Emerging Treatments for Neovascular AMD


Novel treatment options hold the promise of longer-term VEGF suppression.

BY NATALIE HUANG, MD; AND PATRICK OELLERS, MD

Anti-VEGF drugs have revolutionized the treatment of neovascular age-related macular degeneration (AMD), but recent studies have demonstrated substantially worse VA results in the real world than were achieved in earlier prospective clinical trials.[1-3] This discrepancy seems to stem from the relatively high treatment burden associated with current anti-VEGF strategies.[4] Many patients require intravitreal injections every 4 to 8 weeks to adequately combat ongoing disease activity over many years. Some will probably require lifelong treatment. Many patients are unable to maintain such frequent injection cycles; as a result, a large share of our real-world patients are, essentially, undertreated.

On the other hand, evidence is mounting that most patients would benefit from sustained long-term anti-VEGF suppression. Early concerns that frequent anti-VEGF injections might be linked to geographic atrophy seem to have been overstated.[5] Data indicate that long-term, frequent injections are safe and associated with excellent preservation of VA.[6]

Several emerging therapies are making headway in addressing the unmet need of more durable suppression of disease activity. In this article, we review some promising treatment options and the emerging data from their respective clinical trials.

EMERGING THERAPIES

Brolucizumab

Brolucizumab, also known as RTH258 (Novartis), is a novel small (26 kDa) humanized single-chain antibody fragment that is a potent inhibitor of VEGF-A. The small size of the molecule, relative to other anti-VEGF agents, allows higher dosing per volume, which may result in a longer-lasting effect (Figure 1).

Two large phase 3 studies, HAWK and HARRIER, investigated the efficacy and safety of brolucizumab 3 mg (HAWK only) and brolucizumab 6 mg (HAWK and HARRIER) with a dosing frequency of up to every 12 weeks, in comparison with

AT A GLANCE

- Real-world results with anti-VEGF therapies often do not match the results of prospective clinical trials, possibly because the high burden of treatment results in relative undertreatment.
- Several emerging therapies are making headway in addressing the unmet need of more durable suppression of disease activity.
- Approaches under investigation include new anti-VEGF molecules, a refillable implant, molecules targeting other factors, and gene therapy.

Drug	Unlicensed Bevacizumab	Aflibercept	Ranibizumab	Brolucizumab
Format	Full antibody (IgG1)	VEFGR1/2-Fc Fusion Protein	Fab Fragment	Single-Chain Antibody Fragment
Molecular Structure				
Molecular Weight	= 149 kDa	97-115 kDa	= 48 kDa	26 kDa
Clinical Dose	1.25 mg	2.00 mg	0.50 mg	6.00 mg
Equivalent Molar Dose	0.4-0.5	1.0	0.5-0.6	11.2-13.3

Figure 1. Brolucizumab's significantly smaller size allows greater molar doses per volume of injection.

aflibercept 2 mg (Eylea, Regeneron) every 8 weeks. Both brolucizumab arms had an initial loading phase of injections at day 1, week 4, and week 8. The results demonstrated noninferiority of brolucizumab 3 mg and 6 mg to aflibercept 2 mg in BCVA at week 48, the primary endpoint of the studies.

Moreover, brolucizumab-treated patients showed greater reduction in subretinal and intraretinal fluid on average, indicating that it may be a better drying agent than the comparator drug. In terms of durability, in the brolucizumab arm, 49% to 56% of patients were maintained on a 12-weekly injection regimen until week 48, and most of these patients were maintained on that interval up to week 96.[7]

MERLIN is an ongoing phase 3 trial comparing brolucizumab 6 mg every 4 weeks with aflibercept 2 mg every 4 weeks in patients with persistent subretinal or intraretinal fluid despite frequent treatment.[8] The study began in October 2018, and no results have been posted to date.

Novartis submitted a biologics license application to the US FDA for brolucizumab in April with a request for expedited review. If the drug is approved, the company anticipates launching it by the end of this year.

