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<https://reachmd.com/programs/cme/Cases-From-the-Real-World-91-Year-Old-Patient-With-Wet-AMD-and-a-Submacular-Hemorrhage/33168/>

Released: 07/11/2025

Valid until: 07/11/2026

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Cases From the Real World: 91-Year-Old Patient With Wet AMD and a Submacular Hemorrhage

Dr. Mammo:

Hi, I have a 91-year-old patient with neovascular AMD in both eyes who developed a submacular hemorrhage. Here's how I managed this case with second-generation treatment options. This is CME on ReachMD. I'm Dr. Danny Mammo, and joining me today is Dr. Ted Leng.

So I have a 91-year-old patient, pseudophakic in both eyes, with a history of retinal tear in the right eye, status post laserpexy times two. He's a former smoker, has hypertension, hyperlipidemia, CKD, and he takes a baby aspirin. He has neovascular AMD in both eyes, with a strong familial history with his paternal uncle and aunts both with neovascular AMD. The left eye, unfortunately, has inactive end-stage neovascular AMD, as we'll see with a disciform scar, status post multiple anti-VEGF agents, developed a submacular hemorrhage requiring surgery with subretinal TPA, bevacizumab, fluid-air exchange and gas many years ago. The right eye has been receiving aflibercept 2 mg, on a q4 to 5-week interval.

Here are images of the right eye. We see laser from the prior retinopexies. In the center, we see RPE modeling and some atrophy. Here's the left eye at the time of presentation, just showing how severe of a submacular hemorrhage this patient had while he was on q4-week bevacizumab. So very prone to bleeds here. Unfortunately, after surgery in the left eye, the patient had developed a disciform scar, and it's 20/400. The right eye, which is doing very well, converted, unfortunately, to neovascular age-related macular degeneration 3 years later after the surgery in the left eye. Vision dropped to 20/200, and aflibercept 2 mg was started.

Now, the patient did very well. However, he was unable to be extended past q4 or 5 weeks 2 mg of aflibercept. And unfortunately, just like the other eye bled on q4 to 5-week anti-VEGF treatment, this eye developed a submacular hemorrhage. We don't have a fundus photo, but you can see it here in the en face image results, PED with subretinal hyperreflective material, subretinal fluid, suggesting a breakthrough submacular hemorrhage.

So this patient was switched to faricimab. The hemorrhage nicely resolved. We see in the en face image here a resolution in the thickness. We see that the PED has flattened, and we see a resolution in the subretinal fluid. Vision improved to 20/100, and the patient was able to be extended to faricimab q12 weeks, which the patient is currently undergoing treatment for.

So Ted, what has been your experience in switching patients to these newer agents such as faricimab?

Dr. Leng:

Well, I think I'd first like to point out that I think we're very fortunate right now to have so many options for our patients, especially those with neovascular AMD. You mentioned you use bevacizumab in the other eye and aflibercept 2 mg in this eye and then switched to faricimab. So I think we have seen some benefit to switching to these newer second-generation agents in eyes that were recalcitrant or requiring really frequent therapy. And I think both using faricimab and 8 mg aflibercept, and in the past, brolucizumab, we've seen greater efficacy in these types of eyes.

Dr. Mammo:

Definitely. And when you see a patient that has a pigment epithelial detachment with surrounding subretinal fluid or surrounding subretinal hyperreflective material,

let's say they're a new treatment-naïve patient to you, how do you approach those patients? Do you change your use of anti-VEGF at all? Do you counsel them differently?

Dr. Leng:

Well, I think we're all a little bit concerned about the potential for an RPE rip or tear when you do see a PED, especially if it's large. There have been studies looking at the height of those PEDs and the correlation with the risk of a tear or rip. But the reality is, you have to treat the patients regardless, because if you don't treat them, they will still lose vision due to the neovascular AMD activity.

So while there is a potential risk of the RPE tear, I still continue with the anti-VEGF therapy. And sometimes I do bring it up with patients and say there is a risk of this adverse event with anti-VEGF therapy. But oftentimes I don't bring it up because it's not going to change our management. And the patient already has decreased vision from the neovascular lesion, so if they do get a tear or rip, oftentimes their vision will actually be better than they were at baseline. Now, has what your experience been with these types of patients?

