The Use of Faricimab for Neovascular Age-Related Macular Degeneration and Diabetic Macular Oedema in Real Clinical Practice

Arthur Brant and Theodore Leng

Byers Eye Institute at Stanford, Stanford University School of Medicine, Palo Alto, CA, USA

DOI: https://doi.org/10.17925/USOR.2024.18.1.2

Faricimab, a recently approved bispecific antibody targeting both anti-vascular endothelial growth factor and angiopoietin-2 in neovascular age-related macular degeneration (nAMD) and diabetic macular oedema (DME), showed non-inferiority when compared with aflibercept in its phase III trials. Subsequent real-world investigations reveal that faricimab is predominantly administered in previously treated eyes, leading to sustained improvements in best-corrected visual acuity after treatment commences for DME and nAMD. Notably, a majority of patients with nAMD can extend their treatment intervals to every 4 months. In real-world practice, retina specialists have found faricimab to be an important therapeutic option due to its efficacy and convenience of extended treatment intervals.

Keywords

Aflibercept, angiopoietin-2 (Ang-2), anti-vascular endothelial growth factor (VEGF), diabetic macular oedema, faricimab, neovascular age-related macular degeneration, real-world data, real-world evidence

Disclosures: Theodore Leng has served as a consultant to Roche/Genentech. Arthur Brant has no financial or non-financial relationships or activities to declare in relation to this article.

Review process: Double-blind peer review.

Compliance with ethics: This article is an opinion piece and does not report on new clinical data, or any studies with human or animal subjects performed by any of the authors.

Data availability: Data sharing is not applicable to this article as no datasets were generated or analyzed during the writing of this article.

Authorship: Both named authors meet the criteria of the International Committee of Medical Journal Editors for authorship for this manuscript, take responsibility for the integrity of the work as a whole and have given the final approval for the version to be published.

Received: 20 September 2023

Accepted: 12 December 2023

Published online: 22 February 2024

Citation: *touchREVIEWS in Ophthalmology.* 2024;18(1):6-8

Corresponding author: Dr Theodore Leng, Byers Eye Institute at Stanford, Stanford University School of Medicine, 2452 Watson Court, Palo Alto, CA, 94028, USA. E: tedleng@stanford.edu

Support: No funding was received in the publication of this article.

Neovascular age-related macular degeneration (nAMD) and diabetic macular oedema (DME) are two leading causes of visual impairment and blindness in the USA.[1,2] Faricimab is the first bispecific antibody approved by the US Food and Drug Administration in ophthalmology and was made available to retina specialists in January 2022 for treating nAMD and DME.[3,4] The approval of faricimab gave retina specialists an additional option to treat nAMD and centre-involved DME, adding to existing treatment options such as aflibercept, off-label bevacizumab, brolucizumab and ranibizumab.

Faricimab differentiates from anti-vascular endothelial growth factor (*VEGF*) therapies by inhibiting both *VEGF-A* and angiopoietin-2 (*Ang-2*). The Ang-2 pathway is believed to affect both inflammation and vascular permeability. Inhibition of both *VEGF-A* and *Ang-2* by faricimab could potentially have a more durable and/or efficacious effect compared with inhibition of *VEGF* alone.[5] In this article, we review clinical trial evidence to date around faricimab, as well as real-world clinical experience since its commercial launch.

Review of clinical trial evidence

Neovascular age-related macular degeneration

There were two phase III clinical trials for faricimab in nAMD (A Study to Evaluate the Efficacy and Safety of Faricimab in Participants With Neovascular Age-Related Macular Degeneration [TENAYA]; ClinicalTrials.gov identifier: NCT03823287 and A Study to Evaluate the Efficacy and Safety of Faricimab in Participants With Neovascular Age-Related Macular Degeneration [LUCERNE]; ClinicalTrials.gov identifier: NCT03823300).[6–8] Patients were randomized to the faricimab 6 mg arm or the active comparator arm (aflibercept 2 mg). Faricimab was found to be non-inferior to aflibercept in its primary endpoint (mean change in best-corrected visual acuity [BCVA] from baseline) at week 48 in both the TENAYA trial (adjusted mean change 5.8 letters versus 5.1 letters) and the LUCERNE trial (6.6 letters versus 6.6 letters). Treatment with faricimab showed reductions in central subfield thickness (CST) starting at 4 weeks after the start of treatment, comparable with aflibercept every 8 weeks (Q8W), and no significant difference in CST between faricimab and aflibercept at 48 weeks in both TENAYA and LUCRNE trials. Two-year data showed that 60% of patients treated with faricimab were able to increase treatment intervals to every 4 months and received a median of 10 injections over the 2 years versus 15 injections in the aflibercept arm.[9] Overall, faricimab was well tolerated, and adverse event rates were similar between faricimab and aflibercept arms.

