Developments in Therapy for Neovascular AMD

Treatments on the horizon move beyond the paradigm of monthly anti-VEGF therapy.

BY PRAVIN U. DUGEL, MD

The advent of intravitreal injection of VEGF inhibitors for neovascular age-related macular degeneration (AMD) has revolutionized the clinical management of this disease. At the same time, however, a gap has opened between the manufacturer's recommended dosing of the available drugs and actual clinical practice.

The package insert for ranibizumab (Lucentis, Genentech) recommends injection of the 0.5 mg dose monthly (approximately every 28 days).[1] The randomized clinical trials that supported the regulatory approval of the drug used an every-4-week administration schedule. A study examining current practices in administration of anti-VEGF agents in neovascular AMD, however, found that in 2011 the mean number of ranibizumab injections given per year was 5.8, and for bevacizumab (Avastin, Genentech) it was 4.5 per year.[2]

Rarely do we talk about this gap between what ophthalmologists "should" be doing with anti-VEGF therapy and what we are doing in real life. And as we gain experience with these drugs, it becomes increasingly clear that we may have to continue injecting them indefinitely. The HORIZON extension study showed that, in patients who had been treated monthly in the original randomized trials, after monthly injections of ranibizumab stopped, visual acuity gains tended to diminish.[3] The findings of the European SECURE study were similar.[4]

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OTHER SOLUTIONS

Angiogenesis in AMD is a complex cascade of events, including endothelial cell activation, basement membrane degradation, endothelial cell proliferation and migration, and tube formation and remodeling.[5-7] Our current paradigm, out of the hundreds if not thousands of factors involved in this process, is to treat VEGF with anti-VEGF agents. This concentration on 1 type of monotherapy in a multifactorial disease process does not seem to make sense.

What can we do instead, or in addition? Other solutions may include finding a better anti-VEGF agent, finding a better way to deliver anti-VEGF therapy, or identifying some type of combination therapy that is additive or even synergistic with current monotherapy options. There are currently drug candidates in each of these areas in various stages of development.

A BETTER ANTI-VEGF AGENT

At least 2 promising new approaches to VEGF inhibition are under development. ESBA1008 (AL-86810, Alcon) is a humanized single-chain antibody fragment with a molecular weight of approximately 26 kDa. This pan-VEGF inhibitor binds to the receptor binding site of VEGF-A, preventing the interaction of VEGF with impor-

tant receptors. The potential attractiveness of this agent is that its binding capacity may be greater than those of current therapies. A phase 2 trial has been completed, and hopefully data will be presented soon.[8]

Another potential anti-VEGF agent under development by Allergan is based on designed ankyrin repeat proteins, or DARPins. These are genetically engineered proteins, typically with high affinity binding to target sites, that can be used as platforms for protein therapeutics. They can be made into custom-designed therapeutics with optimized properties, including small size (14–20 kDa), high stability and solubility, and low immunogenicity.

A phase 2 study of this drug candidate was initiated. The study design included an initial open-label dose-escalation trial, followed by a second randomized stage with 3 arms, comparing the highest tolerated dose from stage 1, the second-highest dose, and ranibizumab. The primary endpoints were (1) central retinal thickness at 16 weeks and (2) the time between initial treatment and the recurrence of active disease. Results of this phase 2 study were expected to be presented at Retina Subspecialty Day before the American Academy of Ophthalmology (AAO) meeting later this year, but Allergan recently indicated a need to redesign the trial in its 2013 first-quarter earnings conference call.[9]

A BETTER DELIVERY SYSTEM

If a better way to deliver anti-VEGF therapy could be identified and developed, it might be possible to reduce the current treatment burden of monthly or frequently repeated injections. At least 2 approaches in this category are being investigated.

