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New Insights on Treating Diabetic Retinopathy & Diabetic Macular Edema from the 2018 AAO Meeting

Announcer:

Welcome to CME on ReachMD. This activity, titled "New Insights on Treating Diabetic Retinopathy & Diabetic Macular Edema from the 2018 AAO Meeting," is brought to you by ASiM and supported by an educational grant from Regeneron Pharmaceuticals, Inc.

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Here's your host, Dr. John Russell.

Dr. Russell:

425 million people worldwide are affected by diabetes, and complications from this disease are the leading cause of vision loss in working-age adults. And since the number of people with diabetes is projected to double by the year 2045, so too are the number of diabetic retinopathy cases expected to increase.

Coming to you from the ReachMD studios, this is CME on ReachMD. I'm Dr. John Russell, and joining me to discuss recent insights on the treatment of diabetic macular edema and diabetic retinopathy, based on new data from the 2018 American Academy of Ophthalmology Meeting, is Dr. Fernando Arevalo and Dr. Quan Dong Nguyen. Dr. Arevalo is a Professor of Ophthalmology at the Wilmer Eye Institute of the Johns Hopkins University School of Medicine, and Dr. Nguyen is a Professor of Ophthalmology at the Byers Eye Institute of the Stanford University School of Medicine.

Dr. Arevalo, Dr. Nguyen, it's great to have you both with us.

Dr. Arevalo:

Thank you for having us.

Dr. Nguyen:

It's a great pleasure for us to be here with you today.

Dr. Russell:

So, Dr. Arevalo, let's start with you and talk about new insights from recent clinical trials regarding the role of anti-VEGF agents in diabetic macular edema, also known as DME. Considering the 3 anti-VEGF agents utilized in DME—afibercept, bevacizumab and ranibizumab—is there a difference in patient outcomes, and does that affect your treatment selection?

Dr. Arevalo:

Based on what we saw at the Academy in Chicago, there were discussions about the most recent clinical trials, including Protocol T from the DRCR Net that evaluated the 3 agents that we have available—afibercept, ranibizumab and bevacizumab—and the results demonstrated at 2 years of follow-up that for patients with good visual acuity, 20/40 or better, the results are very similar and the 3 agents are beneficial, but for patients with poor visual acuity, 20/50 or worse, afibercept seems to have an advantage. When we look at the data at 1 year, there was a clear statistically significant difference in favor of afibercept compared to ranibizumab and bevacizumab, but at 2 years of follow-up, there was no significant difference between afibercept and ranibizumab. However, when you look at the

visual acuity results in the area under the curve, you can see that over the 2 years of follow-up, there were better visual acuity on patients treated with aflibercept. For those reasons, we prefer as clinicians to use aflibercept on patients with poor visual acuity. In addition, the trial showed that injections decrease over time. There were 9 injections as an average in the first year and decreased to 5 injections during the second year, and the number of patients that needed supplemental laser also decreased during the second year.

Dr. Russell:

So, Dr. Nguyen, through many clinical trials, we've seen that anti-VEGF therapy has great potential in reversing the progression of diabetic retinopathy in addition to DME. Dr. Nguyen, can you walk us through the results found in some of these trials?

Dr. Nguyen:

Certainly. The question for all of us has been: What will be the window of maximum efficacy between diabetic retinopathy? So, at our recent 2018 annual meeting of the American Academy of Ophthalmology, we have seen the meta-analysis of 4 major trials in our field for diabetic retinopathy and diabetic macular edema, and that is the RIDE and RISE study as well as Protocol I and Protocol T study. In this study the main goal was to look at the role in diabetic macular edema of an anti-VEGF agent, in this case ranibizumab. However, we were also able to learn about diabetic retinopathy. So we have learned that for nonproliferative diabetic retinopathy, for those with a diabetic retinopathy severity scale of 43 or less, about 11% of those treated with ranibizumab compared to about 2% of subjects treated with sham showed 2-or-more-step improvement in diabetic retinopathy severity scale, DRSS, at year 2. Nonproliferative diabetic retinopathy with DRSS of 47 to 53, for those, 73% of those treated with ranibizumab compared to 14% of those treated with sham show a 2-or-more-step improvement. And then for proliferative diabetic retinopathy, for those with DRSS score of 60 or more, 44% of those treated with ranibizumab compared to 8% of those treated with sham show a 2-or-more-step improvement in diabetic retinopathy severity scale at year 2. Thus, based on this result, it appears that the window of maximum efficacy when treating diabetic retinopathy is stage 47 to 53, which also provides great rationale for many of the clinical trials currently going on in the United States and elsewhere in the world looking at the way to improve diabetic retinopathy.