Diabetic macular oedema

There were two phase III trials for faricimab in DME (A Study to Evaluate the Efficacy and Safety of Faricimab (RO6867461) in Participants With Diabetic Macular Edema [YOSEMITE]; ClinicalTrials.gov identifier: NCT03622580 and A Study to Evaluate the Efficacy and Safety of Faricimab (RO6867461) in Participants With Diabetic Macular Edema [RHINE], ClinicalTrials.gov identifier: NCT03622593).[10–12] Patients were randomized to faricimab 6 mg every 8 weeks arm, faricimab 6 mg with personalized

treatment interval (PTI) arm or active comparator arm (aflibercept 2 mg). Both faricimab treatment arms showed non-inferiority compared with the aflibercept arm in the mean change in BCVA from baseline at year 1 in both trials (differences were within 1.5 letters and not statistically significant). In both dosing regimens, faricimab showed a greater reduction in CST than the aflibercept control. More patients achieved the absence of pre-defined DME (CST <325 µm) in faricimab arms (77–87% in the Q8W arm and 80–82% in the PTI arm) versus 64–71% in the aflibercept arm in the YOSEMITE trial, with similar improvements shown in the RHINE trial. Faricimab showed durable treatment effects, and more than 50% of patients reduced their treatment interval to every 16 weeks at year 1, which further increased to 60% at year 2.[13] Additionally, faricimab treatment led to a greater reduction in macular leakage area compared with aflibercept, demonstrating its efficacy in treating vascular instability.[14,15] Overall, faricimab was well tolerated, and adverse event rates were similar between faricimab and aflibercept arms.

Review of real-world evidence

As the approval of faricimab in nAMD and DME was based on the aforementioned phase III trials, multiple studies have been published to examine the efficacy and safety of faricimab in real-world practice, as well as how retina specialists have adopted the new treatment in their practices. A prospective study (TRUCKEE) of 475 eyes with nAMD by Khanani et al. showed that for both treatment-naïve patients and patients previously treated with other anti-*VEGF* agents, faricimab showed improvements in BCVA and CST and resolution of subretinal fluid in 37% of eyes and intraretinal fluid in 16% of eyes.[16] The TRUCKEE study found only one case each of intraocular inflammation and endophthalmitis, both of which were treated and resolved. A study by Maruyama-Inoue et al. compared the effect of three every four week (Q4W) intravitreal brolucizumab doses versus three Q4W intravitreal faricimab doses on eyes with treatment-naïve nAMD.[17] They found a similar response in visual acuity and CST at 4 months. However, physicians must consider adverse side effects in addition to efficacy when selecting therapeutics, and notably, 1 of the 42 eyes treated with brolucizumab developed intraocular inflammation, a previously documented adverse event.[17,18]

Several studies have investigated the efficacy of faricimab in patients who already received other therapeutics for nAMD. A retrospective study by Rush et al. found that among patients with nAMD refractory to intravitreal aflibercept (CST >300 µm), 39% of eyes that were switched from aflibercept to faricimab had a CST of less than 300 µm compared with 7% who remained on aflibercept.[19] They also noted that 39% of faricimab-treated eyes gained at least two lines of visual acuity compared with only 7% of eyes remaining on aflibercept. Another study by Szigiato et al. investigating the effect of intravitreal faricimab on nAMD refractory to intravitreal aflibercept, bevacizumab, ranibizumab or brolucizumab found a small (11.6 µm) but significant reduction in the mean CST and no significant change in visual acuity.[20] Of note, the patient population of this study had a smaller mean CST at the start of the treatment (267 µm) than that in the study by Rush et al. (393 µm).[19,20] Kishi et al. investigated patients with nAMD non-responsive or refractory to intravitreal aflibercept less than Q8W.[21] They were switched to faricimab using treat-and-extend with at least three doses. They found no significant difference in visual acuity but did notice a significant reduction in CST. In summary, these studies consistently found significant structural changes; however, only one of the three real-world studies noted a functional change.

