Ziv-Aflibercept as a Possible Alternative to Aflibercept

Will the story of aflibercept and ziv-aflibercept be a case of déjà vu that recalls the case of ranibizumab and bevacizumab?

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A medication is formulated and tested for intravitreal use with outstanding results. The systemic analog of this medication, normally given by intravenous infusion, is compounded for intravitreal use and becomes an effective and less expensive off-label alternative with a similar safety profile. Sound familiar? This scenario calls to mind the story of ranibizumab (Lucentis, Genentech) and off-label use of intravitreal bevacizumab (Avastin, Genentech).[1] A recent report by Farah presented at the Angiogenesis, Exudation, and Degeneration 2014 meeting in Miami, Florida,[2] suggested that it could one day be the story of aflibercept (Eylea, Regeneron) and ziv-aflibercept (Zaltrap, Regeneron).

THE PAST

The impact of intravitreal anti-VEGF therapy cannot be overstated. These agents have permanently changed the prognosis and management of choroidal neovascularization, age-related macular degeneration (AMD), retinal vein occlusion (RVO), and diabetic macular edema (DME).

In 2004, pegaptanib (Macugen, Valeant) became the first anti-VEGF agent approved by the US Food and Drug Administration (FDA) for treating patients with AMD, but it had limited efficacy: The average patient with neovascular AMD who received intravitreal pegaptanib injections lost vision over time, albeit at a slower rate than if the patient were left untreated.[3] In 2005, the results of the ANCHOR[4] and MARINA[5] trials demonstrated that intravitreal ranibizumab could provide visual improvement, not just stability; the drug was approved the following year by the FDA for treating wet AMD. Before ranibizumab even completed its journey through the regulatory cycle, however, speculation began to arise that bevacizumab—a chemotherapeutic agent approved for use in patients with colorectal cancer, and the anti-VEGF agent from which ranibizumab is derived—would be as effective as ranibizumab if compounded for intraocular use. After reports evaluating intravenous bevacizumab for patients with neovascular AMD demonstrated impressive efficacy,[6,7] bevacizumab was used to treat patients via an intraocular route with positive results. Because of the lower cost and greater availability associated with bevacizumab, it was rapidly and widely adopted into regular retina practice.[1]

THE PRESENT

It is still not entirely clear what role bevacizumab should play in the management of retinal pathologies, with research in different disease states (ie, AMD, RVO, and DME) supplying conflicting results about its ultimate safety and efficacy compared with ranibizumab. Additionally, although CATT and other head-to-head trials demonstrated similar efficacy of ranibizumab and bevacizumab,[8] controversies persist regarding differences in systemic absorption[9] and proper methods of compounding the latter.[10] According to the 2013 annual Preferences and Trends survey by the American Society of Retina Specialists, 61% of US retina specialists and 42% of international retina specialists chose compounded bevacizumab as their primary therapy for neovascular AMD.[11] Thus, bevacizumab can arguably be considered a standard of care for the management of neovascular AMD.

Recently, another anti-VEGF medication, aflibercept, has gained favor for its reportedly robust treatment effects. Trials demonstrating similar efficacy with a lower frequency of treatment,[12] and reports of

improvement in patients with poor responses to ranibizumab and bevacizumab,[13] have rapidly made aflibercept an alternative, if not a first-line, therapy for AMD and RVO. Ziv-aflibercept, which has the same mechanism of action as aflibercept, is a systemic chemotherapeutic agent approved for use in treating colorectal cancer. A major difference between the 2 medications is osmolarity: The osmolarity of aflibercept is 250 to 260 mOsm, whereas the osmolarity of ziv-aflibercept is 815 to 820 mOsm. Marmor has reported that injection of 0.05 mL of a solution of greater than 500 mOsm may lead to retinal toxicity and changes, including retinal detachment.[14] Thus, it would seem that intravitreal ziv-aflibercept has the potential to cause intraocular toxicity, unlike intravitreal aflibercept. In an evaluation of the safety of intravitreal injections of ziv-aflibercept in rabbits, no differences were found in histopathologic or electroretinography examinations between groups receiving aflibercept or ziv-aflibercept[2]; however, ziv-aflibercept may affect cultured retinal pigment epithelium cells in vitro at near-clinical doses.[16,17]

THE FUTURE

Early reports on ziv-aflibercept are promising because they suggest that another, less expensive intravitreal anti-VEGF agent may soon be available for patient care. However, the efficacy of this agent is still unknown in ocular applications, and early animal data are far from convincing about its systemic availability. In addition, sterile inflammation simulating endophthalmitis has been reported to occur in some patients receiving intravitreal aflibercept,[15] and whether there is a similar risk with intravitreal ziv-aflibercept is unknown. Researchers have indicated that they next plan to evaluate ziv-aflibercept's safety and efficacy in nonhuman primates.

CONCLUSION

The retina community may be witnessing the first steps in the availability of another anti-VEGF therapy for retina specialists. Although the introduction of intravitreal ziv-aflibercept may not be as ground breaking as that of intravitreal bevacizumab, its potential development for ocular conditions would add another low-cost medication to the expanding treatment arsenal against VEGF-driven pathologies. ■

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