EXTENDED-DURATION THERAPEUTICS FOR TREATMENT OF WET AMD

Promising treatment options under investigation may someday lead to more successful disease management.

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Age-related macular degeneration (AMD) is a leading cause of blindness in the industrialized world; as many as 11 million people in the United States have some form of the disease.[1] The neovascular or wet form of AMD affects only 10% to 15% of those with AMD but accounts for 90% of the severe visual acuity loss caused by the disease.[2] It is projected that 196 million people worldwide will be affected by AMD in 2020, and by 2040 that number will increase to 288 million.[3]

Treatment options for wet AMD include laser photocoagulation, photodynamic therapy, steroids, and intravitreal injections of antineovascular agents. These agents, currently the preferred treatment approach, down-regulate the cytokine VEGF, which promotes new blood vessel growth that can lead to AMD. Limitations exist for all of these treatment approaches; lasers cause scarring, and anti-VEGF medications typically have to be injected every 4 to 6 weeks.[4] Therefore, new treatment options continue to be investigated.

There is a pressing need for a long-term therapy solution for patients with AMD. Such an option would free patients from the burden of frequent office visits to receive injections. Much work has been done on developing extended-release therapeutics and intraocular drug-delivery devices.[5-7] This article explores the future of extended-duration treatments for AMD with an overview of some of the intravitreal injection approaches and intraocular implants that are undergoing clinical trials.

EXTENDED-DURATION TREATMENTS FOR AMD

Intravitreal Injections

DARPin

Abicipar pegol (Allergan) is a designed ankyrin repeat protein (DARPin) therapeutic with high affinity for VEGF-A. DARPins have smaller molecular weight, higher binding affinity, and longer vitreous half-life than either ranibizumab (Lucentis, Genentech) or aflibercept (Eylea, Regeneron). Recently completed phase 1/2 clinical trials showed that three monthly doses of 1.0-mg or 2.0-mg intravitreal injections of abicipar pegol were at least as effective as five monthly doses of ranibizumab, despite higher rates of baseline inflammation in the abicipar group. Also, data suggest that abicipar may have better visual outcomes and longer duration of action, with the possibility of administration every 12 weeks after several loading doses.[8-9] Phase 3 clinical trials are under way.

Anti-PDGF

Intravitreal E10030 (Fovista, Ophthotech), an anti–platelet-derived growth factor (anti-PDGF) agent, has been shown to induce pericyte loss in preclinical studies. This anti-PDGF aptamer alters neovascularization by destabilizing pericytes and making new blood vessels more susceptible to anti-VEGF therapy. It is believed that a combination treatment of anti-PDGF and anti-VEGF agents may be more effective than anti-VEGF injections alone, especially in recalcitrant disease. A recent phase 1 clinical trial showed a favorable

AT A GLANCE

- Although wet AMD affects only 10% to 15% of people with AMD, it accounts for 90% of severe visual acuity loss from macular degeneration.
- Treatment options have improved, but all come with limitations, including the requirement for regular office visits and injections.
- Proposed long-term therapy solutions could help to alleviate this burden.

safety profile for intravitreal E10030 administered with ranibizumab.[10] A phase 3 clinical trial is under way.[11]

Combination Injectables

DARPins provide a platform for creation of drugs with multiple binding target proteins, and Allergan has an anti-VEGF/PDGF DARPin in preclinical studies.

