One Year After Aflibercept: Where Are We With Therapeutic Approaches for Retinal Vascular Diseases?

BY ARON SHAPIRO WITH DAVID BOYER, MD; AND QUAN DONG NGUYEN, MD, MSC

Almost 1 year ago, we wrote about the impact of vascular endothelial growth factor (VEGF) inhibitors on the neovascular age-related macular degeneration (wet AMD) market, and also made mention of the recent approval of aflibercept (Eylea, Regeneron). Beginning with aflibercept's approval in November 2011, the subsequent year proved to be a banner year for retinal therapies.

Although the approval of the third anti-VEGF agent for wet AMD broadened the therapeutic landscape for the posterior segment, there is still much to be learned about how these therapies are best used. Most desired, perhaps, are supplemental clinical trials that may offer information on head-to-head comparisons, treating subgroups of patients, and treatment regimens.

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Previously approved to treat wet AMD and macular edema following retinal vein occlusion, ranibizumab (Lucentis, Genentech) was also approved for the treatment of diabetic macular edema (DME). This US Food and Drug Administration (FDA) approval was based on 2 parallel, phase 3, multicenter, double-masked, sham injection-controlled, randomized studies, termed RISE and RIDE, conducted at private and university-based retina specialty clinics in the United States and South America.[1] A total of 759 patients were randomized into 3 groups for both studies: 0.3 mg ranibizumab injection (n=250), 0.5 mg ranibizumab (n=252), or sham injection (n=257). By the 24-month follow-up, 33.6% to 44.8% of those who received 0.3-mg injections and 39.2% to 45.7% of those who received 0.5-mg injections gained at least 15 ETDRS letters, compared with only 12.3% to 18.1% of those who received sham injections.[1] Ranibizumab injections also improved macular edema, with low rates of ocular and nonocular adverse events.

In October, ocriplasmin (Jetrea, Thrombogenics) became the first drug approved for the treatment of symptomatic vitreomacular adhesion (VMA). Two multicenter, randomized, double-masked phase 3 clinical trials enrolled 652 patients to compare a single intravitreal injection of ocriplasmin (125 µg) with a placebo injection in patients with symptomatic VMA.[2] The primary endpoint was resolution of VMA at day 28. VMA resolved in 26.5% of the ocriplasmin-injected eyes (n=464) and in 10.1% of placebo-injected eyes (n=188).

Additionally, after the approval of aflibercept for wet AMD, the drug was also approved for the treatment of macular edema following central retinal vein occlusion (CRVO) in September. Aflibercept appears to provide

longer duration of efficacy compared with the current standard of care, ranibizumab, in wet AMD.[3] The approval came after positive data from two phase 3, randomized, multicenter, double-masked, sham-controlled studies: COPERNICUS and GALILEO.[4,5] A total of 358 patients were treated and evaluable for efficacy (217 with aflibercept). Patients were randomly assigned in a 3:2 ratio to either 2 mg aflibercept or sham injections administered every 4 weeks for a total of 6 injections. After 6 monthly injections, patients continued to receive aflibercept treatment during weeks 24 to 52 only if they met prespecified retreatment criteria, except for patients in the sham control group in the GALILEO study, who continued to receive sham injections through week 52. In the COPERNICUS study, 56% of patients receiving aflibercept 2 mg gained at least 15 letters of best corrected visual acuity (BCVA) from baseline, compared with 12% of patients receiving sham injections after month 6, the primary endpoint of the study.[6] In the GALILEO study, 60% of patients receiving aflibercept 2 mg gained at least 15 letters of BCVA from baseline, compared with 22% of patients receiving sham injections at 6 months, also the primary endpoint.[6]

FUTURE DIRECTIONS

The approval of aflibercept offered an exciting addition to therapies indicated for the treatment of wet AMD and subsequently may change the way many practices made treatment decisions going forward. Still, postmarketing clinical trials are in high demand in order to provide supplemental information about the drug's safety, efficacy, and optimal use.

