Practical Retina
Incorporating current trials and technology into clinical practice

Current concepts in managing wet AMD suboptimally responsive to anti-VEGF therapy

by James C. Major Jr., MD, PhD

Drugs that target vascular endothelial growth factor — bevacizumab, ranibizumab, and most recently aflibercept — have revolutionized the management of neovascular age-related macular degeneration, causing a positive response in many patients. Nevertheless, many patients with wet AMD experience persistent vascular leakage despite treatment with a monthly injection of an anti-VEGF. This poses an everyday challenge to their care providers.

The 2012 Preferences and Trends Survey administered by the American Society of Retina Specialists revealed that 66.5% of retina specialists use bevacizumab monotherapy to treat typical wet AMD with subfoveal choroidal neovascularization (CNV) of up to 1 disc diameter in size. Of the survey respondents, 44% indicated that they would recommend a switch to aflibercept after previous non-response to bevacizumab monotherapy. Switching was needed in the case of persistent cysts, subretinal fluid, or pigment epithelial detachment (PED), with subretinal fluid being the strongest determiner to switch. In the Comparison of AMD Treatments Trials (CATT), vascular leakage persisted at 1 year in more than half of study participants: 53% in the ranibizumab group and 71% in the bevacizumab group. Thus, many patients with wet AMD respond suboptimally to continued anti-VEGF therapy. Some patients may incompletely anatomically respond with improvement in measured OCT leakage, while other patients show essentially no improvement. Tachyphylaxis, differences in anti-VEGF drug levels between patients, and the rate of medication clearance can theoretically help to explain these suboptimal results. More importantly, what can be done to manage disease in these patients?

Because we assume that better anatomical results (eg, no diffuse or intraretinal cysts, subretinal fluid, or pigment epithelial detachment) translate to better visual results, it becomes important to dry the macula. In the PIER study, eyes with no qualitative optical coherence tomography activity showed an improved visual outcome compared with those exhibiting OCT activity. There are essentially three approaches for accomplishing this goal.

The first approach would be to increase the frequency of the anti-VEGF injection regimen. Clinically, this amounts to injecting with a biweekly bevacizumab injection or alternating monthly ranibizumab with monthly bevacizumab for net biweekly anti-VEGF injection. The improvement in drug binding has been theoretically summarized and anecdotal evidence exists, but clinical prospective data are lacking. Moreover, the treatment

doi:10.3928/23258160-20130503-01
burden is high, with patients returning every 2 weeks for an intravitreal injection.

Treatment with a higher dose of anti-VEGF with monthly injections offers a second strategy. In the HARBOR trial, 1,097 treatment-naïve wet AMD patients were randomized to treatment frequency and dosage, and endpoints were evaluated at 1 year. In these treatment-naïve eyes, 2.0 mg ranibizumab showed no benefit over the currently approved 0.5-mg dose in terms of visual acuity. No safety issues were observed with the fourfold increase in dosage.³

In the SAVE trial, 2-mg high-dose ranibizumab was given monthly or every 6 weeks in treatment-naïve eyes. Seventy-nine patients with previously injected recalcitrant disease were followed over 1 year. A gain of 4.1 letters in best corrected visual acuity was observed and maintained over 1 year in both dosing regimens. Treatment every 6 weeks showed diminished anatomic gains on OCT when compared to monthly treatment. Similar to the HARBOR study, no significant safety concerns arose.⁴

Lastly, switching anti-VEGF drugs, and more specifically switching to an anti-VEGF drug with a higher binding affinity such as aflibercept, might result in improved anatomical and visual outcomes. The VIEW 1 and 2 trials offer robust phase III data on administering aflibercept to 1,200 treatment-naïve patients, yet clinical data on switching patients from other anti-VEGF treatment to monthly aflibercept injections are lacking. Two small prospective studies, HOLD and EVER, including a total of 15 study participants, looked at patients with a suboptimal response to other anti-VEGF treatments switched to aflibercept. Final follow-up after several months showed that mean visual acuity improved by 11 letters, mean central retinal thickness decreased 41 µm, and mean PED height decreased by 103 µm.⁵

In our recent analysis, 65 eyes with serous PED refractory to previous anti-VEGF treatment were retrospectively examined for 1 year after switching to aflibercept. An improvement of at least 10 µm in PED height that persisted over 1 year was observed in 79% of eyes. Mean PED height decreased by 22% and also persisted beyond 1 year. Visual acuity was essentially unchanged.⁶

Looking to the future, Fovista (anti–platelet-derived growth factor aptamer; Ophthotech, Princeton, NJ) combined with ranibizumab has demonstrated promising early results in a phase IIb trial. The medication works by stripping pericyte cells in the active CNV membrane complex that protect the underlying VEGF-secreting endothelial cells. In 449 patients who were given monthly anti-PDGF injection combined with ranibizumab vs. ranibizumab monotherapy, no toxicity and no adverse events were observed. The trial met its endpoint of superiority, with a 10.6-letter visual acuity improvement over 6 months, constituting a 62% improvement with combination therapy over ranibizumab alone. The investigators also observed regression of the actual CNV membrane, which does not typically occur with anti-VEGF monotherapy.⁷

Despite our advances in treating exudative AMD, a large number of patients remain “treatment refractory,” or respond less than expected, resulting in a persistently leaking macula. When blockage of VEGF falls short, we can resort to more frequent injections, higher-dose injections, or change to medications with a stronger binding effect and improved pharmacokinetics. Practical limitations such as patient and caregiver travel burdens, insurance carrier mandates, drug cost, and other socioeconomic constraints make some anti-VEGF drugs inaccessible to many clinicians. Hopefully, our anti-VEGF armamentarium will grow, advance, and exhibit continued positive clinical results for our patients.

REFERENCES


