Spotlight on Faricimab in the Treatment of Wet Age-Related Macular Degeneration: Design, Development and Place in Therapy

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Abstract: The advent of anti-vascular endothelial growth factor (VEGF) agents has revolutionized the treatment of retinal neovascular diseases including neovascular age-related macular degeneration (nAMD), a leading cause of irreversible blindness. Multiple agents and methods for drug delivery are emerging to increase the duration of treatment effect and treatment interval, reducing the overall treatment burden on patients and clinicians. The newest agent on the market is faricimab. This medication targets two distinct pathways in retinal angiogenesis, VEGF-A and Ang-2, to create a more durable effect. Phase 3 trials for this drug compared treatment intervals up to 16 weeks against aflibercept dosed at 8-week intervals for both nAMD and diabetic macular edema (DME). While the drug shows similar functional and anatomic outcomes with a low adverse effect profile and trial data demonstrating increased treatment duration, its exact place in the VEGF marketplace is yet to be determined. In this article, we discuss the mechanism of action, pivotal clinical trials leading to approval, and the anticipated role for faricimab in the treatment of retinal neovascular disease.

Keywords: neovascular age-related macular degeneration, nAMD, macular degeneration, anti-vascular endothelial growth factor, anti-VEGF, faricimab, choroidal neovascularization, CNVM

Neovascular age-related macular degeneration (nAMD) is a leading cause of irreversible blindness in industrialized nations. Approximately 11 million patients in the United States alone are affected by AMD with a global burden of nearly 180 million individuals. About 10% of these patients suffer from nAMD. Vascular endothelial growth factor (VEGF) has been identified and isolated as pivotal factor in ocular angiogenesis and in the development of choroidal neovascularization. This clinical discovery led to a transformational emergence of new therapies and treatments for nAMD. In 2004, the FDA approved the first anti-VEGF agent, pegaptanib sodium (Macugen, OSI Pharmaceuticals, Melville, NY), a pegylated VEGF 165-specific aptamer after clinical trials showed promising results. Since the approval of the initial drug, additional anti-VEGF drugs have been approved, along with a significant expansion of indications for treatment. Current treatment paradigms aim to control the disease activity in order to maintain and/or improve visual acuity. Various markers on optical coherence tomography (OCT) have been associated with decreased long terms vision including the presence of intraretinal fluid (IRF), subretinal hyperreflective material, scar, and retinal thinning. Multiple studies have shown that minimizing IRF correlates to better long-term visual outcomes. However, the association between subretinal fluid (SRF) and visual prognosis is unclear and recent research shows that many patients can tolerate SRF over 2 years without visual decline. Studies looking at long-term outcomes have also demonstrated the need for continued treatment to maintain good visual acuity and anatomic outcomes, with the potential for relapse and regression when treatment is stopped or treatment intervals are extended too greatly. This need for regular and frequent treatments creates a high overall treatment burden for patients and providers.

The currently available FDA-approved anti-VEGF agents include ranibizumab (Lucentis, Genentech, San Francisco, CA, USA), aflibercept (Eylea, Regeneron, Tarrytown, NY, USA), brolucizumab (Beovu, Novartis, East Hanover, NJ, USA), and faricimab (Lucentis-Farinica, Genentech, San Francisco, CA, USA).
USA), and most recently faricimab (Vabysmo, Genentech, San Francisco, CA, USA) (Table 1). Ranibizumab is a recombinant immunoglobulin fragment that binds to all isoforms of VEGF-A.\(^2\) In 2005, the initial clinical trials of ANCHOR and MARINA evaluated the efficacy of monthly ranibizumab injections in the treatment of nAMD compared to sham and photodynamic therapy (PDT): patients were found to have significantly improved visual acuity at 2 years with ranibizumab.\(^13\)–\(^15\) Concurrently, many ophthalmologists began off label use of bevacizumab (Avastin, Genentech, San Francisco, CA, USA) for treating nAMD given its similar target specificity and cost effectiveness.\(^16\) Bevacizumab binds to all isoforms of VEGF-A and has been widely used for various systemic cancers. Its clinical equivalence to ranibizumab with monthly injections over 2 years was proven in the landmark CATT trial and is now a mainstay of treatment.\(^17\)

An improvement in clinical detection through advances in imaging capabilities combined with our improved understanding of the vast disease processes that are treated with anti-VEGF have substantially increased the treatment burden on retina clinics and patients\(^18\),\(^19\) promoting an unmet need of longer acting medications and decreased treatment frequency. Unfortunately, results in clinical practice do not perfectly mimic clinical trial results as studies have shown that clinicians administer fewer injections in real-life, leading to a higher rate of irreversible vision loss.\(^20\) Older patients and patients with worse baseline vision are more likely to lose vision due to undertreatment.\(^21\),\(^22\) Furthermore, it is well-established that there is a proportion of patients who have a poor disease response to inhibitors of VEGF-A and therefore a longer-acting agent or a shorter treatment interval may be needed for these patients.\(^23\) Despite the well-established need for more frequent treatment, many patients are being undertreated and consequently losing vision. This has prompted further research and development for more durable treatment options.