Dr. Mammo:

Yeah, that last point you mentioned is great. I've been surprised sometimes when a rip happens that sometimes the patient doesn't even notice, sometimes the vision is better. But then I've also been burned by when the vision also gets a lot worse. And those cases, I think, have kind of scarred me, where for most PEDs, I don't really mention much. But for those very large PEDs, I do get a little bit worried, and I kind of just tell the patient, you know what, this is kind of a catch-22 here. Damned if you do, damned if you don't. I have to treat you. If I don't treat you, it's going to get worse, but there's a small chance that my treatment works too good, and if this thing shrinks too fast, it might actually lead to more vision loss. But honestly, there's not much you can do. I would get this treatment if it was me. And I just kind of say that so they know if it does get worse, that it was a possible outcome. Especially with these new treatments, which, as you mentioned, have been shown to be really good at drying up these PEDs, which we'll go through some of the data in a little bit.

When you have a monocular patient, like this case; this case, the patient unfortunately became monocular, then developed a conversion in this eye. And the patient asks you, 'Doc, when can I stop this treatment? Can I ever stop this treatment?' What do you tell them?

Dr. Leng:

That's a really interesting and tough question to deal with with these patients, Danny. If you've lost vision in one eye, you only have one functional good eye left, you've really got to protect that as much as possible. So I'm really upfront with patients and let them know that, unfortunately, I think that this is a lifelong therapy right now with the current technology, that we need to keep on treating that eye so that they can remain functional.

On top of that, I like to be as conservative as possible with as much treatment as possible. So I'll tend not to extend those eyes out as much as I would with patients who don't have monocular vision. So with our older generation agents, such as ranibizumab or aflibercept 2 mg, I typically won't extend beyond 8 weeks in a monocular eye. And with the newer agents, I might go out to 12 or 16 weeks, but I still don't have a lot of experience going out further than that.

Dr. Mammo:

Yeah, I totally agree. I think conservative management would be to maintain the injection. So I'm pretty upfront, and tell these patients if it was my eye, I would want injections for life.

I feel a little bit uneasy about going all the way out past 20 weeks, which we know we can do with some of these newer agents based on the TENAYA, LUCERNE, and PULSAR studies. But I will try to keep them usually somewhere around 12 to 16, 18 weeks I've pushed it. But once it gets 20 plus, I get a little bit uneasy.

You made a great point about overtreating potentially rather than undertreating. I think we're entering a very exciting time, because currently we have Protocol AO that's being undertaken by the DRCR that's going to allow us to talk about home OCT. Right now, treat-and-extend is the way we need to treat patients, because frankly, we don't know which patients require a few injections versus a lot of

injections. And we do overtreat because we know that compared to a PRN treatment, treat-and-extend leads to better vision outcomes on aggregate. But home OCT, I think, is going to allow us to offer more personalized treatment.

What are your thoughts on that, Ted?

Dr. Leng:

I think home monitoring is a future of our field. To be honest, I think every patient who has active macular disease and is being treated with drugs should be monitoring themselves at home. And it's really going to allow us to personalize the treatment and the treatment intervals for the patient's benefit, reduce the number of visits in the clinic, and also reduce the number of the procedures we have to do to their eyes. So only treating when there's actually a signal, a biologic signal, that we can see in OCT that requires a treatment, I think it's going to be the optimal treatment strategy for these patients.

Dr. Mammo:

I totally agree. Yeah. And for the listeners, Protocol AO is going to be a multi-center, randomized trial with hopefully around 600 eyes. And patients are being randomized to treat-and-extend, the most common way we treat neovascular AMD today, versus home OCT-guided treatment. And the primary outcomes are going to be a superior comparison of mean change in visual acuity, as well as the difference in number of injections from baseline all the way out to 2 years, 104 weeks. And the treatment arms are going to be receiving faricimab, one of our newer agents for their treatment.

So this case that we talked about, if we go back to it, had a submacular hemorrhage in both eyes. Do you change which agent you use when you see a patient with a submacular hemorrhage, Ted?