It will be interesting to see how availability of this drug might change the management of our patients with neovascular AMD. Research results to date suggest that this drug could reduce the burden of neovascular AMD treatment to a quarterly dosing regimen for a substantial number of patients, which would be a welcome change.

Port Delivery System

Another method of extending the duration of VEGF suppression is by use of an indwelling depot. Genentech is developing a surgically implanted drug delivery system, the Port Delivery System (PDS) for use with ranibizumab (Lucentis, Genentech). *(Editors' Note: The article "*Use of the Port Delivery System in AMD*" on page 34 in this issue contains images of the PDS.)*

A phase 3 clinical trial, ARCHWAY, is evaluating the efficacy, safety, and pharmacokinetics of the PDS implant, filled with 100 mg/mL of ranibizumab at a 24-weekly interval, in comparison with monthly intravitreal ranibizumab injections for the treatment of neovascular AMD.[9]

The phase 2 LADDER trial compared the efficacy, safety, and pharmacokinetics of three doses (10 mg/mL, 40 mg/mL, and 100 mg/mL) of ranibizumab delivered via the PDS. In that trial, 79.8% of patients who received the highest dose did not require refills for at least 6 months.[10] There were concerns about the frequent occurrence of vitreous hemorrhage in the early phase of the trial, but this may have been addressed by modification of the surgical technique.

The ARCHWAY trial is rapidly enrolling patients and we look forward to learning about what the availability of this implant might bring to the field. If the PDS is found to be adequately safe, it may introduce a whole new treatment paradigm, moving away from the peak-and-trough phenomenon seen with intravitreal injections.

Faricimab

Faricimab (Genentech; Figure 2) is a bispecific antibody for both VEGF-A and angiopoietin 2 (Ang-2). Ang-2 is a cytokine associated with vascular destabilization and microvascular inflammation. It is hoped that dual blockade of VEGF and Ang-2 may bring synergistic effects in the treatment of neovascular AMD.

The completed phase 2 STAIRWAY trial compared two extended dosing regimens of faricimab 6.0 mg, given every 12 and every 16 weeks, to ranibizumab 0.5 mg given every 4 weeks. Results of the study showed noninferior BCVA and anatomic outcomes with these regimens compared with monthly ranibizumab, and the drug was well tolerated with no concerning safety signals.[11]

TENAYA and LUCERNE are two identically designed phase 3 clinical trials commenced in early 2019 by Roche and Genentech to evaluate the safety, efficacy, and durability of faricimab given every 16 weeks, with an option to decrease the treatment interval to every 12 or 8 weeks based on clinical indications, compared with aflibercept given every 8 weeks.[12,13] The primary outcome of the studies will be BCVA at 48 weeks.

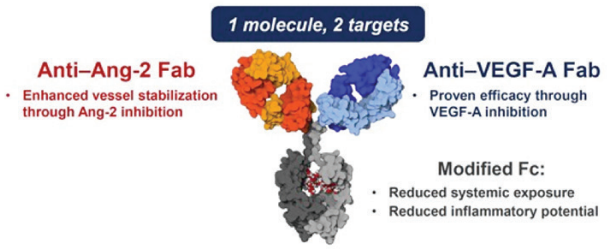

Figure 2. Faricimab is a bispecific antibody that shows potential for increased durability in treatment of neovascular AMD.

With its dual blockage mechanism, faricimab may allow longer dosing intervals. We anticipate learning more about the rollout of the phase 3 trials.