Dr. Russell:

Dr. Arevalo, would you tell us about the role of other treatment modalities in combination with anti-VEGF therapy, specifically lasers and corticosteroids?

Dr. Arevalo:

Sure. I think there is still a role for laser and corticosteroids. In patients with diabetic macular edema that is extrafoveal, I think that laser photocoagulation is still an option, or you can observe those patients and treat with anti-VEGF when they affect the central foveal region. In addition, if you look at the results that were discussed at the Academy as well of Protocol I, you can see that laser is an option. Protocol I showed that patients treated with prompt laser with ranibizumab compared to ranibizumab and deferred laser had improvements in terms of visual acuity. However, patients that had the prompt laser had better visual acuity, especially on those patients that were treated with a visual acuity that was poor, 20/50 or worse of visual acuity. But patients that have a visual acuity that is poor are those patients that, at the end of the day, may need laser photocoagulation if there is persistent diabetic macular edema. So, for those eyes that have persistent diabetic macular edema but that we have treated with anti-VEGF injections for at least 6 months, there may be a role for laser photocoagulation if we treat first with anti-VEGF injections.

In terms of intravitreal steroids, Protocol U was presented as well, and that compared the results of the treatment of ranibizumab versus combination of ranibizumab plus the dexamethasone implant, and the result showed at 6 months of follow-up that there was no difference in terms of visual acuity, but the combination therapy was able to dry the macula better. I think that more studies are needed, even though there was no significant difference in terms of visual acuity. Other studies have shown that patients with persistent diabetic macular edema and patients with chronic diabetic macular edema can benefit from intravitreal steroid injections, including the Ozurdex implant or the dexamethasone implant, such as the MIRA study, or the fluocinolone implants, such as the FAME study. So I think there is a role, especially on patients with chronic diabetic macular edema. We have to also consider other indications, patients that have a history of recent CVA or myocardial infarction or patients that are pregnant.

Dr. Russell:

For those just joining us, this is CME on ReachMD. I'm Dr. John Russell and today I'm speaking with Dr. Fernando Arevlao and Dr. Quan Dong Nguyen about optimizing treatment outcomes for diabetic macular edema and diabetic retinopathy.

Now that we have more insight on the new clinical trial data presented at the 2018 AAO meeting, let's consider how this data may impact everyday clinical practice.

Dr. Russell:

Now, the results from Protocol T study give us insights on the comparison of VEGF agents and injection frequency. But, Dr. Arevalo, what's the situation in real-world clinical practice regarding the use of anti-VEGF agents?

Dr. Arevalo:

That's a very good question. In real-world clinical practice, things are suboptimal in terms of number of injections and the agents that we use. In clinical practice worldwide, bevacizumab is used more frequently, and that's because of cost issues, even though many studies have shown that aflibercept and ranibizumab are superior to bevacizumab. The other thing is that the lower number of injections leads to not as good results as we see in clinical trials, and there are many studies already showing that at 5 years of follow-up, including our own study from the Pan-American Collaborative Retina Study Group, we follow our patients for 5 years, and the gains obtained during the first 3 years were lost at years 4 and 5, basically because we undertreated our patients. So the number of injections that our patients receive are important to maintain the visual gains that we gain initially.

Dr. Russell:

So, Dr. Arevalo, you were talking about injection frequency. What is the optimal injection frequency to achieve the best possible outcomes for our patients with DME?

Dr. Arevalo:

So, in different studies, including studies that were discussed at the Academy—Protocol I and Protocol T—patients were given 6 initial injections as a loading dose, 1 monthly injection for 6 months, and those results demonstrated that the number of patients that have persistent diabetic macular edema decreases over time, so that seems to be the best way to treat our patients. It's the best way to obtain better visual acuity from the beginning, and later on then we treat our patients with PRN or treat-and-extend regime, depending on your preference. So it's a large number of injections at the beginning, maybe the first year, but then the number of injections decrease progressively during the first, second year and third and fourth until maybe 0 injections needed during the fifth year. So we can tell our patients that this is a chronic disease, that they will need a significant number of injections during the first year, but that the number of injections will decrease progressively, and maybe no injections will be needed after 4 to 5 years of treatment.

