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Cases From the Real World: 61-Year-Old With Wet AMD With a High Treatment Burden

Dr. Leng:
I have a 61-year-old patient with neovascular AMD who needs frequent injections with a high treatment burden. Fortunately, there are several new, more durable treatment options available, and we're going to talk about some of the considerations around determining which treatment is best for each patient. This is CME on ReachMD. I'm Dr. Ted Leng, and joining me today is Dr. Danny Mammo.

Dr. Mammo:
It's great to be here.

Dr. Leng:
So let me tell you a bit about this patient. She has a past medical history of prediabetes, hyperlipidemia, osteopenia, had some knee surgery and is on AREDS vitamins, and calcium. Her past ocular history includes some mild cataracts in both eyes and epiretinal membrane on the right eye, which I'll show you in just a moment, along with some intermediate dry macular degeneration. And the left eye has neovascular AMD.

So here's that right eye with the mild epiretinal membrane, which you can see here on the surface of the retina, and some large drusen consistent with the intermediate AMD. She has good visual acuity at 20/25 in that right eye. Looking at the left eye, this is how she presented at baseline, with a vision of 20/70, and you can see here intraretinal fluid next to the choroidal neovascular membrane.

Over the course of the time I've been taking care of her, we've tried almost every anti-VEGF agent that we have in our arsenal. We started initially with bevacizumab, and she had 5 of those without a good anatomic or functional response. So we switched her to aflibercept 2 mg, and she eventually received aflibercept 8 mg. And most recently, she's been on faricimab 6 mg, and has received 40 injections of that agent.

Here are some examples of the high treatment burden. She developed metamorphopsia, even on monthly treatment on bevacizumab. And there was evidence of OCT leakage after 5 weeks on aflibercept 2 mg, and even after 4 weeks after aflibercept 8 mg. While she is stable at 4 weeks on faricimab, if you let her go 5 weeks on faricimab, she also shows leakage. So this is obviously a patient who has a very high treatment burden.

Danny, have you had any patients similar to this woman?

Dr. Mammo:
Thanks, Ted. Yeah, unfortunately, I have a handful. First off, though, kudos to you. I mean, this patient's lucky to have you. It's not easy to have to see this patient every month, there's still fluid. Sometimes the patient will get sick of you, but obviously she likes you, and she stuck with you, and you didn't give up on her. You switched her to different agents. You kind of went all out, and you used our newer-generation agents. Unfortunately, I have some patients like this, and they're humbling, because we have this higher molar dose aflibercept 8 mg. We have this faricimab that now provides Ang-2 protection, which seems to have some effect.

But why do some patients continue to have fluid? Why did it occur so much? Maybe there's other mechanisms that we're not aware of. So these are very tough. I think you managed it great here. But unfortunately, I have some too that need to be stuck at q4, q5 weeks.

Dr. Leng:

Have you ever tried doing combination therapy with photodynamic therapy at all in these eyes?

Dr. Mammo:
Especially with some of the issues with patient assistance programs right now and patients struggling to get some medications, I've really been using photodynamic therapy to help reduce some persistent fluid, to allow patients to gain extension. I usually reserve it for CSR, but more recently, I've been also kind of pulling it into our arsenal for some neovascular AMD patients as well.

Dr. Leng:
Wonderful. Thanks for sharing that.

Let's go into some of these examples of the fluid. So here's after 8 mg of aflibercept. This is 4 weeks. You can see here a trace amount of subretinal fluid here in the center of the fovea. And while the patient was 20/20 -3, she did note metamorphopsia, even with that small amount of fluid. So there was both anatomic and functional evidence of disease activity.

So if you went 5 weeks after faricimab, she also had subretinal fluid and intraretinal fluid, as you can see here in this OCT. But if you kept her on 4 weeks of treatment with faricimab, there was no disease activity on the OCT here, without any fluid, and she had some slight improvement in vision at 20/20 -1.