Abicipar

Abicipar pegol (Allergan) is a designed ankyrin repeat protein, or *DARPin*, a 34-kDa molecule that inhibits both VEGF and platelet-derived growth factor. Two parallel 52-week phase 3 clinical trials, CEDAR and SEQUOIA, evaluated abicipar pegol 2.0 mg, injected either every 8 weeks (after three initial monthly injections) or every 12 weeks (after injections at day 1, week 4 and week 12) in comparison with monthly ranibizumab.[14,15]

In those trials, abicipar was found to be noninferior to ranibizumab in VA results, even in the quarterly treatment arms. However, an ocular adverse event rate of 15.0% was reported, mostly in the form of intraocular inflammation, compared with 0.3% in the ranibizumab arm.[16] It is possible that Allergan may be able to address these issues, but for now we are concerned that these inflammatory reactions may significantly limit clinical use in a field full of potent and safe competitors.

Conbercept

Conbercept (Chengdu Kang Hong Biotech) is an anti-VEGF–receptor fusion protein that blocks isoforms of VEGF-A, VEGF-B, VEGF-C, and platelet-derived growth factor. It was approved for the treatment of neovascular AMD in China in 2013 based on the PHOENIX trial, which reported effectiveness of conbercept with three initial monthly injections followed by quarterly injections.[17] In the United States, the PANDA-1 trial is a recently launched phase 3 clinical trial comparing the efficacy and safety of intravitreal injection of 0.5 mg conbercept, 1.0 mg conbercept, and 2.0 mg aflibercept.[18] Patients in each arm will receive injections at day 1, week 4, and week 8, followed by injections every 8 weeks (conbercept 0.5 mg, aflibercept 2.0 mg) or every 12 weeks (conbercept 1.0 mg) for a total of 96 weeks.

GENE THERAPY

In the more distant future, there may be even greater promise for patients with neovascular AMD through one or more of the gene therapies that are now being explored in phase 1 and 2 clinical trials.

ADVM-022

The OPTIC trial is a phase 1 study that is investigating the safety of the ADVM-022, also known as AAV.7m8-aflibercept (Adverum Biotechnologies), a gene therapy product designed to express aflibercept protein within retinal cells after a one-time intravitreal injection.[19] The OPTIC trial will evaluate three doses in a small number of patients under active treatment who have already demonstrated a meaningful response to anti-VEGF therapy. With improved gene vector efficiency, this therapy has the potential to achieve long-term sustained anti-VEGF suppression with a single administration.

HMR59

HMR59 (AAVCAGsCD59; Hemera Biosciences) is an adeno-associated virus 2 gene therapy that produces a soluble form of CD59, which blocks complement activity at the membrane attack complex. This gene therapy is being tested in phase 1 clinical trials for both wet and dry AMD. In the phase 1 HMR-1002 trial, treatment-naïve patients will receive an intravitreal anti-VEGF injection at day 1 and a single injection of HMR59 injection at day 7, followed by anti-VEGF treatment on an as-needed basis.[20]

RGX-314

RGX-314 (RegenxBio) is a recombinant adeno-associated virus gene therapy vector carrying a coding sequence for a soluble monoclonal antibody fragment that binds to and neutralizes VEGF.[21] A phase 1/2a clinical trial is evaluating the safety of subretinal injection of RGX-314 in patients with previously treated neovascular AMD.[21] The study is designed to assess whether a single dose of RGX-314 will allow expression of a therapeutic level of anti-VEGF proteins by retinal cells.

It will be intriguing to see how this product, which is being delivered surgically by subretinal injection, will pan out in this well-designed clinical trial.

QUESTIONS TO BE ANSWERED

There are a number of questions about the pipeline of AMD treatments. Regarding conbercept, will the promise of the PHOENIX trial hold up in the PANDA-1 trial? Will Allergan be able to adjust for the inflammatory reactions seen after administration of abicipar pegol in CEDAR and SEQUOIA? Will the phase 3 studies of faricimab show that longer dosing intervals can become a reality for patients?

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How will brolucizumab and the PDS, if they are approved, change the ways we treat patients?

There is a significant unmet need of undertreatment due to the relatively high treatment burden of AMD therapy, and we are looking forward to seeing if the newer treatment options discussed here may really help further our field. ■

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