A form of anti-VEGF gene therapy for AMD is being developed by Genzyme. In this approach, a promoter gene is packaged in an adenoviral vector. When administered to the patient, it causes cells within the patient's body to produce the desired therapeutic protein. In this case, the vector is adeno-associated virus type 2 (AAV2), and the therapeutic protein is a type of tyrosine kinase inhibitor called sFLT01, a novel chimeric protein that binds to VEGF receptors.[10] Tyrosine kinase is a potent antagonist of VEGF receptor 1 and 2 signaling and is the final common pathway in many anti-VEGF products.[11]

Animal models have shown that the promoter is capable of producing expression of the desired product within the eye in a dose-dependent manner. Results in nonhuman primate models suggest that the effect of local delivery may last for 6 or even 8 months.[12]

A phase 1 study is under way, with the objectives of assessing safety and demonstrating proof of concept in patients with AMD based on optical coherence tomography, visual acuity, and detection of sFLT01 protein levels in aqueous humor to verify transgene expression. Results, again, are expected to be presented at AAO Retina Subspecialty Day this year.

Another way to deliver anti-VEGF therapy is to implant a protein factory in the eye, an approach being explored by Neurotech. The company's encapsulated cell technology uses genetically modified retinal pigment epithelial cells to achieve controlled, continuous production of the desired biologic for up to 24 months. The implanted device, measuring 6 mm by 1 mm, has ports that are large enough to allow therapeutic proteins to go out and oxygen and nutrients to come in, but small enough to keep out immune system components.

Phase 1/2 dose escalation studies in patients with treatment-naïve choroidal neovascularization are ongoing outside the United States. In early phase studies with small sample sizes, some patients have responded quite well. In the first patients evaluated with the highest dose administered to date, with 2 devices implanted together, anatomic and functional results have been comparable to those seen in the CATT study, according to the company.

Now under development is a modular structure for delivery of the same type of anti-VEGF therapy, in which multiple cassettes can be combined to release up to 16 µg of the anti-VEGF product, equivalent over 1 month to injecting 0.5 ranibizumab, according to the company.

COMBINATION TREATMENT

A third option to improve treatment of AMD is to move beyond VEGF monotherapy and attempt a combination approach to therapy. Currently the most encouraging drug candidate in this category is 1 that inhibits platelet-derived growth factor (PDGF), called Fovista (E10030, Ophthotech), which is being investigated as a combination therapy with an anti-VEGF agent.

I have written about this combination anti-PDGF/anti-VEGF therapy before in these pages ("Anti-PDGF Combination Therapy in Neovascular Age-related Macular Degeneration: Results of a Phase 2b Study," March 2013), and Richard S. Kaiser, MD, writes about E10030 elsewhere in this issue, so my remarks here will concentrate on the rationale for this combination approach to AMD therapy.

As noted above, although anti-VEGF monotherapy is more effective than any previous treatment for neovascular AMD, its effect plateaus. That is, patients improve to a certain point, but no further, and anti-VEGF injections could theoretically be needed indefinitely. With the standard of care of monthly injections, visual outcome at 3 months is reflective of the visual outcome at 1 year. The curve we are familiar with from MARINA,[13]

ANCHOR,[14] and other studies, showing improvement in the first 3 months followed by a plateau despite monthly treatment, illustrates this phenomenon.

What is at work here in this apparent resistance to anti-VEGF therapy? The answer can be found in the oncology literature; most of the works cited in the following section are by investigators in oncology, not ophthalmology.