DE-120 (Santen) is a double kinase receptor inhibitor that blocks both VEGF and PDGF. Delivered via intravitreal injection, DE-120 is being evaluated in a phase 2 clinical trial in patients with wet AMD.[12] Santen also began a phase 1/2 trial to assess safety and tolerability of intravitreal DE-122, an anti-endoglin antibody (TRC105) inhibiting the VEGF pathway.[13]

REGN2176-3 (Regeneron) is a combination therapeutic consisting of aflibercept and an antibody to the PDGF receptor (rinucumab). A phase 1 open-label study investigated intravitreal REGN2176-3 in four cohorts of three patients with wet AMD who received REGN2176-3 combined with aflibercept at baseline and at 4 weeks. Visual acuity was stable or increased in most patients, and there were no reports of treatment-related serious adverse events. A phase 2 study (CAPELLA) is recruiting participants.[14]

Antiinflammatory/Antiangiogenic

ICON-1 is a human fusion immunoprotein that belongs to a class of human immunoconjugate proteins (ICONs) being developed by Iconic Therapeutics. ICON-1 is constructed using a structural variant of the natural ligand of a disease-target protein to achieve high specificity and efficacy. When it binds to cells that aberrantly express tissue factor, it signals the body's immune system to remove pathologic tissue while leaving normal blood vessels and organ functions intact. In a phase 1 investigation, ICON-1 was reported to be well-tolerated and to lead to improvement in visual acuity, reduced retinal thickness, and regression of neovascularization.[9] A phase 2 trial to evaluate the safety and biological activity of repeated intravitreal administration of ICON-1 in patients with CNV secondary to AMD is under way, with an estimated primary completion date of September 2016.[15]

Anti-VEGF

Brolucizumab (Alcon) is a humanized single-chain variable fragment VEGF inhibitor that has high affinity to all isoforms of VEGF-A. Early human trials in patients with wet AMD indicated that brolucizumab may produce greater visual acuity improvement with longer intervals between injections than ranibizumab.[16] A phase 2 trial evaluating the efficacy and safety of the compound versus aflibercept in patients with wet AMD met its primary endpoint, demonstrating promising visual acuity gains that were noninferior to those of aflibercept.[17] A phase 3 study is ongoing.

> **"DARPins provide a platform for creation of drugs with multiple binding target proteins ... ."**

Intraocular Implants

Encapsulated Cell Technology

Encapsulated cell technology (ECT) is a first-in-class genetically engineered drug delivery platform. NT-503 is Neurotech's lead clinical program, an implant that continuously produces a soluble VEGF receptor protein for at least 2 years. Engineered retinal pigment epithelium cells are contained in a semipermeable polymer capsule that is sutured to the sclera, providing long-term secretion of a therapeutic agent. Phase 1 and 2 trials are recruiting participants and will evaluate safety and compare NT-503 with aflibercept in the treatment of recurrent CNV secondary to AMD.[18]

Refillable Implant

The Port Delivery System (developed by ForSight Vision4 and in-licenced by Genentech/Roche) is a nonbiodegradable, refillable drug delivery implant that, when affixed to the sclera, provides sustained delivery of ranibizumab into the vitreous for months. The 0.05-mL reservoir is placed subconjunctivally at the level of the pars plana and can be refilled by transconjunctival injection through a 3.2-mm scleral opening. A phase 1 study showed a good safety profile with results similar to those with intravitreal injections. The phase 2 LADDER study is further evaluating long-term delivery of ranibizumab.[19]

Refillable Pump

The Ophthalmic MicroPump System (Replenish) is a microelectromechanical system including a drug reservoir, flexible port, battery, and electronics. It consists of four subsystems: anterior micropump, posterior micropump, EyeLink, and drug refill system. For retina patients, the device is implanted subconjunctivally with a cannula inserted into the posterior segment, allowing micro doses of a drug to be released into the vitreous at a programmed interval. The reservoir is refillable using a disposable refill tubing kit and a 31-gauge needle.[20] The micropump has been studied with ranibizumab in patients with diabetic macular edema; additional studies would be needed to evaluate its role in the treatment of patients with AMD.[21]

CONCLUSION

With a drastic rise in the prevalence of AMD expected over the next few decades, the need for long-term treatment solutions for patients with wet AMD is tremendous. Extended-duration treatments such as those described in this article have the potential to decrease the treatment burden for patients and health care systems and would be welcome additions to the current treatment armamentarium. ■

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