NOVEL TREATMENT STRATEGIES FOR DIABETIC EYE DISEASE

Next-generation anti–VEGF-A drugs and combination agents show potential.

BY PRAVIN U. DUGEL, MD

There is no doubt that anti–VEGF-A monotherapy has revolutionized the treatment of diabetic macular edema (DME). However, studies looking at data from the Centers for Medicare and Medicaid Services and from prospective randomized studies have shown that some patients have resistant or persistent disease that does not respond to this form of therapy. The unmet need presented by these patients forms the impetus for developing new options for the treatment of DME. In this article, I discuss some of the agents now in the pipeline.

NEXT-GENERATION ANTI-VEGF-A DRUGS

Agents that inhibit the activity of VEGF-A have been used for years, but scientists have been working on new, or next-generation, options. There are three that I would like to highlight: brolucizumab (RTH258; Alcon/Novartis), abicipar pegol (Allergan), and conbercept (KH902; Chengdu Kanghong Biological Science & Technology).

Brolucizumab

Brolucizumab is a humanized single-chain antibody fragment. It is the smallest active unit of VEGF-A antibody, and it allows concentrated molar dosing at 22 times the dose of ranibizumab (Lucentis; Genentech) and more than 11 times that of aflibercept (Eylea; Regeneron). Clinical trials of this agent for the treatment of DME may begin in the near future. The drug has already shown promise for treatment of age-related macular degeneration, including reductions in central retinal thickness on optical coherence tomography (OCT) with a greater durability, in the HAWK and HARRIER clinical trials.[1]

Abicipar Pegol

This drug belongs in the class of genetically engineered antibody mimetic proteins called designed ankyrin repeat proteins (DARPins). It is small in size and has high-potency stability and solubility. Results from the phase 2 PALM study showed that abicipar pegol, injected every 8 or 12 weeks in patients with DME, offered functional and anatomic effects similar to those of ranibizumab injected monthly.[2] Patients receiving 2 mg of the drug required fewer injections than those treated with ranibizumab over a 28-week period.

Conbercept

Clinical studies of this recombinant human VEGF receptor-Fc fusion protein, which inhibits VEGF-A, VEGF-B, and placental growth factor (PlGF) have been conducted. The FRONTIER and SAILING studies showed improvements in visual acuity and concomitant decreases in retinal thickness on OCT in patients with DME.[3,4] Additional trials in DME are being planned.

ANGIOPOIETIN COMBINATION DRUGS

Angiopoietin, a part of the family of growth factors, plays an important role in angiogenesis. Several drugs that affect the action of angiopoietin are in development. It is important to understand the mechanism of action for this drug class. In health, angiopoietin-1 (Ang-1) is crucial for vessel development. It maintains healthy vasculature by activating the Tie2 receptor. In disease states, Ang-2 is upregulated. This cytokine is an antagonist of Ang-1, which attracts proangiogenic and inflammatory cytokines. Its activation is often coupled with upregulation of VEGF-A, causing increased vascular permeability.

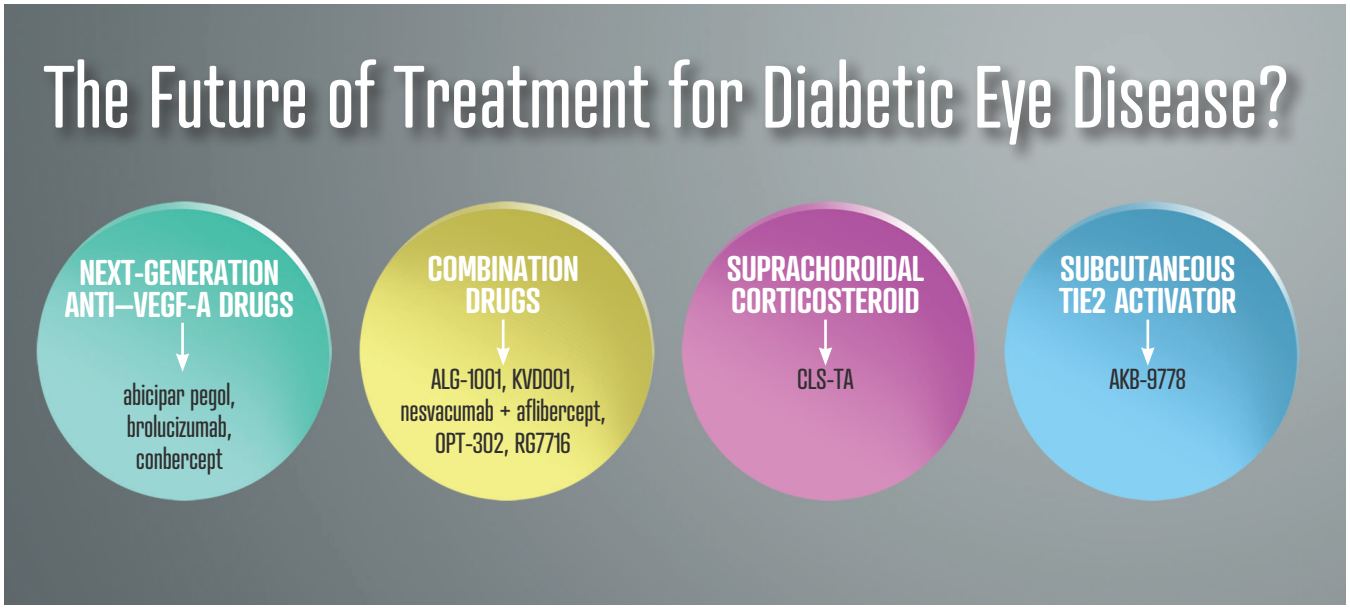
Two products in this category are notable in the DME pipeline: RG7716 (Genentech/Roche) and a combination of the Ang-2 antibody nesvascumab plus aflibercept (Regeneron/Bayer).