It appears that pericyte coverage causes anti-VEGF resistance. Pericytes are a type of cell that covers and protects the neovascular complex as new vessels form and mature. These cells provide VEGF and other factors to the proliferating endothelial cells.[15-17]

PDGF controls pericytes, driving their recruitment, proliferation and survival and regulating the maturation of new vessels.[18] In the laboratory, PDGF-deficient mice lack pericytes on their microvasculature,[18] and over-expression of PDGF leads to increased pericyte proliferation.[19]

Neovascular membranes grow in a very directed fashion. Sprout or "tip" cells lead the growth of the neovascular membrane, and these are the only endothelial cells in the neovascular complex that are not covered by pericytes. As the tip cells grow, they produce PDGF, the PDGF recruits pericytes, and pericytes cover the neovascular complex. The only cells vulnerable to anti-VEGF therapy, therefore, are those tip cells, because the rest are covered by the pericyte armor.[20]

This explains the shape of the anti-VEGF monotherapy response curve mentioned above. In treatment-naïve patients, the tip cells are killed by anti-VEGF therapy, causing a decrease in exudation and initial improvement in visual acuity. But as most of the neovascular complex is covered by pericyte armor, the anti-VEGF therapy fails to penetrate there, and the effect of the treatment plateaus. As soon as treatment stops, the tip cells begin to grow again, and disease progression recommences.

Furthermore, chronic anti-VEGF treatment appears to promote vascular maturation. VEGF antagonism causes PDGF to be upregulated, so that pericytes are recruited and the neovascular membrane matures.[21] In giving chronic anti-VEGF monotherapy, that is, we are accelerating the maturation of the neovascular membrane by encouraging the proliferation of pericytes.

The role of PDGF has been hinted at in ophthalmology. Davuluri and colleagues reported an increase in activated PDGF receptors in the vitreous correlated with anti-VEGF administration.[22] Pachydaki and colleagues reported that pathologic specimens from patients unresponsive to bevacizumab displayed well-formed neovascular units consistently exhibiting pericytes.[23]

Clues about the role of PDGF have been dropped in our field, therefore, but we have not necessarily recognized their significance until now.

If anti-VEGF resistance occurs because of pericytes, then it makes good physiologic sense to combine an anti-PDGF agent with an anti-VEGF agent. The anti-PDGF agent would bind to and strip the pericytes, rendering the neovascular membrane more susceptible to the anti-VEGF agent.

This is the rationale for current investigations of E10030, a PEGylated DNA aptamer with a molecular weight of approximately 50 kDa. Laboratory studies have shown that it binds to PDGF-B and strips pericytes from endothelial cells,[24] and that an anti-PDGF and anti-VEGF combination results in maximal inhibition and regression of neovascularization.[25]

In a small phase 1/2 study, the safety profile of the drug combination was excellent. Patients in this phase 1 trial had advanced disease, so there was no expectation of improvement in vision. Despite this, 59% of patients in the study gained 3 or more lines of vision. Also surprising in this patient population, but consistent with the preclinical data, was that regression of the neovascular membrane was seen.

With this encouragement, a large phase 2 study was performed to assess the safety and efficacy of combination therapy with anti-PDGF E10030 and anti-VEGF ranibizumab, compared with ranibizumab monotherapy, in patients with treatment-naïve neovascular AMD.

My colleague Dr. Kaiser describes the results of this study elsewhere in this issue, but I will mention the top-line results: The combination therapy met the trial's prespecified primary endpoint of superiority over anti-VEGF monotherapy ($P = .019$), demonstrating a 62% additional benefit with classic dose-response profiles at all time points and diverging efficacy curves over time, and with a consistency of results in all prespecified subanalyses.

CONCLUSIONS

The current best practice of monthly treatment for neovascular AMD, with monthly or some other frequent treatment schedule of anti-VEGF injection, is a burden on patients, practices, and the health care system. Now it also appears that this chronic monotherapy actually may be increasing resistance to anti-VEGF therapy by accelerating the maturation of the neovascular complex.

Future options for improvements in the care of neovascular AMD may include better anti-VEGF agents, better anti-VEGF delivery systems, or a combination approach that takes advantage of some of the other pathways involved in the complex disease mechanism of AMD. Encouraging results have been seen in early clinical trials with 1 such combination—an anti-PDGF/anti-

VEGF therapy approach. We look forward to learning more about this and other therapies on the horizon for treatment of neovascular AMD. ■

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