Faricimab has also demonstrated efficacy in eyes with aflibercept-resistant DME. A study by Rush et al. found that among patients who developed aflibercept-resistant DME and switched over to faricimab, 21.6% of patients had sustained three lines of improvement or more in BCVA at 12 months and 39.2% of patients had no macular oedema when extended to at least Q8W.[22] Finally, a *post hoc* analysis of the YOSEMITE/RHINE study showed that faricimab-treated eyes had a 52% lower risk of developing an epiretinal membrane compared with those treated with aflibercept.[14]

For registry-based analyses, the largest real-world evidence study to date came from the US Intelligent Research in Sight (IRIS) registry database[23]FARETINA-AMD study demonstrated that among 15,533 eyes with nAMD treated with faricimab, 85% were previously treated with anti-*VEGF* agents and then switched to faricimab treatment.[24] Overall, 63.3% of eyes had at least one extended interval injection (greater than 6 weeks), suggesting the resolution of leakage. The FARETINA-DME study also showed that 83% of eyes receiving faricimab were previously treated and 10 letters were gained for treatment-naïve and previously treated groups.[25] Similar to FARETINA-AMD, 61% of previously treated eyes with DME underwent extended injection intervals (greater than 6 weeks). The FARWIDE-nAMD study by Patel et al., investigating practice patterns in the UK by analyzing the National Health Service Medisoft database, showed that in the first 3 months, both treatment-naïve and previously treated eyes received an average of 2.92 and 2.73 faricimab injections, respectively, but by 18 weeks, 81% of treatment-naïve eyes received injections compared with 47% of previously treated eyes.[26] After five injections, they found that previously treated eyes had no significant change in BCVA, whereas newly treated eyes showed a significant improvement in BCVA.

Finally, faricimab shows promise beyond nAMD and DME. A multicentre study in Japan among treatment-naïve patients with nAMD or polypoidal choroidal vasculopathy (PCV) found that after three Q4W treatments with intravitreal faricimab, 82% of eyes had complete resolution of intraretinal or subretinal fluid and 52% of those with PCV had complete resolution of polypoidal lesions.[27]

To date, no real-world studies have raised concerns about adverse events associated with faricimab. The adoption of faricimab among retina specialists (how many retina physicians have used faricimab, how many use faricimab as a first-line agent and how long retina specialists trial aflibercept or other agents prior to switching to faricimab) remains to be determined and may change in the next year.

Conclusions

Given the increase in options for nAMD and DME treatments, it is still an open question how faricimab will be incorporated into clinical practices. Overall, evidence from both clinical trials and real-world studies shows durable treatment effects of faricimab in both nAMD and DME.

It remains to be seen whether the loading dose regimen used in phase III nAMD and DME studies will be mirrored in clinical practice. Early evidence suggests the ability to extend treatment intervals in both DME and AMD, possibly out to Q16W. Should faricimab demonstrate the potential for more extended intervals in usage compared with alternatives, it could reduce the need for frequent appointments, benefitting both patients and healthcare providers. Faricimab has shown effectiveness in patients with DME who are resistant to aflibercept, offering a much-awaited treatment option for this group of patients who previously faced a bleak outlook. The percentage of patients initiating faricimab who were previously treated versus treatment-naïve may change, and physician practice patterns should be investigated further. Long-term clinical experience is also required to understand the durability of faricimab after

years of follow-up with long-interval dosing, including visual acuity and other outcomes. Data directly comparing faricimab with variable-dose anti-*VEGF* treatments would be needed to show superior durability and increased convenience for patients by extending treatment intervals.[28] Real-world evidence has also become an important part of clinical research, demonstrating clinical adoption post approval, monitoring adverse events not previously reported in clinical trials and examining clinical outcomes in broader patient populations not covered in clinical trials. While future real-world investigations are essential, we believe that faricimab is both a reasonable first-line therapeutic for nAMD and DME and a reasonable second-line drug for nAMD and DME refractory to alternative anti-*VEGF* agents. ❑

