we are talking about a disease that affects the eye, but the underlying cause is a systemic disease that the patient needs to manage with diet and exercise and proper medication. If she is somebody who has good systemic control of her diabetes, she is prone to having good follow-up and not someone who you are concerned might disappear and not present for care in six months or eight months or a year, I think I would be inclined to follow her at this point. If you saw progression in the OCT central subfield thickness, the severity of her center-involved diabetic macular edema or else a decline in her vision, then I might pull the trigger and consider initiating treatment with intravitreal anti-VEGF therapy.

Dr. Do: I agree with you completely, and that is what I did. I am still following up with her and monitoring that mild amount of diabetic macular edema. Let us move to the second case. This is a gentleman who came in complaining of two months of decreased vision, and the visual acuity actually dropped to 20/60 in the affected left eye. On examination, he had moderate nonproliferative diabetic retinopathy, and on the OCT scan, there is significant diabetic macular edema. How would you manage this patient?

Dr. Solomon: Unlike the first patient you described, Diana, this patient sounds like he has begun to meet the threshold for treatment, for initiation with anti-VEGF therapy both on the OCT central subfield thickness criteria as well as the level of visual acuity. I think I would certainly start with an intravitreal anti-VEGF agent as the first line of therapy, and if we were to go based on the results of Protocol T from the Diabetic Retinopathy Clinical Research Network, I would be inclined to start with treatment with aflibercept since you said the vision was worse than 20/50. In the Protocol T clinical trial, there was a slight advantage in patients receiving intravitreal aflibercept if vision was worse than 20/50.

Dr. Do: That is a perfect recommendation, and that is exactly what I did. Often when I tell patients about these treatments, they are very concerned about how often and how long will they need treatments? Is this a lifelong therapy that they will need? What do you tell your patients?

Dr. Solomon: I think you bring up a critical point, Diana. I often tell patients, again because they have an eye disease that is driven by an underlying systemic disorder, diabetes mellitus, that they are in this for the long haul. The patient has to understand again that he is

involved in the management of his diabetes mellitus by maintaining a good hemoglobin A1c level from diet, exercise, and taking his medications. I make it clear to the patient that, especially with diabetic macular edema, this tends to be a chronic disorder. Diabetic retinopathy in general tends to be a chronic disorder. We can get the edema oftentimes and surprisingly even the retinopathy into a status of remission, but unless therapy is continued or unless the underlying disease is kept at bay, it is possible and often likely that the patient will come out of remission and need further treatment. Patients really need to understand that they are going to have to be committed to coming in frequently for observation and for management.

Dr. Do: You are absolutely correct. Recently there have been many clinical trials conducted looking at eyes who have this severe nonproliferative diabetic retinopathy and testing whether or not intravitreal VEGF inhibitors can help improve the level of retinopathy and decrease the risk for vision-threatening complications. Has this new data changed your practice patterns of treating these patients?

Dr. Solomon: Absolutely, Diana. If you look at one of the cases that we have here today, a 67-year-old gentleman with type 2 diabetes, as you can see from the case, he has 20/25 vision in the right eye where there is less center-involved diabetic macular edema and vision was lower at 20/80 in the eye that had more edema in the center of the fovea. He actually had moderate-to-severe nonproliferative diabetic retinopathy in each eye, and because of the diabetic macular edema, I did opt to start anti-VEGF therapy early in both eyes. One could argue that the better-seeing eye, the 20/25 eye, according to the new Protocol V data, maybe we could have watched that eye because the vision was so good, but it was actually the level of background retinopathy and our knowledge from other clinical trials that we had actually seen regression in the staging and the steps of that retinopathy level that made me decide to treat the diabetic macular edema and the background retinopathy with intravitreal anti-VEGF therapy.

Dr. Do: I agree with you. I actually am starting to treat many of my patients who have severe nonproliferative diabetic retinopathy with VEGF inhibitors because there is Level 1 evidence now to suggest that these VEGF inhibitors are very effective in reducing the retinopathy severity levels.

Dr. Solomon: Absolutely, and that is something we thought we would never see.

Dr. Do: You have given us so much useful information today. If you had the top five practice pearls that we should think about as we are managing patients with diabetic eye disease, what would those key points be?

Dr. Solomon: I think that it is often overwhelming for patients to think that gee, I have to plan to come in every month. I may have to get an injection in my eye. Some patients are getting bilateral treatment. They have to get both eyes treated every month. I think the first thing is patients have to have a sense that I do have some control over the situation. I think it is important for patients to understand if I follow my diet, if I exercise, if I take my medication, I am under the care of my internist or my endocrinologist, that I may have a chance of making my diabetic retinopathy at least not progress as quickly or stabilize over time and that this is not necessarily a diagnosis that will result in blindness. I think it is important for the patient to have sense of control over his condition. The second thing that is important is for the patient to understand that with that control comes the responsibility of having adequate follow-up. That being said, I reassure patients that at no time in the past did we have such an armamentarium of therapies available to us that can maintain and actually improve vision. Even when patients come in and they are already suffering from vision loss, I let them know that we have an intervention where we can likely regain vision and maintain those gains and acuity. It is a chronic condition. It is not something that is going to go away until we find a cure for diabetes mellitus, but the prognosis is good with proper follow-up and proper management.

Dr. Do: Wonderful. I think those are absolutely perfect pearls to end this discussion today. I really want to thank you, Sharon, for all of your medical expertise.

Dr. Solomon: Diana, it was my pleasure to participate. Thank you for having me.