Brolucizumab in the Treatment of Neovascular Age-related Macular Degeneration

An Expert Interview with Pravin U Dugel

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Neovascular age-related macular degeneration (nAMD) is the leading cause of severe vision loss and irreversible blindness in people aged over 65 years in North America, Europe, Australia, and Asia.[1] Anti-vascular endothelial growth factor (anti-VEGF) therapies have led to great improvements in outcomes for patients with nAMD.[2] However, currently available anti-VEGF treatments require frequent clinic visits to monitor patient response to treatment and, in some cases, monthly or bimonthly intravitreal injections; a substantial treatment burden for patients and healthcare providers.[2] Brolucizumab (RTH258) is a humanized single-chain antibody fragment, and is a small molecule (26 kDa) that has shown potent inhibition of, and high affinity to, all VEGF-A isoforms.[3,4] Its small size allows enhanced tissue penetration and rapid clearance from the circulation.[4] The HAWK (NCT02307682)[5] and HARRIER (NCT02434328)[6] trials are phase III, 96-week, double-masked, randomized, prospective, multicentre studies investigating the efficacy and safety of brolucizumab compared with aflibercept in patients with nAMD. Primary data from these studies were presented at the American Academy of Ophthalmology (AAO) 2017 Annual Meeting on November 10, 2017, in New Orleans, US.[7] Data from a pre-specified analysis of the HAWK and HARRIER studies were presented at the Association for Research in Vision and Ophthalmology (ARVO) 2018 Annual Meeting, Honolulu, Hawaii.[8] In an expert interview, Dr Dugel discusses these data.

Q. What are the major unmet needs in the treatment of nAMD?

There are three major areas of unmet need. The first is improved efficacy in the short term, then increased durability of treatment, and finally maintenance and even improvement of efficacy in the long term. A drug or device that could address one of these three areas would be valuable; anything that could address two or three would be extremely valuable.

Q. How does brolucizumab differ from other anti-VEGF treatment options in nAMD?

Firstly, the structure of the molecule is unique. It is the first single-chain monoclonal antibody fragment; this contains only the active end of the molecule but not the constant repeats. From a clinical aspect, this allows a higher molar concentration because it is such a small molecule. As a result, the treatment interval can be extended for more patients. I think of it as the next-generation anti-VEGF therapy.

Q. What were the major findings of the HAWK and HARRIER studies comparing brolucizumab with aflibercept in patients with nAMD?

Brolucizumab met its primary endpoint of non-inferiority at week 48. Most of the patients were dosed every 12 weeks compared with every 8 weeks on-label treatment for aflibercept. Most importantly, in the comparison at week 16 where the dosing regime was identical in the two treatment arms, brolucizumab was superior to aflibercept in every anatomical (i.e., structural optical coherence tomography) parameter that was measured. For instance, in resolving intraretinal and/or sub-retinal fluid, brolucizumab was superior both at week 16 (the head-to-head comparison) and week 48 (the primary endpoint). When disease activity was assessed by an investigator, brolucizumab was also superior.[7]

Q. Could you tell us about the recent analysis of the HAWK and HARRIER data investigating the reliability of response to an initial 12-week treatment interval in predicting long-term response to this dosing regimen?

Not all patients respond the same way to treatments for nAMD; there is a wide variability in the disease. One unique aspect of the HAWK and HARRIER studies was that they were the first phase III studies to address this variability and the need for individualized treatments. Disease activity assessments were done by the masked investigator at various pre-specified time points to be certain that the appropriate patients were being extended to 12 weeks. If any of these disease activities were present, the patient was adjusted to an 8-week dosing interval for the remainder of the studies. There were numerous opportunities for the masked investigator to adjust dosing intervals to 8 weeks. Results showed that, after the first adjustment following the first cycle of 12-week dosing, more than 80% of patients continued on this regimen up to week 48. This suggests that, once the patients have been selected as appropriate for 12-week dosing, they tend to remain on this regimen.[7]

Q. What are the next steps in the clinical development of brolucizumab for nAMD?

Novartis intends to file for approval in the US at the end of this calendar year. Another study (NCT03386474)[9] has recently completed recruitment.

Q. What will this mean in terms of your clinical practice?

As a clinician, I like to have choices, and ultimately we are dictated by our preferences, our patients' preferences and, most importantly, the disease itself. We are looking for a drug that is most efficient in suppressing a validated target, VEGF-A. The week 16 data of HAWK and HARRIER show that brolucizumab is more efficient than aflibercept in suppressing VEGF-A. When the drug becomes available, I believe it will be very valuable for the treatment of nAMD. ❑

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