RG7716

This bispecific molecule can simultaneously inhibit Ang-2 and VEGF-A. Those are two important targets. The phase 2 BOULEVARD study is investigating the safety and efficacy of RG7716 in patients with DME, and results are expected early this year.[5]

Nesvacumab and Aflibercept

This is a co-formulation agent, as opposed to a bispecific agent,



as described above. A phase 1 dose-escalation study of this co-formulation showed signals of increased efficacy and durability. The phase 2 RUBY study evaluated two different doses of nesvacumab in combination with aflibercept, both of which were administered together as a single intravitreal injection. These were compared with aflibercept monotherapy. Results did not provide sufficient differentiation between the combined and monotherapy treatments to warrant phase 3 development.[6]

OTHER COMBINATION AGENTS

Other mechanisms of action are also being explored in combination with anti-VEGF therapy.

OPT-302

This "trap" molecule binds and neutralizes the activity of VEGF-C and VEGF-D by blocking and binding to the receptors VEGFR-2 and VEGFR-3. It is thought that combining OPT-302 (Opthea) with currently available anti–VEGF-A therapies may achieve true VEGF inhibition. Patients are being enrolled in a multicenter phase1b/2a clinical trial. The first part will be a dose-escalation evaluation of OPT-302 (0.3 mg, 1.0 mg, and 2.0 mg) in combination with aflibercept. This will be followed by a phase 2a randomized, controlled dose expansion trial with patients allocated in a 2:1 ratio to treatment with either OPT-302 in combination with aflibercept or to aflibercept monotherapy.

ALG-1001

ALG-1001 (Luminate; Allegro) is a first-in-class integrin peptide therapy; the molecule binds to specific integrin receptor sites and affects multiple angiogenic pathways and inflammation. The phase 2b DEL MAR study evaluated ALG-1001 in combination or as sequential therapy with anti-VEGF therapy in patients previously treated with an anti-VEGF agent, looking for signs of increased durability and efficacy with the investigational drug. The patients who did best with this therapy were those treated sequentially, with an anti-VEGF agent followed by ALG-1001.[7,8]

Most impressive, the patients who really drove the study were those who were previously resistant to anti–VEGF-A monotherapy, suggesting that such patients may benefit from this treatment with this drug.[6,7]

KVD001

KVD001 (KalVista Pharmaceuticals) is a protease inhibitor that targets plasma kallikrein, a VEGF-independent mediator of DME. Levels of this enzyme are elevated in the vitreous of patients with DME. According to the company, plasma kallikrein inhibition targets a pathway independent of VEGF and may therefore serve as an addition to existing DME treatment options. A phase 1 open-label study in patients resistant to anti–VEGF-A monotherapy showed improvement with a single injection of KVD001.[9] A phase 2 study will begin enrolling soon.

SUPRACHOROIDAL CORTICOSTEROID

The injection of a proprietary suspension formulation of the corticosteroid triamcinolone acetonide (CLS-TA; Clearside Biomedical) into the suprachoroidal space is a novel approach to the treatment of patients with DME. The phase 1/2 exploratory HULK clinical trial examined suprachoroidal CLS-TA with and without intravitreal aflibercept and showed signs of increased efficacy and durability with the investigational drug.[10] The ongoing phase 2 TYBEE study is comparing suprachoroidal CLS-TA plus intravitreal aflibercept with intravitreal aflibercept alone.[11]

SUBCUTANEOUS TIE2 ACTIVATOR

AKB-9778 (Aerpio Pharmaceuticals) is a Tie2 activator that takes a different approach, aiming to prevent the development of DME rather than treat existing disease. AKB-9778 is self-administered subcutaneously. In the phase 2a proof-of-concept TIME-2 study, AKB-9778 monotherapy showed the ability to improve underlying diabetic retinopathy by 2 or more steps in both eyes of 10% of patients.[12] The company is now recruiting patients with moderate to severe nonproliferative diabetic retinopathy for a phase 2b study (TIME-2b) studying AKB-9778 administered once or twice daily versus placebo.

THE FRONTIER IN DME TREATMENT

Although anti–VEGF-A drugs have revolutionized the treatment of DME, a large unmet need remains. There is great opportunity to change the treatment paradigm for this chronic disease with the next generation anti–VEGF-A drugs and combination drugs currently in development. ■

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