Dr. Leng:

I think I tend to go to a more powerful medication if I see submacular hemorrhage, because that indicates to me a higher level of disease activity. So I wouldn't choose something like bevacizumab, for example. And now that we have these newer generation agents, I'd probably steer towards one of those when I initiate therapy in an eye with submacular hemorrhage, just to get the most activity possible to really clear up that hemorrhage and improve vision and preserve photoreceptors.

Dr. Mammo:

Yeah, I totally agree. You kind of want to go all out for these patients. And going all out right now I think means one of these newer generation agents, whether it's 8 mg aflibercept or faricimab. We also have brolucizumab, but that's not really used much anymore because of the adverse effects and IOI and vasculitis.

There was a retrospective study of over 9,000 eyes in the American Journal of Ophthalmology that looked at anti-VEGF agents and the rates of submacular hemorrhage. Notably, this study did not include aflibercept 8 mg. But when we look at the newer agent, faricimab, or brolucizumab, compared to older agents like aflibercept 2 mg, bevacizumab, ranibizumab, those agents saw anywhere from 25 to 38% submacular hemorrhage occurrence, whereas faricimab saw 1.7%. There is some data suggesting that these newer agents may prevent or treat submacular hemorrhages a little bit more effectively. That could be due to the higher molar dose of 8 mg, or it could also be due to the Ang-2 effect of faricimab.

What do you think about this purported Ang-2 effect, Ted, when it comes to faricimab?

Dr. Leng:

I definitely think that the Ang-2 is giving us something beyond just anti-VEGF. We've seen some data recently where, looking at central subfield thickness in different trials, that there has been an additional benefit from the Ang-2 inhibition compared to VEGF inhibition alone.

Dr. Mammo:

Yeah, I think the data that we went through that shows the improvement in fluid really speaks to the Ang-2 benefit. In TENAYA and LUCERNE, we were able to see and compare faricimab to aflibercept 2 mg. And PULSAR also allowed us to compare aflibercept 8 mg to 2 mg. Unfortunately, we don't have a head-to-head comparison of the newer second-generation agents, but we do have a comparison of these newer agents to aflibercept 2 mg. And in TENAYA and LUCERNE, we see that at all weeks from week 4, week 8, to week 12 through the loading phases, when comparing aflibercept 2 mg to faricimab, we saw a greater absence of intraretinal fluid and subretinal fluid in the faricimab groups, which suggests a greater drying effect.

PULSAR showed us similar findings. When we looked at the central subfield in patients that were getting aflibercept 2 mg every 8 weeks, compared to those getting aflibercept 8 mg every 12 or 16 weeks, after the loading doses and at year 1, a greater percentage of patients in the aflibercept 8 mg group had less fluid in the center compared to aflibercept 2 mg.

And it's also notable, this case, we kind of talked about PED heights and risk of tears. In TENAYA and LUCERNE with faricimab, there was actually a greater reduction in PED thickness and height when compared to aflibercept head-to-head dosing at weeks 4, 8, and 12. And if you looked at serous PED thickness for the post hoc analysis, faricimab also showed a reduction in thickness by 50% compared to aflibercept 2 mg.

When you see that the PEDs are getting improved so much, you kind of ask the question about, is there an increased risk of retinal pigment epithelial tears? And these were associated with larger PED heights at baseline. And in the faricimab group up to q16 weeks, there was 2.9% rate of RPE tears, whereas in the aflibercept q8 weeks, there was a 1.5% risk of RPE tears. So definitely something to be mindful for in our patients getting these newer generation treatments.

We have some take-home messages from our discussion today. Early real-world data shows lower rates of submacular hemorrhage associated with faricimab when compared to aflibercept 2 mg, the newer agents such as faricimab or aflibercept 8 mg, seem to have increased drying effect and durability. We're still waiting for real-world data around treatment with aflibercept 8 mg as it relates to submacular hemorrhage. And home OCT may allow for early detection of conversion to neovascular AMD in at-risk patients and more personalized treatment regimens.

Well, that's all we have time for today. Thank you to our audience for joining us, and a big thank-you to Ted for joining me today.

Dr. Leng:

Thank you, Danny.