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Retina Clinic: Emerging Treatment Options in Diabetic Retinopathy

Announcer:
Welcome to CME on ReachMD. This activity, entitled "**Retina Clinic: Emerging Treatment Options in Diabetic Retinopathy**" is provided by **Prova Education**.

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Dr. Goldberg:
New more durable treatments are available for patients with diabetic macular edema, but how might these approaches be used for patients with diabetic retinopathy?

This is CME on ReachMD, and I'm Dr. Roger Goldberg.

Dr. Campochiaro:
And I'm Dr. Peter Campochiaro.

And that's a great question, Roger, and we may be able to get some insights from currently available data. In RISE and RIDE, monthly injection of 0.3 or 0.5 mg of ranibizumab was compared to placebo. In the total study population, at 1 year, 35% and 33% of patients in the ranibizumab groups had improvement in diabetic retinopathy severity score of 2 steps or more, compared to 2% in the placebo group. And at 2 years, it was 42% and 40% in ranibizumab groups compared with 6% in the placebo group. Improvement in diabetic retinopathy severity score was greatest in patients with moderately severe or severe nonproliferative diabetic retinopathy. 80% of those patients treated with monthly ranibizumab improved by 2 steps or more at 2 years, compared with 11% in the placebo group. In that same group of patients, the percentage who developed proliferative diabetic retinopathy by year 2 was 18.6% in the placebo group, versus only 0% or 2.7% in the ranibizumab groups.

In PROTOCOL W, the percentage of patients who developed proliferative diabetic retinopathy by year 2 was 13.5% in the aflibercept group, which is much worse than the 0% to 2.7% in the ranibizumab groups in RISE and RIDE. But that's not a difference between aflibercept and ranibizumab. It's because the aflibercept was given much less frequently – every 4 months, after a loading dose – and the population was slightly milder, with diabetic retinopathy severity score of 43 to 53 at baseline, versus 47 to 53.

In PANORAMA, in patients with moderately severe or severe nonproliferative diabetic retinopathy, the 2Q8 PRN group received 9 injections of aflibercept in the first year, and roughly 80% improved by 2 or more steps, which is comparable to monthly ranibizumab in RISE and RIDE, while the 2Q16 group received 6 injections and only 65% had a 2-step improvement. In Year 2, the 2Q8 PRN group received PRN injections, and the percentage with 2-step improvement regressed from 80% to 50%.

So anti-VEGF injection frequency is critical for optimal outcomes in diabetic retinopathy.

Roger, you have new data from a new post hoc analysis of RISE and RIDE. Can you walk us through what you found?

Dr. Goldberg:

Sure. So in RISE and RIDE – which is primarily, by the way, a study designed to treat and see the efficacy of ranibizumab for the treatment of diabetic macular edema – we certainly have learned a lot about the impact on diabetic retinopathy and how all of these agents seem to have a sweet spot in terms of their maximum efficacy in those patients with moderately severe or severe nonproliferative diabetic retinopathy. Well, after the 3-year RISE and RIDE studies ended, patients rolled into an open-label extension study called OLE, and in that study, patients were only given injections based on changes in visual acuity or in central retinal thickness, how their DME was doing. The injection frequency was not related in any way to diabetic retinopathy levels. And so we use this as an opportunity to see, well, what happens to patients once you've gotten their diabetic retinopathy better? You've caused that 2-step regression, for example, that you've just commented on, with induction therapy with monthly treatment. What happens when you treat these patients less frequently? And we found some very interesting findings. First of all, those diabetic retinopathy severity scores are not true regression of diabetic retinopathy. The patients who had improved to mild or moderate NPDR do not behave like patients who have mild or moderate NPDR natively.

What we see is that they have a much more volatile phenotype. They're much more likely to backslide or get worse when less frequent treatment is administered. This was actually most profound in the patients who had proliferative diabetic retinopathy at baseline. Although you can get them to look better with monthly intravitreal injections of an anti-VEGF agent, those are the ones much more likely to backslide and get worse when you pull back the frequency of treatment.

And so I think it should be considered a real goal of treatment, not only to cause a 2-step improvement, but frankly, to prevent patients from progressing to the proliferative stages because then you're going to have a much more difficult disease to treat and manage.

Dr. Campochiaro:
Roger, that's really interesting, and given those data and the other data that I mentioned, have you changed your approach to managing severe nonproliferative diabetic retinopathy?