The newer medications on the market have been developed to try to extend treatment intervals to help decrease overall treatment burden, while at the same time improving efficacy, by attacking different VEGF targets. Afibercept, a fusion protein that binds to VEGF-A, VEGF-B, and placental growth factor,\(^24\) was initially FDA approved for treatment of nAMD using 8-week dosing interval in the VIEW-1, VIEW-2 trials.\(^25\) Potential duration of treatment was further extended to 12-week dosing with brolucizumab, a humanized, single-chain variable fragment that inhibits VEGF-A, in the HAWK and HARRIER trials.\(^26\),\(^27\) Single chain variable fragments are an attractive format for pharmacologic treatment due to their small size. Studies with these molecules have shown better target-tissue penetration and thus greater local efficacy and potentially better durability of effect.\(^28\) In key trials, brolucizumab was shown to be non-inferior to afibercept with a longer treatment interval.\(^26\) Unfortunately, wide adaptation of the drug was confounded by the risk of occlusive retinal vasculitis and intraocular inflammation in patients receiving brolucizumab.\(^29\) This devastating, potentially vision-threatening side effect if diagnosed
late and left untreated has caused many retina providers to be hesitant to add this medication to their nAMD armamentarium with only 0.1% of retina specialists in the US reporting use of bevacizumab as a second-line agent.\textsuperscript{30}

Faricimab is the most recent therapeutic to be approved by the FDA for the treatment of both nAMD and diabetic macular edema (DME). It is a bispecific monoclonal antibody that inhibits both VEGF-A and angiopoietin 2 (Ang-2)\textsuperscript{31} made up of 2 heavy chains and 2 light chains. Ang-2 is a novel therapeutic target that has been shown to play a role in inflammation and vascular destabilization in animal models.\textsuperscript{32} Its role is mediated through Tie2 a transmembrane receptor located on endothelial cells which plays a role in vascular stability and angiogenesis.\textsuperscript{32,33} Ang-1 and Ang-2 competitively bind to Tie2. Binding of Ang-1 to Tie2 activates downstream pathways that ultimately maintains vascular stability and inhibits vascular permeability.\textsuperscript{34} Binding of Ang-2 with Tie2 has the opposite effect: deactivating the pathway and decreases vascular stability.\textsuperscript{35} Ang-2 is known to be elevated in ischemia or oxidative stress.\textsuperscript{36} It is also shown to sensitize blood vessels to VEGF; inhibition of this pathway is believed to have a synergistic effect with anti-VEGF agents by further decreasing vascular leakage and inflammation compared to anti-VEGF alone and, therefore, deliver a stronger therapeutic effect.\textsuperscript{37}

\textbf{AVENUE and STAIRWAY} were the Phase 2 trials comparing this drug with ranibizumab. The AVENUE trial compared varying doses of faricimab every 4 weeks to ranibizumab and was found non-inferior to ranibizumab.\textsuperscript{38} The STAIRWAY trial evaluated Faricimab with extended treatment intervals out to every 12 to 16 weeks depending on disease activity, following a loading injection of every 4 weeks for 4 injections. Of those patients, 65% of patients had no disease activity at week 24, which was 12 weeks after the last loading injection.\textsuperscript{39} The phase 3 clinical trials for Faricimab, TENAYA and LUCERNE, were randomized control trials designed to compare aflibercept to faricimab for the treatment of nAMD. Concurrent trials were also done to evaluate the drug’s efficacy in diabetic macular edema.\textsuperscript{40} Patients were randomized to aflibercept 2 mg every 8 weeks after receiving 3 monthly injections of 6 mg faricimab up to every 16 weeks after receiving 3 monthly injections of either agent. Patients in the faricimab group were extended to up to 16-week treatment intervals based on disease activity. Those patients who were found to have active disease 8 weeks after the last monthly injection remained on 8-week injection frequency till the completion of the study. Of the remaining patients, those who had disease activity at 12 weeks continued to have injections every 12 weeks. Finally, the remaining patients stayed on 16-week injection frequency. Notably, patients in the aflibercept arm were not extended beyond 8-week injection frequency.

These trials showed impressive durability data in patients randomized to faricimab. By week 48, about 80% of the patients treated with faricimab were on either every 12 or 16-week dosing. Specifically, 12-week dosing was achieved in 34% of patients in TENAYA and 32.9% of patients in LUCERNE; and 16-week dosing was achieved in 45.7% of patients in TENAYA and 44.9% of patients in LUCERNE. About 21% of patients remained at 8-week intervals. Faricimab was non-inferior to aflibercept with regards to clinical outcomes at the completion of the trial. Baseline change in BCVA in TENAYA was 5.8 letters for faricimab vs 5.1 letters for aflibercept and 6.6 letters for both aflibercept and faricimab in LUCERNE. Change in mean central subfoveal thickness (CST) was comparable between the faricimab groups (−136.8 μm in TENAYA and −137.1 μm in LUCERNE) and the aflibercept groups (−129.4 μm in TENAYA and −130.8 μm in LUCERNE). The rate of serious ocular adverse events was similar between both aflibercept and faricimab with notably no evidence of occlusive retinal vasculitis.\textsuperscript{31}

The results from TENAYA and LUCERNE make a compelling case for the potential durability of faricimab with similar visual and anatomic outcomes to aflibercept dosed every 8 weeks.\textsuperscript{41} However, as noted above, prior clinical trials with other anti-VEGF agents have shown that outcomes in clinical practice do not perfectly mimic clinical trial data; thus, the true durability of the medication compared to currently available treatment options is yet to be confirmed. Additionally, as with all newly approved medications, real-world data provides new insight as to the efficacy and safety of these drugs when used on a more heterogenous population of patients.