So while in the clinical trials of TENAYA and LUCERNE they were able to extend patients out to 12 and 16 weeks and even beyond. Why do you think we're not seeing that consistently in patients in the real world, especially in this example, which is a very extreme example, I'll be honest, where we have to treat her monthly, essentially, with this latest generation anti-VEGF, anti-Ang2 agent with faricimab. Tell me a little bit about your experience and why you think we're not seeing this in the real world.

Dr. Mammo:
That’s a great, great question, because sometimes we'll get these medications into the real world and we'll say, huh, why is this not looking like how the trial data that I'm looking at looks like? Well, one big part of it is that the patients we’re treating might not be like the trial data. These trials, while they provide us with great information, they provide the patient with excellent medication, really their goal is to get approved, and they have strict inclusion and exclusion criteria, which makes sense. But our patients, our clinics, don't have inclusion/exclusion criteria, besides maybe some sort of insurance coverage. So we see patients with a variety of health issues and lesion types and vision ranges that might not have been included in the trials.

Also a lot of us, at least me, I usually dip my toes with these newer agents and patients that are maybe treatment resistant or recalcitrant, you could say, had already been using other medications. They're not treatment naïve, their fluid’s not drying up, so then let me try some of these newer agents. So it’s sometimes a little bit of an unfair test with these newer agents, because I'm using it on some harder to treat patients.

In trials, they're also very strict about doing loading doses. Not everyone in the real world is going to do 3 or 4 loading doses, so that might also affect how durable these medications might be in the real world.

And lastly, in these newer trials, so like PULSAR, TENAYA, LUCERNE, these patients really couldn't drop below q8 weeks. And we know that's not really what happens in our real world. So for example, this patient in the trial might not have been allowed to go less than q8 weeks. So trial and real world is a little bit different.

What's been your experience?

Dr. Leng:
I completely agree with you. I think you brought up a lot of really great points here. I think the trials are limiting in certain ways and also overoptimized in other ways, right? We're not seeing patients monthly, like we do in clinical trials, where we get to monitor a lot of

parameters. Maybe with the home OCT monitoring, that'll be kind of a different story, where it's also almost mimicking a clinical trial and as far as observation of patients. But in these trials a lot of patients were excluded because of different criteria. And you also mentioned the minimum dosing, they weren't allowed to fall below q8 weeks.

But talk a little bit about the amount of fluid in these trials, like, are we tolerating less fluid in the real world than you would do in a clinical trial?

Dr. Leng:
For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Ted Leng, and here with me today is Dr. Danny Mammo. We're discussing real-world use of second-generation retina treatment in patients with neovascular age-related macular degeneration who have a high treatment burden.

Dr. Mammo:
Yeah, that's another great question. Here we're talking about a case with neovascular AMD, which is a little bit different than diabetic macular edema, where we know we can tolerate some fluid for diabetes, but really, many retina specialists don't like to tolerate too much fluid when it comes to neovascular AMD. But we know that in these trials, the retreatment criteria or the rescue criteria, does allow some increase in fluid, whether it's intraretinal or subretinal. They have different micron limits. Whereas in our clinics, where we're seeing so many patients, many of us might be programmed to just look oh yes or no, is there fluid? Is there not fluid? We're not really counting the microns all the time. So while the trial might tolerate some fluid and not rescue a patient, where in our clinic we might see any amount of fluid and go ahead and rescue it, or give another injection.

And in clinic, I think a lot of us also do differences when it comes to intraretinal fluid or subretinal fluid. Do you approach those any differently at all, Ted?

Dr. Leng:
Yeah, I think there's been some data, especially from the group out in New York, that showed a small amount of subretinal fluid can be tolerated even if the patient's vision is still good and they're not symptomatic. So I think in my practice, I do tolerate a little bit of subretinal fluid, especially if the patient isn't mentioning any increasing symptoms.

I also have some colleagues that are in very busy practices where they're seeing 80 or 110 patients in a given day, and so they have to be very algorithmic with their treatment strategies. So if they see a little bit of fluid, they might initiate a series of a few injections before they reevaluate the patient again. And that's just the reality of the demand that's placed in our clinics and our workflows right now.

