RETINA
SPECIALIST

CLINICAL TRIAL CLOSEUP

A Smaller, Faster Anti-VEGF Therapy

How brolucizumab may extend dosing out to 12 weeks.

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The quest for vascular endothelial growth factor antibodies that require less than monthly dosing has been ongoing since ranibizumab (Lucentis, Roche/Genentech) gained approval for treatment of wet age-related macular degeneration. The paradigm shifted in 2014 when aflibercept (Eylea, Regeneron) was approved for eight-week dosing for diabetic macular edema, and while treat-and-extend protocols have made significant progress in stretching the intervals between injections, patients and retina specialists have to go through months of trial and error before they arrive at a routine.

The paradigm may shift again. Results from the HAWK and HARRIER trials reported at the Association for Research in Vision and Ophthalmology have shown that retina specialists may be able to ramp up quickly to 12-week intervals with Novartis' anti-VEGF candidate brolucizumab.

Pravin Dugel, MD, of Retinal Consultants of Arizona, first reported the HAWK and HARRIER results at the American Academy of Ophthalmology Retina Subspecialty Day Meeting in 2017. He reported that 57 percent and 53 percent of patients in the trials, respectively, could be extended to every 12-week dosing after a loading dose.[1] He additionally reported that in a head-to-head comparison vs. aflibercept (Eylea, Regeneron) at week 16, brolucizumab showed superior results on optical coherence tomography.

Brolucizumab, also known as RTH258, is a single-chain antibody fragment (scFv). Its small molecular size of 26 kilodaltons (kDa) enables the agent to penetrate tissue more effectively and clear more rapidly from systemic circulation than large-molecule drugs.[4–6] By comparison, the average protein has a molecular weight of 34 kDa, while ranibizumab's (Lucentis, Roche/Genentech) is 48 kDa and aflibercept's 115 kDa.

At ARVO, Glenn J. Jaffe, MD, of Duke University reported on important anatomical markers from HAWK and HARRIER that demonstrated brolucizumab was non-inferior to aflibercept for mean change in best-corrected visual acuity, but superior in terms of reductions in central subfield thickness and incidence of intraretinal and subretinal fluid after 48 weeks.[2]

Dr Dugel also reported predictability rates of 82 percent and 87 percent in HAWK and HARRIER in patients who successfully completed the initial 12-week cycle remaining on this cycle up to week 48.[3]

In its annual report, Novartis noted that this year it would file new drug applications in the United States, Europe and Japan for brolucizumab for treatment of nAMD and begin Phase III trials for diabetic macular edema, with filing expected for that indication in 2020. Analysts say they expect the Food and Drug Administration to approve brolucizumab for nAMD next year.

Here, Dr. Dugel, a principal investigator of HAWK and HARRIER, answers questions about brolucizumab.

Brolucizumab is unique in that it's the first single-chain antibody fragment in ophthalmology. The target is the same as other anti-VEGF antibodies: VEGF-A. What's different is the structure of the drug. An antibody is shaped like a Y, but only the tips of the Y carry the active component that interacts with the target; the rest of the structure provides stability. Brolucizumab is different because it is essentially only the tips of the Y. This gives the drug a smaller size and a higher molar concentration than existing anti-VEGF treatments.

The molar concentration of brolucizumab is 11 to 13 times higher than aflibercept. The smaller molecule size and high molar concentration means that the time of action may be earlier and the durability may be longer. An analogy is soccer, where you have 11 players on either side with the same size goal. The pharmacokinetics of brolucizumab are like having 144 players on the other side. The dimensions of the goal haven't changed, but the probability of achieving that goal has.

What unmet need does brolucizumab meet?

Wet AMD and diabetic macular edema are extraordinarily variable diseases. Some patients need to be treated intensely, others less so. We need a drug that can address individualized treatment needs. That is, how can we have a drug that has a higher molar concentration, that acts earlier and lasts longer in both types of patients? HAWK and HARRIER were designed to address treatments in both types of patients. In that regard, what HAWK and HARRIER showed was that at week 16, which is a very important milestone, brolucizumab was superior to aflibercept in every anatomical parameter studied by optical coherence tomography.

What was new about the HAWK and HARRIER results reported at ARVO?

HAWK and HARRIER had several prespecified time points of disease activity assessment; if patients had active disease, they were adjusted to q8-week dosing. The results presented at ARVO looked at the likelihood that those who completed the first q12-week dosing cycle would remain on q12-week dosing through the primary endpoint at year one.

The high percentage of patients that were able to continue on q12-week dosing in the latest HAWK and HARRIER results is consistent with the Phase I and Phase II OSPREY trials.[1,7] That's quite impressive in my opinion. This says that if you use the clinically defined criteria, and you are able to extend somebody to a q12-week cycle at initial treatment, the chance that that person is going to stay on that q12-week cycle is almost 90 percent. That should give the clinician greater confidence, in terms of predictability, to extend patients.

What are the next steps in the HAWK and HARRIER trials?

There is still a great amount of data from these trials that needs to be analyzed. Those results will be reported at upcoming meetings. There's also an extension study, per the FDA, that's a perfunctory study to ensure that the drug's manufacturing is consistent. The

filing will follow that. As with other anti-VEGF agents, I personally would like to see trials of this drug in diabetic retinopathy and diabetic macular edema, as well as vein occlusion.
RS

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