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A primer on latest treatment options for AMD

BY AVNI PATEL FINN, MD, MBA, AND MRINALI GUPTA, MD

WET AGE-RELATED MACULAR DEGENERATION

The current treatments for wet age-related macular degeneration (wAMD) inhibit a molecule called vascular endothelial growth factor (VEGF). This molecule leads to abnormal blood vessel growth and instability. Currently available anti-VEGF drugs—Avastin (Genentech), Eylea, (Regeneron), Lucentis (Genentech)—are remarkably safe and very effective for wAMD. However, with current treatments, most patients need frequent injections indefinitely. More recently, a new anti-VEGF agent, Beovu (Novartis), was FDA-approved for wAMD with suggestion of longer duration of action and reduced need for injections; however, safety concerns related to inflammation have limited widespread use of this agent. Fortunately, several clinical trials are underway to evaluate new therapies that target other pathways and/or are formulated to produce a more longer-lasting effect and, in turn, reduce treatment burden. Here, we summarize several such therapies under investigation, primarily focusing on late-stage trials (Phases 2 & 3).

PORT DELIVERY SYSTEM (GENENTECH): This treatment consists of a small refillable device that is implanted into the wall of the eye during a surgical procedure. The small implant stores and continuously releases anti-VEGF medication into the eye by diffusion, taking the place of frequent injections. The device can be refilled in the office. Current studies have evaluated refills every 6 months, and some early studies showed that patients could go on average about 15 months without needing a refill.[1] The Port Delivery System has completed a Phase 3 clinical trial and we expect the data will be filed with the FDA soon.[2]

FARICIMAB (GENENTECH): Faricimab inhibits two pathways leading to abnormal blood vessel growth and leakage: It binds and inactivates a molecule called angiopoietin-2 (Ang-2) in addition to the VEGF molecule that current medications inhibit.[3] By binding both molecules, faricimab may lead to improved outcomes and longer treatment duration.[4] In current trials, the medication is being given up to every 4 months after a series of monthly doses. Phase 3 trials are ongoing, and we expect data in 2021.

CONBERCEPT (CHENGDU KANGHONG): Conbercept is an engineered anti-VEGF that has been widely used in China since its approval there in 2013. It has been reported that conbercept may be a more potent medication because of its ability to address multiple targets, potentially resulting in a longer-lasting treatment (~3 months). Phase 3 trials in the U.S. are ongoing.[5-6]

KSI-301 (KODIAK SCIENCES): KSI-301 is a specially formulated anti-VEGF drug called an antibody polymer conjugate. The medication is expected to stick around the eye for a longer time and deliver a greater dose of medication with one injection.[7] Patients in the ongoing trials are receiving treatment with the medication every 3 to 5 months, and some have gone up to 6 months before needing retreatment with an injection.[8] A larger trial comparing KSI-301 to currently available medications is ongoing, and we expect to get data in 2021.

OPT-302 (OPTHEA): OPT-302 inhibits VEGF-C and VEGF-D, and is designed to be used in combination with the existing anti-VEGF-A therapies. The rationale is that blocking additional VEGF family members will yield a more potent anti-VEGF effect. A Phase 2 trial found that OPT-302 in combination with Lucentis was more effective than monthly Lucentis.[9-10] Phase 3 trials are expected to start soon.

SUNITINIB (GRAYBUG): Sunitinib is a specially formulated depot medication that slowly dissolves over time in the eye.[11] The medication acts in a slightly different way to inhibit VEGF. Because it is a depot, the medication releases over time, allowing for the possibility of extended treatment effect. In recent trials, 90% of patients were able to go 3 months without needing re-treatment, and 70% of patients were able to go to 6 months without needing retreatment. The medication is currently in a Phase 2 clinical trial.[12]

AKST4290 (ALKAHEST): AKST4290 is a small molecule inhibiting the immunomodulators playing a role in inflammation and neovascularization; two processes important in wAMD. This medication is unique from the others in that it is administered *by mouth*. Two small trials showed initial benefit of AKST4290 therapy in terms of vision stabilization and improvement.[13-14] A larger Phase 2 trial evaluating this medication is underway.[15]