Dr. Goldberg:
Thanks, Peter. When I look at the totality of the data, I have changed my treatment approaches for severe NPDR in 2 important ways. Number 1, I find myself less concerned about getting regression of diabetic retinopathy – moving from severe to mild or moderate – because I know that they're not truly mild or moderate in the way that we think of native or insipient diabetic retinopathy. Number 2, I'm much more motivated to keep patients from progressing to proliferative diabetic retinopathy because I don't want them to enter that most volatile phenotype, where, yes, I can get them to look better, but they're going to need continual and very frequent treatment, otherwise I know that they're much more likely to backslide. Secondly, patients who have perhaps a little bit of diabetic macular edema that I wouldn't necessarily treat on its face, if they do have severe NPDR, I'm kind of feel like I'm treating both – a little bit of the DME and also that severe NPDR so I'm kind of getting – killing 2 birds with one stone, so to speak.

So when we think about patients with both diabetic macular edema and diabetic retinopathy, that certainly makes me think about some of these newer agents that have recently gotten approved for diabetic macular edema, like brolucizumab or faricimab.

Peter, what can you tell us about the effects of these agents for the treatment of diabetic retinopathy?

Dr. Campochiaro:
Well, Roger, both brolucizumab and faricimab are approved for diabetic macular edema, not for diabetic retinopathy, but the DME trials provided some data in diabetic retinopathy. In KITE and KESTREL, patients received 7 injections of brolucizumab in the first year, and about 29% of patients improved by 2 steps or more, versus the 33%-35% from monthly ranibizumab in RISE and RIDE. We don't know the baseline diabetic retinopathy severity score for KITE and KESTREL, so we can't really compare outcomes, but it appears that monthly ranibizumab is certainly not worse and probably better than somewhat less frequent brolucizumab.

In YOSEMITE and RHINE, in year 1, patients received 9 injections of faricimab in the fixed dosing arm and 9 of aflibercept in the comparator arm, and the percentage of patients with improvement of 2 steps or more was comparable: 44%-46% for 4 faricimab groups, and 36% and 47% for aflibercept groups.

So these agents work quite well, but they require frequent injections.

Roger, what about the port delivery system? What do you think about this for diabetic retinopathy?

Dr. Goldberg:
Sure. So the port delivery system is currently approved for the treatment of wet macular degeneration, and this is a surgically implanted device that slowly releases ranibizumab into the vitreous and can last 6 months or longer, and it's being studied currently in the PAVILION study, which is patients with moderately severe or severe nonproliferative diabetic retinopathy without DME, to see if a little, slow-released, sustained ranibizumab can control diabetic retinopathy. I'm pretty optimistic that it can. My sense in general is that it is

that continual treatment that's most important, because as you mentioned, we saw with, for example, brolucizumab that the control arms also did quite well in these studies. So it's that regular treatment that really seems to help here.

Another promising approach is being developed by REGENXBIO, and their gene therapy, RGX-314. This is a gene therapy. It's a one-time injection into the suprachoroidal space, and it's being developed in a clinical trial called the ALTITUDE study, looking at the effect of this gene therapy, that produces a VEGF inhibitor, on diabetic retinopathy severity scores.

And in the early data, what we've seen so far at 3 months, is that 33% of patients in the treatment arm had a 2-step improvement in their diabetic retinopathy severity scores, versus no patients in the observational control group.

Peter, what are your thoughts? Can we stabilize eyes with severe NPDR and minimize treatment burden, either with PDS or with something like RGX-314?

Dr. Campochiaro:
Yes, I think so, Roger. I think that, you know, as we've seen in the injection studies, that very frequent injections really provide pretty good improvement and stability, and I think these new approaches that provide sustained suppression of VEGF are really treating this disease in the right way. So I think that whether you provide sustained delivery of ranibizumab from an implantable reservoir or you provide a gene therapy that provides constant expression of an anti-VEGF protein, I think those approaches really are the right way to treat diabetic retinopathy.

And I think that, you know, frequent anti-VEGF injections are a burden for patients and physicians, and many asymptomatic patients with severe nonproliferative diabetic retinopathy decide against getting any injections. I think these new, sustained delivery approaches may be more acceptable, and more efficacious, in patients with diabetic retinopathy.

Dr. Goldberg:
I couldn't agree more. Well, that's all the time we have for today. Before we go, Peter, any final thoughts for our audience?

Dr. Campochiaro:
Yes. Sustained delivery of VEGF receptor tyrosine kinase inhibitors are also being tested in neovascular AMD and DME, and that is potentially another promising approach for diabetic retinopathy. And, Roger, I'm also looking forward to seeing the effects of agents that directly activate Tie-2.

Dr. Goldberg:
I agree, Peter. I think this is a very exciting time as we think about new therapies for the treatment of diabetic retinopathy. I'm excited for the upcoming port delivery system data, for programs like RGX-314, and some of these TKI inhibitors. I think faricimab may end up getting a label extension to treat diabetic retinopathy. And so I do think it's a very exciting time overall.

I want to thank our audience for tuning in today. Peter, thank you for this interesting discussion. It was truly a pleasure speaking with you today.

Dr. Campochiaro:
Thank you, Roger. Pleasure speaking with you, too.

Announcer:
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