# The Neovascular AMD Pipeline

What might the future of wet AMD therapy look like?

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The names of new drugs, studies, and companies fly around at retina meetings. It can be difficult to keep the names straight, particularly now, when there is such strong momentum for innovation in the retina space. In this article, we hit the pause button to discuss a handful of drugs in the pipeline for the treatment of wet age-related macular degeneration (AMD). I have divided them into two categories for the sake of discussion: the next generation of anti-VEGF agents, and novel technologies that address treatment burden.

## NEXT GENERATION ANTI-VEGF AGENTS

### Brolucizumab

In October, brolucizumab-dbll injection 6 mg (Beovu, Novartis), a humanized single-chain antibody fragment, was approved the US FDA for the treatment of wet AMD. Although it is no longer a pipeline candidate per se, it is so new to clinicians that it is appropriate to mention it here, in the context of other up-and-coming therapeutic options.

The humanized single-chain antibody fragment, with its small size, enhanced tissue penetration, and rapid clearance from systemic circulation, offers a novel treatment option for wet AMD. A single dose of brolucizumab may contain a high concentration of drug given its low molecular weight.

On page 16, Michael Ammar, MD, and Jason Hsu, MD, address the structure and results of the phase 3 HAWK and HARRIER studies, the pivotal phase 3 clinical trials that assessed the safety and efficacy of brolucizumab in wet AMD therapy.[1] In brief, brolucizumab was found to be noninferior to aflibercept (Eylea, Regeneron) in mean change in BCVA at week 48. The drug's labeling calls for 3 monthly loading doses followed by retreatment every 8 to 12 weeks. With the potential for durability of up to 12 weeks, it's possible that brolucizumab could alter wet AMD treatment patterns in the coming years.

### Abicipar Pegol

Abicipar pegol (Allergan) is a designed ankyrin repeat protein (DARPin) that binds to all forms of VEGF-A. As a member of this new class of binding proteins, abicipar offers an alternative to antibody-based drugs for inhibition of VEGF. With an extended half-life of 6 to 7 days, abicipar may offer extended treatment intervals for patients with wet AMD.

In this issue, Drs. Ammar and Hsu also review the specifics of the phase 3 CEDAR and SEQUOIA studies, as well as the results of the open-label MAPLE study. In CEDAR and SEQUOIA, researchers found that treatment every 8 or 12 weeks with abicipar was noninferior to monthly ranibizumab (Lucentis, Genentech).[2]

The open-label MAPLE study was undertaken to explore whether a new manufacturing method could lower rates of ocular inflammation observed in the two phase 3 studies and subsequently found that the new formulation of abicipar was associated with a lower rate of intraocular inflammation.[3]

The FDA has accepted the biologics license application for abicipar and is expected to make a decision on its approval in 2020.

### KSI-301

KSI-301 (Kodiak Sciences) is a

## AT A GLANCE

- A number of technologies that may improve upon anti-VEGF strategies for wet AMD treatment are in the pipeline; another, brolucizumab, was recently approved by the US FDA.
- Pipeline candidates that decrease treatment burden could reduce the number of visits patients must make to the clinic each year.
- Extended duration of VEGF inhibition and sustained release of VEGF receptor tyrosine kinase inhibition are two of the main avenues by which researchers are approaching wet AMD therapy.

full-length anti-VEGF antibody stably linked to a biopolymer to create an antibody-biopolymer conjugate. The biopolymer's high molecular weight is intended to help retain the drug in the vitreous and enhance durability.

Researchers are investigating if KSI-301 can safely and efficaciously be dosed every 3, 4, or 5 months in patients with wet AMD.

At this year's AAO Annual Meeting, Charles C. Wykoff, MD, PhD, shared data about an ongoing phase 1b trial investigating the use of KSI-301 in patients with wet AMD; the same trial is also evaluating the drug in patients with diabetic macular edema or with retinal vein occlusion.[4]

Patients with wet AMD (n = 25) received KSI-301 at weeks 0, 4, and 8, after which they were observed for 8 weeks. At week 16, the investigators noted an increase from baseline of 5.4 letters and a decrease in central subfield thickness (CST) by 72 µm as measured on OCT.

