The Case for Judicious Use of Anti-VEGF Agents

Judicious use of anti-vascular endothelial growth factor agents is reasonable in the treatment of neovascular age-related macular degeneration.

BY ELIAS REICHEL, MD

The inhibition of vascular endothelial growth factor (VEGF) has been proved to be a safe and effective treatment for neovascular age-related macular degeneration (AMD). There are, however, some biological and clinical responses to this therapy that support the case for judicious use of anti-VEGF agents. From a biological standpoint, VEGF receptor 2 is expressed by Mueller and photoreceptor cells; therefore, anti-VEGF use may lead to apoptosis of these critical cells. In addition, there are cautionary observations to keep in mind, including sustained elevated intraocular pressure (IOP), tachyphylaxis, and reduced ocular perfusion pressure, all of which can occur with anti-VEGF therapy. Lastly, there are case examples to support the judicious use of anti-VEGF agents, including those of non-responders, robust responders, and patients who are presumed to be poor responders but who actually respond well.

BIOLOGICAL RATIONALE

The biological rationale for the judicious use of anti-VEGF agents has been pioneered by Patricia A. D’Amore, PhD, of the Schepens Eye Research Institute at Harvard Medical School. D’Amore and colleagues injected adult mice with soluble VEGF receptor 1 and found that reducing the levels of VEGF caused the death of Mueller and photoreceptor cells. Because there is VEGF receptor 2 on both Mueller and photoreceptor cells, chronic VEGF blockade can lead to apoptosis due to interaction with the receptors. It is probable that there are also other aspects of anti-VEGF agents that could have detrimental effects on the retina.

CAUTIONARY OBSERVATIONS

There are a number of cautionary observations to consider when treating patients with anti-VEGF agents. First, as several investigators have shown, there is the potential for sustained elevated IOP to occur after single or multiple intravitreal injections of anti-VEGF agents.

A second cautionary observation is tachyphylaxis; it is important to understand that some patients may respond initially to anti-VEGF agents but exhibit waning response over time. This raises the question, “Could there potentially be resistance to biological agents that are administered over long periods of time?” For example, with carcinomas, a resistance to various drugs can occur.

Finally, my colleagues and I looked at ocular perfusion pressure at the time of injection and found that in about 40% of patients there is a significant reduction in ocular perfusion pressure immediately after injection. Therefore, it is necessary to consider the effect that multiple injections may have on aging eyes. Pressure reduction is not purely a volumetric response; there are direct effects of the drug that may cause vasoconstriction or affect the retinal and choroidal vasculature. Additionally, approximately 8% to 10% of patients had ocular perfusion pressure reduced to 0 mm Hg, whereas normal ocular perfusion pressure in an age-matched control should be around 30 mm Hg.

ATYPICAL CENTRAL SEROUS RETINOPATHY

One case example that supports the judicious use of anti-VEGF agents is that of the nonresponders—those patients who masquerade as having potential wet AMD. These masquerade syndromes are something I believe we all see as central serous-like AMD or atypical central serous retinopathy (CSR) in an older individual. The following case represents such a scenario.

A man, aged 70 years, presented with 20/40 vision and subretinal fluid in the right eye with elevation of the retina. Hyperfluorescence was present on the macula that was consistent with CSR (Figure 1). The left eye was otherwise normal. The patient received photodynamic therapy and two doses of ranibizumab (Lucentis, Genentech). He did not, however, respond to either treatment.

As I followed the patient, his vision improved to 20/30 initially and his fluid regressed without treatment. His vision, however, fluctuated to 20/40 or 20/50, with an increase of subretinal fluid (Figure 2). Five years after his initial presentation, his fundus photos showed a small area of subretinal hemor-
rhage, and optical coherence tomography (OCT) revealed a subretinal process consistent with choroidal neovascularization (CNV; Figure 3). We treated the CNV with intravitreal ranibizumab. Interestingly, the subretinal fluid persisted, and his vision remained stable at 20/50.

Central serous-like AMD looks like CSR on fluorescein angiography (FA) and OCT, and it behaves somewhat like CSR in that subretinal fluid can wane and wax. There is typically no hemorrhage associated with this condition unless the patient develops a secondary CNV membrane. As this case illustrates, the CSR component is a poor responder to anti-VEGF therapy.