"Even though it has been 1 year, we don't have any large studies comparing ranibizumab or bevacizumab failures, or patients with large retinal pigment epithelial detachments, with aflibercept and vice versa. The only information we have is what was done in the drug approval trial," said David Boyer, MD. "A caveat of clinical research is that we always want to standardize the population so there are no outliers, but when a drug is approved and labeled for an indication some of the inclusion/exclusion criteria initially used to garner a fairly homogeneous looking group doesn't quite capture all of the patients we end up seeing in clinical practice," he said. "So we extrapolate data from clinical trials and make assumptions to try to best treat our patients in our office and in a real life situation. To that end, a head-to-head study enrolling a larger number of patients would be interesting for a more real-world take, something that we can bring back and apply directly to clinical practice."

Dr. Boyer also expressed interest in seeing trials conducted utilizing the treat-and-extend regimen. "The treat-and-extend approach allows us to take full advan-

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tage of the drug's duration of action by treating a patient with monthly injections until signs of exudation have resolved, at which point the interval between visits is sequentially lengthened as long as there are no signs of recurrent exudation," he said. "Fewer injections may lead to fewer complications in the long run, so long as we can keep the patient's vision up to par."

With the trend toward personalized medicine, Quan Dong Nguyen, MD, MSC, said he believes that genetic testing may soon play a pivotal role in the screening, prevention, and management of wet AMD.

"For those of us who treat this disease [wet AMD], we do recognize that there are certain patients who may not respond as well to anti-VEGF therapy as other patients, so certainly the disease is not homogeneous," said Dr. Nguyen. "In addition, individuals with high-risk fundus characteristics (ie, [CNV] in 1 eye and large drusen and pigmentary changes in the other eye) for the development of wet AMD may benefit from genetic testing to further characterize their risk profile."

There are 2 questions to consider in regard to genetic testing, Dr. Nguyen said. First, how accurate and predictive are these tests? Second, how will test results change patient management? "For example, if I know the patient has a specific genetic marker but he or she does not yet have CNV, will I treat or follow the patient differently?" Dr. Nguyen said. "So far, there has not been a consensus, but it is my hope that we can work to address some of these questions by working in the area of genetic testing."

Both Dr. Boyer and Dr. Nguyen also noted the need for investigating other modes of treatment, both alone and in combination with anti-VEGF therapies. "Based on what we have learned so far, we have maximized the potential benefit of VEGF antagonists as a mechanism to control this disease. Even with a very powerful anti-VEGF agent like aflibercept, we are still not able to reach beyond the approximate 36% of patients who achieve more than 3 lines gained in visual acuity," said Dr. Nguyen. "Anti-VEGF agents work well in the antiangiogenic pathway, but there are other components to consider, such as subretinal fibrosis and inflammation. Agents that have the ability to act through multiple mechanisms are likely to fulfill the unmet need associated with wet AMD." Dr. Nguyen said.

Additionally, regarding recently approved ocriplasmin, Dr. Nguyen said it may have an additional role beyond releasing VMA. "Application of ocriplasmin may change the oxygenation status of the vitreous, which may affect retinal vascular diseases such as DME," he said. "Perhaps synergistic use of ocriplasmin and VEGF antagonists like ranibizumab may improve overall efficacy in gaining visual acuity or alter the need for frequent injections. I expect that such studies will be conducted to evaluate other potential roles of ocriplasmin and similar class of agents."

Dr. Boyer also said that additional mechanisms of action or adjunctive therapies will improve treatment outcomes. "Antifibrotic agents could be game changers. If you can reduce the fibrosis that's associated with AMD and reduce the overall scarring, I think you'll get better vision and better visual results. In terms of adjunctive therapies, consider the recent phase 2 clinical data that showed that combination therapy with an anti-PDGF and an anti-VEGF [agent] resulted in considerably better outcomes than monotherapy with anti-VEGF," he said. "I'm very excited to see how anti-PDGF plays a role in making lesions more sensitive to anti-VEGF therapy, and am hoping that the phase 3 study will also produce positive data."

CONCLUSION

Although the therapeutic landscape for retinal disease is continually expanding, it is clear from those immersed in the field that anti-VEGF therapies may be only the beginning. We anticipate interesting developments in the near future. ■

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