Durability of KSI-301 in this phase 1b trial was encouraging. Only one patient had to be retreated before week 20 (3 months after the initial monthly loading doses), and only two patients had to be retreated at week 20; 80% of patients were able to go without retreatment for 4 months after the loading dose phase.

No intraocular inflammation was observed. The study has been extended to 18 months to allow collection of more data on durability.

The DAZZLE study, which will compare KSI-301 to aflibercept for the treatment of wet AMD, is now enrolling patients.

### OPT-302

OPT-302 (Opthea) is an anti-VEGF R3 receptor fusion protein that serves as a "trap" molecule to block activity of VEGF-C and VEGF-D. Brolucizumab, ranibizumab, and bevacizumab (Avastin, Genentech) bind to VEGF-A alone, and aflibercept binds to VEGF-A, VEGF-B, and placental growth factor. Because OPT-302 binds to VEGF-C and VEGF-D, it offers a novel mechanism of action and thus has the potential to be given in combination with any of the approved anti-VEGF therapies, potentially providing an added benefit in terms of vision improvement, disease control, and treatment durability.

A phase 1/2a trial evaluating OPT-302 in patients with wet AMD enrolled patients into one of two arms: OPT-302 monotherapy or OPT-302 and ranibizumab combination therapy.[5] In the monotherapy group, patients demonstrated a mean improvement of 4.4 letters from baseline at week 12; patients who did not require rescue therapy showed a mean improvement of 5.6 letters at week 12. In the combination therapy arm, patients who were treatment-naïve showed a mean gain of 10.8 letters and a CST reduction of 119 µm at week 12; patients who had previously been treated with anti-VEGF therapy showed a 4.9-letter improvement and a CST reduction of 54 µm at week 12.

OPT-302 demonstrated a good safety profile in both arms. No dose-limiting toxicities were observed; the maximum tolerated dose was not reached.

In a randomized, double-masked, controlled phase 2b study evaluating OPT-302 in patients with wet AMD, investigators enrolled 366 treatment-naïve patients. Patients were randomly assigned 1:1:1 to receive intravitreal dosing of one of the following every 4 weeks: combination therapy with 2.0 mg OPT-302 plus 0.5 mg ranibizumab; 0.5 mg OPT-302 plus 0.5 mg ranibizumab; or 0.5 mg ranibizumab monotherapy.

The primary endpoint of the study, mean change in BCVA from baseline to week 24, was met. The 2.0 mg OPT-302 plus 0.5 mg ranibizumab arm demonstrated superiority in VA gains compared with the ranibizumab monotherapy arm, with a mean 14.22-letter improvement in the this combination therapy group compared with a 10.84-letter improvement in the 0.5 mg ranibizumab monotherapy arm.

The safety profile in the combination therapy arms was similar to that in the ranibizumab monotherapy arm.[6] These promising data suggest strong potential of improved vision outcomes for OPT-302 administered in combination with other anti-VEGF agents.

## WHY BIOSIMILARS?

A biosimilar is a biologic medical product highly similar to another already approved biologic medicine (ie, the *reference medicine*). It is technically not considered a generic medicine because the more complex manufacturing of a biologic medicine prevents exact replication of the reference medicine on a micromolecular level. Companies that can produce biosimilars and subsequently demonstrate that the safety and efficacy of the biosimilar are comparable to those of the original reference biologic may apply for regulatory approval to bring that biologic to market. This process may soon occur with one or more of the anti-VEGF molecules we are familiar with. These biosimilars have the potential to be significantly less expensive than anti-VEGF agents now on the market.

Efforts to bring biosimilars for wet AMD to market are underway, particularly outside of the United States—but it is likely that we will see the emergence of biosimilars in the United States as well. Whether biosimilars are routinely adopted in clinical practice remains to be seen, and will likely depend on the available clinical evidence for safety and efficacy, on the subsequent real-world clinical experience, and on the requirements set forth by payers, which are increasingly requiring the use of cheaper alternatives (such as bevacizumab [Avastin, Genentech]) before use of more expensive drugs in a process known as *step therapy*.