1. Vyawahare H, Shinde P. Age-related macular degeneration: Epidemiology, pathophysiology, diagnosis, and treatment. *Cureus*. 2022;14:e29583. DOI: 10.7759/cureus.29583.
2. Romero-Aroca P. Managing diabetic macular edema: The leading cause of diabetes blindness. *World J Diabetes*. 2011;2:98–104. DOI: 10.4239/wjd.v2.i6.98.
3. Genentech. FDA Approves Genentech's Vabysmo, the First Bispecific Antibody for the Eye, to Treat Two Leading Causes of Vision Loss. 2022. Available at: www.gene.com/media/press-releases/14943/2022-01-28/fda-approves-genentechs-vabysmo-the-firs (Date last accessed: 18 September 2023).
4. VABYSMO™ (faricimab-svoa). VABYSMO. Available at: www.vabysmo.com/ (Date last accessed: 18 September 2023).
5. Khan M, Aziz AA, Shafi NA, et al. Targeting angiopoietin in retinal vascular diseases: A literature review and summary of clinical trials involving faricimab. *Cells*. 2020;9:1869. DOI: 10.3390/cells9081869.
6. Heier JS, Khanani AM, Quezada Ruiz C, et al. Efficacy, durability, and safety of intravitreal faricimab up to every 16 weeks for neovascular age-related macular degeneration (TENAYA and LUCERNE): Two randomised, double-masked, phase 3, non-inferiority trials. *Lancet*. 2022;399:729–40. DOI: 10.1016/S0140-6736(22)00010-1.
7. ClinicalTrials.gov. A Study to Evaluate the Efficacy and Safety of Faricimab in Participants With Neovascular Age-Related Macular Degeneration (LUCERNE).ClinicalTrials.gov identifier: NCT03823300 Available at: https://clinicaltrials.gov/study/NCT03823300 (Date last accessed: 14 February 2024).
8. ClinicalTrials.gov. A Study to Evaluate the Efficacy and Safety of Faricimab in Participants With Neovascular Age-Related Macular Degeneration (TENAYA). ClinicalTrials.gov identifier: NCT03823287. Available at: https://clinicaltrials.gov/study/NCT03823287 (Date last accessed: 14 February 2024).
9. Genentech. New Two-Year Data Confirm Genentech's Vabysmo Improves Vision With Fewer Treatments for People With Wet-Age-Related Macular Degeneration. 2022. Available at: www.gene.com/media/press-releases/14960/2022-07-14/new-two-year-data-confirm-genentechs-vab (Date last accessed: 18 September 2023).
10. Eter N, Singh RP, Abreu F, et al. YOSEMITE and RHINE: Phase 3 randomized clinical trials of faricimab for diabetic macular edema: Study design and rationale. *Ophthalmol Sci*. 2022;2:100111. DOI: 10.1016/j.xops.2021.100111.
11. ClinicalTrials.gov. A Study to Evaluate the Efficacy and Safety of Faricimab (RO6867461) in Participants With Diabetic Macular Edema (YOSEMITE). ClinicalTrials.gov identifier: NCT03622580. Available at: https://clinicaltrials.gov/study/NCT03622580 (Date last accessed: 14 February 2024).
12. ClinicalTrials.gov. A Study to Evaluate the Efficacy and Safety of Faricimab (RO6867461) in Participants With Diabetic Macular Edema (RHINE). ClinicalTrials.gov identifier: NCT03622593. Available at: https://clinicaltrials.gov/study/NCT03622593 (Date last accessed: 14 February 2024).
13. Lim JI, Wells JA, Eichenbaum DA, et al. Efficacy, durability, and safety of faricimab in diabetic macular edema: 2-year results from the phase 3 YOSEMITE and RHINE trials. Invest Ophthalmol Vis Sci. 2022;63:3850.
