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https://reachmd.com/programs/cme/the-future-is-now-updates-on-durable-vegf-suppression/13278/

Released: 03/31/2022
Valid until: 03/31/2023
Time needed to complete: 15 minutes

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The Future Is Now: Updates on Durable VEGF Suppression

Announcer:
Welcome to CME on ReachMD. This activity, entitled "The Future Is Now: Updates on Durable VEGF Suppression" is provided by Prova Education.

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Dr. Baumal:
It's an exciting time to be an ophthalmologist, especially a retinal physician. We now have multiple new and novel strategies to treat our patients with neovascular age-related macular degeneration [nAMD] and diabetic macular edema [DME]. So what are they, and how should we be using them in practice?

This is CME on ReachMD. I'm Dr. Caroline Baumal, and joining me today for the discussion is Dr. Carl Regillo, who is a colleague, a friend, and a mentor. Carl, it's great to have you here.

Dr. Regillo:
Well, thanks so much, Caroline. Real pleasure to be here with you.

Dr. Baumal:
Let's start with a case. This is a 51-year-old female who is a non-insulin-dependent diabetic and has poor glucose control. It's amazing she'd never seen an ophthalmologist before, and she came in with vision of 20/200 in the right eye and 20/60 in the left eye. And I think what's notable is that if we look at the OCT [optical coherence tomography] here, on the cube as well as on the structural OCT, she has marked center-involving diabetic macular edema. It's also notable that in the right eye, she has a lamellar hole.

This lady was treated with 12 anti-VEGF [vascular endothelial growth factor] injections over 16 months, so she almost had monthly bilateral injections. And this was really the maximal interval that she could come in and have treatment, remembering that she had a job, she had children, and she had other needs that she needed to take care of related to her diabetes. Of note, she also had some other types of treatment. She had a steroid injection, and she had focal laser as well. And we can see, if we look at the OCT on follow-up 16 months later, it certainly looks improved, but it is not back to normal. The swelling now, the edema, is now external to the fovea, but it's still present and marked on the cube.

Dr. Regillo:
Caroline, this is a great case and very typical case of DME – moderately severe, requiring a lot of anti-VEGF therapy, among other things that you utilized here to try to get the edema better. And you did. But going forward, this patient's likely to need more treatment, more therapy. We now have faricimab as an FDA-approved therapy to treat DME. How do you see it fitting in for this patient?

Dr. Baumal:
Well, Carl, this patient highlights so many of the issues that we see every day. Patients who haven't had time to even consider seeing the ophthalmologist, so when they come in, it's too late. Then requiring almost monthly treatment, which we know is effective, but it is a

burden on patients, caregivers, and even on physicians to maintain. It's sort of, really, unrealistic to have monthly treatments in the short term and in the long term. So I think that to have treatments that have longer durability will improve the findings for our patients, for their visions, and will allow us to treat more people successfully.

And I'd like to highlight faricimab, which is a bispecific molecule that targets and neutralizes not only VEGF-A, which is an agent that we've been targeting for the last 15 years, but it also targets and neutralizes Ang-2, which is a key player in vascular stability from the angiopoietin/Tie2 pathway. And faricimab was evaluated in the two phase 3 – YOSEMITE and RHINE – trials, And faricimab demonstrated durable efficacy with the 2-year results most recently released at Angiogenesis.

One thing that's notable is that faricimab was dosed up to every 16 weeks, and this was shown in the PTI – the personalized treatment interval – arm of the study. And looking at this, 78% of patients at the end of 2 years were on every-12-week, or every-16-week dosing, and 62% of patients were on every-16-week dosing. Faricimab also demonstrated comparable visual acuity gain when compared to the aflibercept comparator arm. Faricimab demonstrated improved anatomic outcomes, with dosing up to every 16 weeks, compared to aflibercept dosing every 8 weeks, and this included favorable change in central subfield thickness. More of the faricimab-treated patients achieved absence of diabetic macular edema, and more of these patients achieved absence of intraretinal fluid. Also notable was that faricimab was well tolerated, and there were no unusual safety concerns.

For those just tuning in, this is CME on ReachMD. I'm Dr. Caroline Baumal, and I'm joined by Dr. Carl Regillo to discuss the latest strategies in treatment of diabetic macular edema and neovascular AMD.

Dr. Regillo:
Let's switch gears now and talk about neovascular AMD. I have a case here; it's pretty typical. This is a 77-year-old female with acute distortion and blur symptoms in her left eye for about 3 weeks. She came in, as shown, with a fluorescein angiogram indicating wet AMD. There is leaking choroidal neovascularization here, and the OCT shows typical features – subretinal fluid and CNV [choroidal neovascularization] – and her visual acuity in this affected eye was decreased at 20/60. So we started her on a course of anti-VEGF therapy utilizing aflibercept, initially monthly, and she was responding really well. Her initial course here shows that just after 2 treatments, the macula is drying up nicely and her visual acuity is improving, up to 20/30 now. And we then started to just do the typical treat-and-extend approach. We extended her treatment interval by 2 weeks. At 6 weeks, she still looked really good – 20/30 vision, holding well, but when we tried to get to 8 weeks, this is when we start to see recurrent fluid and her visual acuity started to drop. So that is not something I would want to tolerate, when the visual acuity declines with recurrent exudation, so typical treat-and-extend regimen, we reduced the treatment interval back down to 6 weeks, and again, at 6 weeks, looking good, but 8 weeks just didn't cut it. So we've got a good response, good outcome, at least initially, with aflibercept injections up to every 6 weeks. But unfortunately, not much more durable than that, because every time we went to 8, we got recurrent fluid.