Dr. Russell:

So, Dr. Nguyen, let's talk about the use of anti-VEGF therapy in diabetic retinopathy. How often do we need to employ anti-VEGF therapy to achieve regression of diabetic retinopathy, and how soon can we expect to see changes in diabetic retinopathy after initiating therapy?

Dr. Nguyen:

I'll share with you, to an earlier question, how effective anti-VEGF can be in reducing or reversing diabetic retinopathy. Now, in this question we very much look at the frequency of injections in various pivotal studies. Certainly, as Dr. Arevalo mentioned, in real world we may not be able to administer the drug monthly or similar to what had been done in the protocol. So, first, we can look at the frequency of injection and the insight that we have learned from the 4 pivotal studies—RISE, RIDE, Protocol T and Protocol I—in particular for ranibizumab, either 0.3 or 0.5 milligram. So, in this study the ranibizumab was administered initially every 4 weeks and then as needed, and we have seen that just with our schedule it was very well to be able to see the significant reduction in diabetic retinopathy or the reversing of diabetic retinopathy. If we now look at the frequency of injection in another study, this time the PANORAMA study, looking at the role of aflibercept in diabetic retinopathy, in this protocol after either 3 or 5 loading dose of aflibercept, aflibercept was then administered every 8 weeks or every 16 weeks, and the results were very similar in terms of diabetic retinopathy severity score reduction. In other words, after the initial loading dose, whether it's given 8 weeks or 16 weeks, it appeared that the retinopathy can still be reduced very similar in that regard, so therefore, we certainly can see that in real world, patients with diabetic retinopathy can probably be treated with less frequent administration of anti-VEGF therapy. Now, certainly one asks: Can ranibizumab be given a similar way? And the answer is, probably; but we have not seen the study of that. But certainly, based on what this different anti-VEGF can do, we certainly expect that it probably does not require us to administer them on a monthly basis.

Dr. Nguyen:

Regarding the second part of your question, regarding the onset of improvement for diabetic retinopathy, again, we are looking back at the results that we have learned from various clinical trials—for example, in RISE and RIDE, the 2 studies for ranibizumab; VIVID and VISTA, the 2 studies for aflibercept; and then Protocol T. In this pivotal study, we have noted that the improvement in the ETDRS diabetic retinopathy severity scale was evaluated at 12 months and beyond. Certainly, we have seen that diabetic retinopathy has shown improvement in regressions from this study starting at 12 months. However, recent analysis of the READ-3 study by Yasir Sepah, Muhammad Hassan and colleagues at Stanford has shown a 2-or-more-step improvement in the DRSS score as early as month 3. And in this analysis in the READ-3 study, by month 6 the percentage of diabetic retinopathy improvement was similar to month 12 in VISTA. In other words, the change that we have seen in VISTA at month 12 was already demonstrated by month 3 and month 6 in the READ-3 study. Therefore, we can expect our patients to have just major reduction, 2-step reduction, in the diabetic retinopathy shortly after they have been treated with anti-VEGF therapy. And such finding is very great news for our patients, because we can tell

them that if we begin the treatment now, you do not have to wait very long, and that the benefit can begin as early as 3 months, and certainly by 6 months show significant improvement.

Dr. Russell:

So, Dr. Nguyen, considering these results, should we consider anti-VEGF therapy for all patients with diabetic retinopathy?

Dr. Nguyen:

So this is a difficult question and requires that, as clinician scientists, we should look at several scenarios and several conditions. The potentially severe consequences of interruption in anti-VEGF therapy—for example, when the patients are not able to return for follow-up for whatever reason or they are not compliant with follow-up—those factors should be carefully considered when making initial treatment decisions.