So have you seen patients that are symptomatic, even if the vision is good? So they're measuring 20/25, 20/20 in the eye chart, but they're still complaining of some abnormalities?

Dr. Mammo:

Totally. Totally Ted. I think some patients are particularly attuned to when just the smallest amount of fluid comes back. They know what week it is. They know it's time for a shot. There's also vision parameters that are not best measured by our Snellen visual acuity, contrast sensitivity, low light luminance, visual acuity. These types of things are things I think patients can notice that might not be picked up on the Snellen chart.

Dr. Leng:
Do you think kind of more of a zero-order kinetic treatment, like a port delivery system or implant type thing, could help to even out these variances throughout the month or 2 months between injections?

Dr. Mammo:
Yeah, that's a really interesting question, right? We're talking about second-generation treatments like aflibercept 8 mg and faricimab, and the PDS is kind of like a newer generation treatment modality that allows us to deliver these medications in an interesting way. There is some suggestion that fluctuations may lead to vision loss and fibrosis, potentially. And perhaps, as you astutely alluded to, this zero-order kinetics of constant anti-VEGF delivery may reduce fluctuations in these patients that are very difficult to treat. And I think for these difficult-to-treat patients that are requiring so much treatment burden, there is a role for the PDS implant.

Dr. Leng:
Yeah, I really see that very much akin to the corticosteroid long-duration implants that we have. I've had really great experience with all those agents actually and really helping patients out, because you do get this nice low-level amount of drug that's coming out consistently, and I really do think that affects the pathophysiology of the conditions we're treating.

So let's take a look at a few datapoints here. We did talk about why some patients aren't able to extend out to the different intervals. But if we look back at these trials themselves, this is the TENAYA and LUCERNE results here, and this is the heat map, with each patient being represented by a different row in this very compact slide. But you can see here at the bottom, the patients who are in the kind of beige or brown color, those patients had to remain on the q8-week dosing interval to maintain the vision and the anatomic parameters of the trial, whereas the patients at the top and the pink were able to extend out to 16 weeks. So even in the phase 3 pivotal trials, not all patients were able to extend out to these extended dosing intervals that we're trying to hope for for our patients.

And similarly, in the aflibercept PULSAR trial, the 8-mg aflibercept trial, at the bottom is the gray bars, which are the eyes that remained on the 8-week dosing intervals, whereas in the green and the teal color, were the eyes are able to be extended out to 12 and 16 weeks in this trial.

I also wanted to touch on the addition of Ang2 in the faricimab. Here is a data slide from TENAYA and LUCERNE, looking at the CST data comparing to aflibercept 2 mg, given every 8 weeks, and showing a significant reduction in central CST numbers here on OCT between faricimab at 4, 8, and 12 weeks. This is in the loading phase compared to that aflibercept 2 mg.

And lastly, I do want to touch on some older studies, especially the HARBOR study. On the right here, you can see the HARBOR data study, which is where we took ranibizumab, which is normally given at 0.5 mg, and quadrupled that dose to 2 mg. And so just increasing the dose of anti-VEGF doesn't necessarily result in better anatomic outcomes. As you can see, these bars overlap, and there was no difference in the central CST numbers between that 0.5-mg dose and the 2-mg dose.

On the left, you can see data from PULSAR, looking at aflibercept 8 mg versus 2 mg, and also showing no real difference at 4, 8, and 12 weeks in central subfield thickness on those eyes.

Dr. Leng:
Bringing this home, a subset of patients with neovascular AMD have high treatment burdens, even with second-generation agents. And these agents may offer better disease control. The addition of Ang2 suppression increases drying while increasing in anti-VEGF suppression alone does not.

Unfortunately, that's all the time we have for today. I want to thank our audience for tuning in. And Danny, thank you for being here.

Dr. Mammo:
Thank you.