Neovascular, or wet, age-related macular degeneration (AMD) is a multifactorial disease. Several studies have demonstrated the beneficial effect of treatment with anti-VEGF agents in the management of this disease. Therapeutic response is variable based on clinical presentation, and, although most patients have clinical success, there are patients whose response to anti-VEGF monotherapy is limited.

For example, in the phase 3 VIEW 1 and VIEW 2 studies, approximately 95% of patients treated with either intravitreal aflibercept (Eylea, Regeneron) or ranibizumab (Lucentis, Genentech) maintained their visual acuity (defined as losing fewer than 15 letters on the ETDRS chart) from baseline to week 52. Only about a third of patients achieved an improvement of 15 or more ETDRS letters in BCVA, suggesting that a significant proportion of patients had the potential to gain additional vision. In addition, for many patients in the VIEW 1 and VIEW 2 trials, anatomic abnormalities relating to wet AMD persisted despite treatment every 4 or 8 weeks. Approximately a third of all patients had persistent cystic retinal edema and/or subretinal fluid as measured by time-domain optical coherence tomography at week 52.

Thus, although these anti-VEGF agents are effective treatments, there is an opportunity to further improve outcomes for patients with wet AMD by combining an anti-VEGF agent with a drug that has potentially complementary mechanisms of action. This article explains the role of platelet-derived growth factor (PDGF) in neovascular AMD and discusses treatment of the disease with a single intravitreal injection of a PDGF inhibitor combined with an anti-VEGF agent.

**ROLE OF PDGF-B IN OCULAR NEOVASCULARIZATION**

Angiogenesis is a major feature of several pathologic processes, including tumor growth, chronic inflammatory diseases, and ocular vascular diseases, including wet AMD. In ocular diseases characterized by aberrant angiogenesis, neovascularization can have catastrophic effects on vision, leading to edema, hemorrhage, and, ultimately, blindness. Multiple stimuli, such as PDGF-B, angiopoietin-2, and other factors, may be involved in the development of ocular neovascularization. VEGF-A also...

**AT A GLANCE**

- Various stimuli, including PDGF-B, may be involved in the development of ocular neovascularization; VEGF-A has been previously demonstrated to play a major role in the process.
- A combination PDGFRβ inhibitor and anti-VEGF agent has the potential to provide greater efficacy or sensitivity to treatment in patients with wet AMD by further reducing pathologic vessel maturation and fibrosis.
- In a first-in-human study of combined intravitreal injections of rinucumab and aflibercept in patients with wet AMD, the coformulation was well tolerated.
plays a major role in this process. VEGF is an endothelial cell–specific mitogen and survival factor that also promotes endothelial cell migration, vessel formation, and permeability, in ocular vascular pathologies including wet AMD. Inhibition of VEGF-A and its family members is a clinically validated therapeutic strategy for inhibiting neovascularization and pathologic vascular leakage.

PDGF-B is secreted by vascular endothelial cells, and interacts with PDGFR receptor beta (PDGFRβ) on pericytes (supportive mural cells) to recruit them as components of the mature vasculature. PDGF-B is also thought to participate in the epithelial-mesenchymal transition and in the recruitment of myofibroblasts at sites of fibrosis.

It has been hypothesized that an agent combining PDGFRβ inhibition with VEGF inhibition would provide greater antiangiogenic efficacy than anti-VEGF monotherapy by preventing pathologic vessel maturation and fibrosis. Inhibition of PDGFRβ activation by anti-receptor antibodies would strip pericytes from developing pathologic vessels.

Anti-PDGFRβ treatment has also been shown to increase the sensitivity of newly developing retinal blood vessels to the antiangiogenic effects of aflibercept in an animal model. Additionally, it is well established in the literature that blockade of PDGF/PDGFR signaling can inhibit fibrosis, which is a known component of AMD lesions.

Taken together, these data suggest that combining the distinct molecular and cellular mechanisms of PDGFRβ blockade with VEGF blockade has the potential to provide increased antiangiogenic efficacy over treatment with aflibercept alone in human retinal neovascular disease.

COMBINING PDGFRβ INHIBITION AND VEGF INHIBITION

Pairing a PDGFRβ inhibitor with an anti-VEGF agent has the potential to provide greater treatment efficacy in patients with wet AMD when compared with anti-VEGF monotherapy by further reducing pathologic vessel maturation and fibrosis. Rinucumab (Regeneron) is a fully human monoclonal antibody to PDGFRβ, and aflibercept is an anti-VEGF recombinant dimeric glycoprotein consisting of sequences derived from human VEGF extracellular domains fused to the Fc portion of human immunoglobulin G1. REGN2176-3 (rinucumab + aflibercept, Regeneron) is a coformulation of both drugs in a single 50-μL intravitreal injection.

The first-in-human study of REGN2176-3 was an open-label, dose-escalation study of the safety and tolerability of the combination intravitreal therapy in patients with wet AMD conducted at four clinical sites in the United States. The combination of rinucumab:aflibercept was administered at four dose levels (0.2 mg:2 mg, 0.5 mg:2 mg, 1 mg:2 mg, and 3 mg:2 mg) via intravitreal injection to 12 patients with wet AMD. Three patients received two doses, 1 month apart, at each of the four cohort dose levels. A review of the safety data identified no safety concerns in any of the cohorts when the combination rinucumab:aflibercept was administered, up to a dose of 3 mg:2 mg. No dose-limiting toxicities and no serious adverse events were reported. Intravitreal REGN2176-3 appeared to be well-tolerated in this patient population. A phase 2 multiple-dose, randomized, controlled trial in patients with wet AMD is ongoing.

CONCLUSION

For patients with sight-threatening diseases such as AMD, anything that can be done to safely and effectively help them regain vision or prevent additional vision loss would be a huge boon. Anti-VEGF drugs are effective, but it is possible that they may be leaving some vision on the table. Because PDGF-B may be involved in the development of ocular neovascularization, it stands to reason that a combination PDGF inhibitor–VEGF inhibitor could increase the vision gains seen with anti-VEGF treatment. When the results of the phase 2 trial are available, we will know more.


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