## ADDRESSING TREATMENT BURDEN

HORIZON was a 2-year open-label extension study examining the real-world behavior of patients who underwent 2 years of ranibizumab therapy for wet AMD; at the conclusion of the study, patients had been treated with ranibizumab for at least 4 years, 2 of which were in a real-world setting. The study authors wrote, "With less frequent follow-up leading to less treatment, there was an incremental decline of the VA gains achieved with monthly treatment."[7] In other words, real-world results did not mirror clinical trial results, indicating that treatment burden is a significant barrier to positive results for patients with wet AMD in real-world clinical practice.

In addition to several of the above named agents, which may enable longer dosing intervals, several promising technologies are in the pipeline to address the problem of treatment burden.

### Port Delivery System

The Port Delivery System (PDS, Genentech) is a refillable reservoir that releases a small, consistent dose of ranibizumab. The device is surgically implanted and is refilled as needed in an office setting.

The phase 2 LADDER study was a multicenter, randomized, interventional, active treatment–controlled study of ranibizumab delivery with the PDS.[8] Researchers randomly assigned patients with wet AMD to one of three formulations of ranibizumab (10 mg/mL, 40 mg/mL, or 100 mg/mL) that was delivered via the PDS, or to monthly ranibizumab injection.

Patients in the 100 mg/mL treatment arm demonstrated a mean letter gain of 5.0 letters at 9 months, and patients in the monthly ranibizumab group demonstrated a gain of 3.9 letters at 9 months. The median time to first PDS refill in the 100 mg/mL arm was 15 months.

The phase 3 ARCHWAY trial finished enrolling patients this summer.[9] In this study, patients will be randomly assigned into two arms: PDS with the 100 mg/mL formulation of ranibizumab refilled at 24-week intervals or monthly ranibizumab therapy.

### Tyrosine Kinase Inhibition

Anti-VEGF agents exert their effects on exudation and angiogenesis by blocking VEGF from engaging receptors on the cellular surface. Targeting the cell surface receptor may also be effective. Targeted inhibition of the VEGF receptor tyrosine kinase by small molecules may prevent activation of VEGF-mediated signaling cascades within the cell, offering an alternative mechanism of action to block vascular permeability and angiogenesis. Several small molecule receptor tyrosine kinase inhibitors (TKI) are in development.

GB-102 (Graybug Vision) is a formulation of sunitinib encapsulated in bioabsorbable microparticles. The phase 1/2a ADAGIO study of GB-102 in patients with wet AMD met primary endpoints of safety and tolerability earlier this year. Secondary efficacy outcomes demonstrated that 88% and 68% of evaluable patients were maintained on only a single dose of GB-102 at 3- and 6-months, respectively. The phase 2b, 12-month, 3-arm ALTISSIMO study, initiated in October, will investigate GB-102 (1 mg and 2 mg) administered every 6 months compared with aflibercept 2 mg every 2 months in patients with wet AMD.

PAN-90806 (PanOptica) is a TKI administered as an eye drop. Results from an initial phase 1/2 clinical trial showed that approximately 45% to 50% of patients treated with 1 mg/mL or 2 mg/mL formulations of the drug for up to 8 weeks showed improvements in vascular leakage, lesion morphology, and vision.[10] In a second phase 1/2a trial of the compound completed this year, there were no serious or severe adverse effects, and more than half of participants receiving once-daily topical PAN-90806 for 12 weeks completed the study without needing rescue therapy.[11]

Other TKIs in development include OTX-TKI (Ocular Therapeutix) and KPI-285 (Kala Pharmaceuticals). OTX-TKI is a sustained-release TKI implant formulated with a bioresorbable hydrogel. A phase 1 study of the drug was initiated last year. KPI-285 is a topical formulation in preclinical stages of development.

## LOOKING FORWARD

The future of treatments for wet AMD appears very promising, with the next generation of drugs in the pipeline offering the promise of enhanced durability, improved disease control, and possibly even better vision. These therapies offer the potential of improved real-world outcomes for our patients with wet AMD and may very well alter the landscape and paradigms of wet AMD treatment in the years ahead—just as the first generation of anti-VEGF agents did nearly 15 years ago. ■


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