The impact of faricimab in the anti-VEGF market is yet to be determined. The treat and extend regimen has been well established for the treatment of nAMD\textsuperscript{32} and shown to be efficacious for various anti-VEGF medications for the treatment of nAMD. A study by Mitchell et al evaluated the efficacy of a treat and extend regimen using aflibercept with approximately 50% of patients extending to 12 weeks or longer.\textsuperscript{43} In real-world scenarios, many patients are able to extend treatment intervals beyond FDA dosing labels – beyond 4 weeks for bevacizumab and beyond 8 weeks for aflibercept –therefore, the true potential to decrease in treatment burden is still unknown. Lastly, head-to-head treat and...
extend trials between currently available treatment options will be ultimately helpful in determining the real-world durability of faricimab compared to aflibercept.

With the potential to decrease injection burden to quarterly visits, equivalent efficacy, and durable treatment effect, we anticipate an increasing number of clinicians will adopt faricimab as a first-line agent in patients with nAMD, if no relevant safety signals arise in clinical practice. It is even more likely faricimab will become the second-line agent of choice in patients who have previously been non-responsive to treatment with a prior agent, replacing aflibercept’s role in our current treatment paradigm. Early real-world data for faricimab in the TRUCKEE trial has also shown promising outcomes for visual acuity, safety, and central subfoveal thickness in both treatment naïve and previously treated patients. In this study, looking at real-world outcomes in patients treatment with faricimab, BCVA improved in patients in whom retinal fluid had persisted despite previous treatment. Although most patients have only received one dose of faricimab to date, a mean increase in BCVA of about +0.5 letters, mean decrease in the CST of about 32 microns, and mean decrease in PED height of about 14 microns was seen in the TRUCKEE trial. Most importantly, no new safety signals have been seen up until this point.

For patients requiring frequent injections, faricimab seems to fulfills an unmet need in terms of durability without compromising safety. Furthermore, the data from TRUCKEE are compelling for improved efficacy as well. We anticipate that many clinicians will find the clinical trial results compelling enough to explore using faricimab as either a first-line agent, or as a second-line agent when extended intervals for treatment are desirable, perhaps one day becoming the standard of care for nAMD.

The newest technology on the market, the Port Delivery System (Susvimo, Genentech, San Francisco, CA) (PDS), may challenge the adoption of faricimab. The PDS is a surgically implanted device filled with ranibizumab that provides long-term medication release. The device is approved for 24-week dosing of the medication and in the Phase 3 clinical trial was found to be non-inferior to monthly ranibizumab. However, the clinical trial data suggested that the device may be effective for considerably longer than 24 weeks prior to the need to be refilled. These findings may make the PDS even more attractive. However, there are challenges to the PDS system, including but not limited to conjunctival erosions, endophthalmitis, retinal detachments, and vitreous hemorrhages. Newer surgical strategies are being developed to mitigate these risks, but these complications may limit the widespread adoption of this method of delivering anti-VEGF agents. As both faricimab and PDS are currently marketed by the same company, it is still yet to be seen how the company will be promoting these competing devices. Perhaps, this newer agent that targets multiple pathways could be combined with PDS technology to increase both durability and efficiency, but this is merely speculation and there are no ongoing clinical trials looking at the PDS filled with faricimab.

In conclusion, faricimab is the newest therapeutic amongst the anti-VEGF medications. It provides the advantage of offering the addition of a novel pathway and target for nAMD and other neovascular retinal processes. However, the degree of true treatment benefit and decreased treatment burden over the existing drugs is yet to be determined. Nonetheless, the demonstrated ability to extend treatment intervals to up to 16 weeks is quite attractive, given the increasing overwhelming burden of anti-VEGF treatment for retinal disease and frequent need for patient visits. In an ever-crowded market with new therapies in the pipeline, its true place in the retina world is still to be determined; nonetheless, we anticipate it with its promising durability, efficacy, and safety results it may readily become the second-line agent of choice, if not first-line for many retina specialists.

**Abbreviations**

VEGF, vascular endothelial growth factor; AMD, age-related macular degeneration; nAMD, neovascular age related macular degeneration.

**Disclosure**

Dr Archana A Nair participated on an advisory board for Eyepoint, outside the submitted work. Dr Avni P Finn is a member of the advisory board for Genentech, Allergan, Eyepoint, and Alimera, outside the submitted work. Dr Paul Sternberg Jr reports personal fees from and a consultant for Novartis; personal fees from Outlook Therapeutics and DRCR network, outside the submitted work. The authors report no other conflicts of interest in this work.
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