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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Fluid Dynamics Demystified

Dr. Goldberg:
Second-generation agents are here with better drying and greater durability. So what are the data around improving retinal drying? I'm Roger Goldberg, and joining me today is Ehsan Rahimy.

Dr. Rahimy:
Roger, it's great to be here. Goal number one when treating our patients with exudative diseases is to dry the retina as much as possible, as soon as possible. There is some prognostic value in being fluid free after loading phases, and we've learned this from several of the clinical trials that have been done in our field.

First off, there was a nice post-hoc analysis from the HAWK and HARRIER trial data, which had compared aflibercept to brolucizumab. And it looked at patients with any anti-VEGF treatment, so in both groups essentially, and showed that early resolution of fluid by week 12, which was the end of the loading phase, was actually predictive of continued fluid-free status, greater visual acuity gains, and reductions in central subfield thickness in patients with neovascular AMD.

Separately, we had some of our pivotal studies with faricimab. We had TENAYA and LUCERNE for neovascular age-related macular degeneration, and YOSEMITE and RHINE for diabetic macular edema. Both studies mirrored these findings, which was faster time to first absence of fluid, be it intraretinal fluid and subretinal fluid, compared to aflibercept 2 mg in the neovascular AMD studies. And, in particular, for neovascular AMD, resolution of intraretinal fluid and subretinal fluid between weeks 4 to 12 when you were having these loading doses, was associated with much greater odds of being able to extend treatment out further to potentially q12- or q16-week intervals.

For diabetic macular edema, increased durability was associated with either being treatment naive, having the lower baseline central subfield thickness and greater central subfield thickness reductions at week 16.

And finally, we have our PULSAR and PHOTON clinical trial data, which was for the higher-dose version of aflibercept 8 mg. And in PULSAR, patients with neovascular age-related macular degeneration, more patients were noted to have an absence of fluid in the retina at week 16 and 48 versus the comparator aflibercept 2 mg arm. And a shorter time to having a fluid-free central subfield thickness as well too. In the PHOTON study, we saw a nice secondary analysis that was done that showed patients with DME had greater amounts of fluid reaccumulation after their last monthly injection with 2 mg of aflibercept versus after 8 mg of aflibercept.

Dr. Goldberg:
That's a great summary. I want to highlight two additional studies, just to kind of piggyback what you're just talking about, Ehsan. One was from the PHOTON study, which compared 2 mg versus 8 mg aflibercept in patients with DME. And if you look at the most recalcitrant, difficult to treat eyes, what you saw is that there was a dramatic reaccumulation of fluid 8 weeks after the loading phase in the eyes treated with 2-mg aflibercept, about 55 µm. Those treated with 8 mg aflibercept 8 weeks after their loading injection, only had 5.7 µm of fluid reaccumulation in the central subfield thickness. So again, not necessarily better drying, but better durability.

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And what about when you add Ang2 versus just increasing the dose of VEGF-A inhibition. Well, when you compare the results of TENAYA and LUCERNE versus the HARBOR study, which had four times the dose of ranibizumab, and you didn't see increased drying, in TENAYA and LUCERNE you did see increased

drying with faricimab. And that same result was seen in the DME studies, YOSEMITE and RHINE, in comparison to a study called READ-3, which looked at quadruple the dose of ranibizumab. So again, it suggests that adding Ang2 might actually lead to better drying, kind of, sooner in addition to the durability advantage.

Dr. Goldberg:
So while we don't have head-to-head data comparing high-dose aflibercept to faricimab, this certainly gives us something to think about when trying to pick out what's the best agent to treat our patients with wet AMD or DME.

Dr. Rahimy:
I couldn't agree more, Roger.

Dr. Goldberg:
Well, unfortunately, our time is up. Thank you to our audience who tuned in today, and thank you to Ehsan for joining me tonight.

Dr. Rahimy:
Thanks for having me.

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