14. Goldberg RA, Kolomeyer A, Nudleman E, et al. Faricimab reduces macular leakage vs aflibercept in patients with DME. *Invest Ophthalmol Vis Sci*. 2023;64:2816.
15. Nudleman E, Goldberg R, Csaky K. Faricimab reduces macular leakage vs aflibercept in patients with DME. Presented at: American Society of Retina Specialists Annual Meeting, Seattle, WA, USA, 18, September, 2023.
16. Khanani AM, Aziz AA, Khan H, et al. The real-world efficacy and safety of faricimab in neovascular age-related macular degeneration: The TRUCKEE study – 6 month results. *Eye (Lond)*. 2023;37:3574–81. DOI: 10.1038/s41433-023-02553-5.
17. Maruyama-Inoue M, Yanagi Y, Inoue T, Kadonosono K. Comparison of functional and morphologic changes between brolucizumab and faricimab in neovascular age-related macular degeneration. *Graefes Arch Clin Exp Ophthalmol*. 2023;26. DOI: 10.1007/s00417-023-06241-8.
18. Baumal CR, Spaide RF, Vajzovic L, et al. Retinal vasculitis and intraocular inflammation after intravitreal injection of brolucizumab. *Ophthalmology*. 2020;127:1345–59. DOI: 10.1016/j.ophtha.2020.04.017.
19. Rush RB, Rush SW. Intravitreal faricimab for aflibercept-resistant neovascular age-related macular degeneration. *Clin Ophthalmol*. 2022;16:4041–6. DOI: 10.2147/OPTH.S395279.
20. Szigiato A, Mohan N, Talcott KE, et al. Short-term outcomes of faricimab in patients with neovascular age-related macular degeneration on prior anti-VEGF therapy. *Ophthalmol Retina*. 2023;S2468-6530(23)00437-2. DOI: 10.1016/j.oret.2023.08.018.
21. Kishi M, Miki A, Kamimura A, et al. Short-term outcomes of faricimab treatment in aflibercept-refractory eyes with neovascular age-related macular degeneration. *J Clin Med*. 2023;12:15. DOI: 10.3390/jcm12155145.
22. Rush RB. One year results of faricimab for aflibercept-resistant diabetic macular edema. *Clin Ophthalmol*. 2023;17:2397–403. DOI: 10.2147/OPTH.S424314.
23. Parke Ii DW, Lum F, Rich WL. The IRIS® Registry: Purpose and perspectives. *Ophthalmologe*. 2017;114(Suppl.1):1–6. DOI: 10.1007/s00347-016-0265-1.
24. Borkar DS, Tabano D, Garmo V, et al. FARETINA-AMD – Early treatment patterns and outcomes in patients with neovascular age-related macular degeneration initiating faricimab: An IRIS Registry™ analysis. *Invest Ophthalmol Vis Sci*. 2023;64:2218.
25. Tabano D, Borkar DS, Garmo V, et al. FARETINA-DME- Early treatment patterns and outcomes in patients with diabetic macular edema treated with faricimab: An IRIS Registry™ analysis. *Invest Ophthalmol Vis Sci*. 2023;64:2699.
26. Patel PJ, Talks J, De Salvo G. Real-world use of Faricimab to treat nAMD patients in the UK. Available at: https://medically.gene.com/global/en/unrestricted/ophthalmology/ASRS-2023/asrs-2023-presentation-patel-real-world-use-of-faricima.html (Date last accessed: 18 September 2023).
27. Mukai R, Kataoka K, Tanaka K, et al. Three-month outcomes of faricimab loading therapy for wet age-related macular degeneration in Japan. *Sci Rep*. 2023;13:8747. DOI: 10.1038/s41598-023-35759-4.
28. Chia MA, Keane PA. Beyond anti-VEGF: Can faricimab reduce treatment burden for retinal disease? *Lancet*. 2022;399:697–9. DOI: 10.1016/S0140-6736(22)00105-2.