Dr. Baumal:
Treatment for this patient's interesting Carl, because wouldn't you want to try to extend the treatment interval with one of the newer agents, brolucizumab or faricimab? What's your approach?

Dr. Regillo:
Yeah, absolutely. We now have what a lot of us are calling sort of second-generation anti-VEGFs, recently FDA-approved for treating wet AMD. That includes brolucizumab. It performed well in clinical trials, noninferior to aflibercept, with a bit less frequent dosing. About half the patients were able to be dosed in controlled disease up to 12 weeks at the treatment intervals through years 1 and 2. And that's pretty impressive. And then we have faricimab, also FDA-approved now for treatment of neovascular AMD, and it also performed really well in the pivotal phase 3 studies, again, being noninferior to aflibercept and dosed less frequently. And in fact, the faricimab phase 3 program had dosing intervals at the end of year 1 – the primary endpoint – where over 75% of patients were being dosed every 12 weeks, and about 45 or so percent of patients were dosed even longer, at every 16 weeks. So we have 2 new drugs that are definitely more durable, particularly faricimab, looking very impressive in that regard.

Dr. Baumal:
And, Carl, what about the safety of these agents? We know that brolucizumab can cause intraocular inflammation and has been associated with this uncommon finding of occlusive retinal vasculitis. How should we use brolucizumab, and are there any safety concerns about faricimab?

Dr. Regillo:
Yeah, you're right. Unfortunately, with brolucizumab, even though it performed well clinically in terms of efficacy, there were safety issues with significant imbalance with higher rates of intraocular inflammation that was at times severe, and as you mentioned, with some direct retinal effects with occlusions and vision loss. And so, unfortunately, most people do not consider it something for first line because of the safety concerns, and that's where faricimab, I think, shines. We get that same added durability or even greater durability,

but with a better safety profile. There was a slight imbalance in intraocular inflammation in the phase 3 trials in the neovascular AMD program, but it was really small and there were not any cases of retinal vasculitis or vasculitis-related occlusion. So definitely better safety profile. And so for a case like this where we want to get better durability, I think faricimab's probably the next best choice.

Dr. Baumal:
Carl, what about the port delivery system?

Dr. Regillo:
Yeah, that's another potentially really good option for, really, any of our wet AMD patients that want to decrease the treatment burden, as we've been talking about. And here we have another FDA-approved true, sustained delivery-like approach. So what is port delivery? Of course, it's an intraocular reservoir device. It was FDA-approved back in October 2021, and it delivers a customized, high-concentration version of ranibizumab in a slow-release fashion in this device you can refill in the office. So it's a onetime trip to the OR to put the device in and then refilled in the office, and so that's a consideration for anyone wanting to get some truly sustained delivery of an anti-VEGF. And so, how did it perform? Well, in phase 3, it performed really well. Obviously it met its primary endpoint so it was FDA-approved, and we now have, just recently – shown are the 96 weeks – so end-of-study outcomes for that phase 3 Archway study. And again, port delivery system performed really, really well. It controlled exudation and held vision really well and essentially identical to gold standard monthly injections of ranibizumab.

And even more so, not only is this good demonstration of sustained delivery with no less than 6 months with very, very rare rescue or supplemental treatments needed in the course of the trial, patients also were really satisfied with the notion of having the port. So patients in the study were asked, "Well, you've received injections before to get into this study, and you now have the port. What do you prefer?" And the vast majority were very happy with and preferred the port over getting ongoing injections.

It's also important to consider, of course, because the port delivery system is a device and it takes a trip to the OR to place the device, there are some unique safety issues. And a lot of the safety aspects, adverse events, for example, specifically associated with the device are related to surgical technique, and that's an important consideration. But you can expect patients that have the device will have increased risk for or increased rates of vitreous hemorrhage, conjunctival retraction, erosion, and endophthalmitis, greater than if the patient was to continue with intravitreal injections.

So in terms of safety and learning about the surgical techniques, and for those interested in learning more about best practices with the port delivery system, please visit EyeHealthAcademy.org.

Dr. Baumal:
Carl, what about intraretinal fluid with the PDS? We use OCT to help manage our patients, and should we look at intraretinal fluid with the PDS in the same way as with intravitreal anti-VEGF injections?

Dr. Regillo:
Yeah, that's a really good question because it may not be the same as we currently think about fluid or recurrent fluid in managing wet AMD, mainly because, you know, you're dealing with true sustained delivery. So it basically wears off much, much slower. So we shouldn't be compelled to necessarily jump on every little bit of recurrent fluid with a patient that has the port. It's not as time sensitive or as urgent as it would be if you were doing intravitreal injections, which wear off much faster.

You know, we've discussed several great new treatment options today. As we wrap up here, what are your takeaway messages for our audience?

Dr. Baumal:
Carl, I think with these second-generation and novel agents, we've been able to see better drying on the OCT with these agents, and of course, safety is paramount concern for our patients. We always want any new treatment to be safe and worry free.

Dr. Regillo:
Very true, and I'll add to that. We're talking, you know, significantly greater durability with faricimab being injected intravitreally, and even more so, of course, with sustained delivery, utilizing the port delivery system. And that is going to lead to greater patient satisfaction.

Caroline, thank you so much for joining me today. It was a great discussion.

Dr. Baumal:
Carl, it was great to talk to you, as always, about these upcoming, exciting topics in retina.

Announcer:

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