**PATTERN DYSTROPHY**

Another masquerade syndrome is pattern dystrophy, or adult-onset foveal macular dystrophy, which is illustrated in the following case.

An 80-year-old physician presented with 20/40 vision in his right eye and 20/50 in his left eye and was referred for anti-VEGF treatment. There was hyperfluorescence on FA, which is consistent with staining. On OCT, there was a central void that is consistent with pattern dystrophy (Figure 4); it appeared to be subretinal fluid, but this patient did not respond to anti-VEGF treatment.

Pattern dystrophies can present either as unilateral or bilateral processes, but most often they are bilateral. A foveal space can be observed on OCT, and these eyes typically show staining but no leakage on FA. Because these patients do not respond to anti-VEGF agents, proper diagnosis is important. When these patients develop CNV secondary to their disease process, however, anti-VEGF agents tend to be effective for this indication.

**ROBUST RESPONDERS**

Some patients respond extremely well to anti-VEGF agents. These patients are typically older (aged 80 to 90 years) and present with areas of small (<1 mm), classic, or occult CNV lesions and visual acuity of 20/50 or better.
These robust responders represent approximately 10% of the cases of CNV that are seen in a typical retina practice.

An example of such a patient is a 92-year-old man who presented with 20/40 vision, a small area of hemorrhage beneath the center of the fovea, and a CNV membrane seen on FA (Figure 5). Only by viewing sequential OCT scans could we see subretinal fluid. The patient was injected with ranibizumab and was followed monthly. Five months after the initial injection, OCT showed a recurrence of subretinal fluid, so we reinjected. Figure 6 shows his OCTs as treatment progressed. The patient has been followed for several years, receiving minimal injections and maintaining excellent visual acuity.

**PRESUMED POOR RESPONDERS**

At times, it is difficult to predict a response to anti-VEGF agents, and it is important to keep in mind that some patients who are presumed to be nonresponders to anti-VEGF agents actually respond well. Patients for whom it is hard to predict response include those with large pigment epithelial detachments that are typically associated with retinal angiomatous proliferation or polypoidal choroidal vasculopathy. Further, it is also difficult to determine the endpoint for treatment of these eyes.

A woman aged 64 years presented prior to the availability of ranibizumab with multiple hemorrhages and pigment epithelial detachments seen on OCT (Figure 7). She was diagnosed with polypoidal choroidal vasculopathy. She received intravitreal bevacizumab (Avastin, Genentech), to which she responded well. She returned several months later, however, with an additional hemorrhage near the optic nerve along with subretinal fluid (Figure 8). After two more injections of bevacizumab, her vision remained stable. Four years later, her vision was 20/30, and she had another hemorrhage with a thin area of subretinal fluid underneath the fovea (Figure 9). After three more injections of bevacizumab, the hemorrhaging and subretinal fluid resolved and her visual acuity was stable at last follow-up.

For this case, it was difficult to predict that the patient would respond well because polypoidal choroidal vasculopathy.

(Continued on page 70)
lopathy is presumably a poor responder to anti-VEGF monotherapy. In this case, judicious use of anti-VEGF agents paid off, with a minimal number of treatments required.

**SUMMARY**

VEGF suppression has both positive and negative biological ramifications. Anti-VEGF injections can be associated with elevated IOP, tachyphylaxis, and reduced ocular perfusion pressure. Further, individual cases respond differently to anti-VEGF therapy, so this must be considered when utilizing this mode of treatment. Judicious use of anti-VEGF agents is reasonable considering these biological, clinical, and disease subtype responses.

Elias Reichel, MD, is Vice Chair for Research and Education, Department of Ophthalmology, at New England Eye Center and Professor of Ophthalmology at Tufts University School of Medicine in Boston. Dr. Reichel is a Retina Today Editorial Board Member. He states that he has financial relationships with Akorn, Alimera Sciences, Allergan Inc., Biogen-Idec, Eyetech, Falck Medical, Genentech, Neovista, GlaxoSmithKline, Novartis, Ocular Instruments, and Ophthotech. He can be reached at ereichel@tuftsmedicalcenter.org.