At our recent 2018 meeting of the American Academy of Ophthalmology, we had learned some wonderful information can help to guide us. So, Mark Johnson and colleagues from the Kellogg Eye Center at the University of Michigan as well as Jason Hsu and colleagues at Wills Eye Hospital in Philadelphia have illustrated a study that patients with diabetic retinopathy who are treated exclusively with anti-VEGF therapy but then have an interruption in treatment for whatever reason may experience marked progression of disease with potentially devastating visual consequences. In other words, when they were treated, if for whatever reason they cannot return on a regular basis for treatment, then complications occurred, significant complications. So, therefore, we also learned from just analysis that there's an underutilization of eye care services, so other real-world experience there, so not every patient can come back on a regular basis like when they are in clinical trials.

And then also from that study we learned important factors, particularly for the progressive diabetic retinopathy, or the proliferative diabetic retinopathy. And in this case, in patients with ischemic diabetic retinopathy, especially with the proliferative type, unintentional treatment interruption. In other words, initially we planned to treat patients regularly, but if for whatever reason the patient cannot come back, just unintentional treatment interruption can lead to visually disastrous consequences, including irreversible blindness in these patients. So, therefore, when we have eyes with proliferative diabetic retinopathy treated solely with anti-VEGF injection, we may have a worsened anatomic and functional outcome after loss to follow-up compared to eyes that we see, for example, panretinal photocoagulation.

So, in summary, we have seen how wonderful anti-VEGF therapy can help to reverse and improve diabetic retinopathy, but one needs to keep in mind that these studies were conducted in a very well-controlled environment where the subjects were asked to come back on a very regular basis, that they can be examined very closely, but in real-world experience, if we do not expect our patients for whatever reason cannot come back on a regular basis, then one needs to choose carefully. In such cases, perhaps anti-VEGF alone may not be the best ideal or best approach if the patient may not be compliant. In such cases, one may consider both a combination of anti-VEGF therapy and also laser photocoagulation, so hopefully together they can provide great control in the cases where the patients cannot come back for the indicated visits.

Dr. Russell:

Well, we've covered a lot today, and as a final question for both of you, what would be the key take-home message for our audience in applying these findings in clinical practice? Dr. Arevalo, could we start with you?

Dr. Arevalo:

Sure. My take-home messages are that anti-VEGF therapy is the first-line therapy for diabetic macular edema. Aflibercept is the best treatment for patients with poor visual acuity or patients with a visual acuity of 20/50 or worse. The number of injections needs to be high during the first year, 8 to 9 injections, including the 6 injections loading dose. However, the number of injections will decrease over time. Steroids are useful in specific cases like chronic diabetic macular edema but also in patients that have certain indications like a recent CVA, myocardial infarction, or if they are pregnant. And in addition, laser photocoagulation can still be useful for extrafoveal diabetic macular edema and for patients with persistent diabetic macular edema.

Dr. Russell:

Turning to you, Dr. Nguyen, what would you like to add?

Dr. Nguyen:

Certainly, it's been a great pleasure being with you and Dr. Arevalo and sharing some of our thoughts with our colleagues here. I hope that during the last 30 minutes we were able to share with you some comments. And as for me, some of the departing comments would be that for diabetic macular edema, it appears that it requires aggressive treatment with the best available anti-VEGF agents if possible, especially in the early period, in order for us to achieve the greatest potential for visual gain for our patients. Second, we have learned

that the diabetic retinopathy severity score of 47 to 53 appeared to benefit the most from anti-VEGF therapy in reversing diabetic retinopathy as compared, for example, to a severity score of less than 43 or greater than 60. The third point would be that significant reversal of diabetic retinopathy by at least 2 steps can occur as early as 3 to 6 months after the initiation of anti-VEGF therapy. And finally, for my fourth one, I would like to emphasize again that the consequences of interruption of anti-VEGF therapy, which may occur when patients are noncompliant or unable to return for follow-up visits and treatment, or for whatever reason, should be carefully considered when making initial treatment decisions of laser photocoagulation and/or anti-VEGF therapy for diabetic retinopathy.

Dr. Russell:

Well, that's a great way to round out our discussion on how we can optimize the way we treat diabetic macular edema and diabetic retinopathy using data presented at the 2018 American Academy of Ophthalmology Annual Meeting. Dr. Arevalo, Dr. Nguyen, it was great speaking with both of you today.

Dr. Nguyen:

Thank you for having us today. It certainly has been a great pleasure to be with you and Dr. Arevalo.

Dr. Arevalo:

Thank you for the opportunity.

Announcer:

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