PERSPECTIVE

Faricimab to treat neovascular age-related macular degeneration: perspective

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Abstract

Neovascular age-related macular degeneration (nAMD) is a major cause of vision loss in older adults. Neovascularization is caused by angiogenic mechanisms of the angiopoietin and vascular endothelial growth factor (VEGF) pathways. Standard treatments for nAMD target the VEGF pathway, but the efficacy of single-target anti-VEGF agents is limited by angiopoietin. Some patients may respond inadequately. Faricimab is a bispecific antibody targeting VEGF-A and angiopoietin-2. Its efficacy and safety have been illustrated in the TENAYA, LUCERNE, and TRUCKEE studies. Compared with aflibercept 2 mg, faricimab 6 mg demonstrated rapid best-corrected visual acuity gains and central subfield thickness reductions. A larger proportion of patients did not develop subretinal fluid during the loading phase. Faricimab is well tolerated with a risk-benefit profile comparable to the standard anti-VEGF treatment. Guidelines from the National Institute for Health and Care Excellence and the European Society of Retina Specialists recommend early diagnostic imaging and examinations for timely treatment of nAMD. Faricimab is an efficacious, well-tolerated, and long-acting treatment option for nAMD, with the potential for long-term cost savings.

Key words: Antibodies, bispecific; Faricimab; Intravitreal injections; Visual acuity; Wet macular degeneration

Introduction

Age-related macular degeneration (AMD) is a chorio-retinal vascular disease and the main cause of vision loss in older adults.[1] Most AMD cases start as dry or atrophic AMD, with about 20% progressing to neovascular AMD (nAMD).[2] Although nAMD is less prevalent, it is associated with severe loss of central vision and accounts for nearly 70% of all vision loss in older adults.[2,3] The main cause of AMD is age-related macular damage; other risk factors include a family history of AMD and smoking.[4] In Hong Kong, approximately 500 000 people have AMD, and around 10% of them have nAMD.[5]

Pathophysiology of nAMD

The angiopoietin (Ang)/tyrosine kinase with immunoglobulin and epidermal growth factor homology domain receptor-2 (Tie-2) pathway and vascular endothelial growth factor (VEGF) play an important role in the pathogenesis of nAMD.[6] Ang-1 activates the Tie-2 receptor on the retinal vessels' endothelial cells to maintain vascular homeostasis. Ang-2 binds to Tie-2 receptors in a similar affinity as Ang-1 but induces the opposite effect: angiogenesis and inflammation.[6,7] It is important to suppress the Ang-2/Tie-2 pathway in order to stimulate the Ang-1/Tie-2 pathway for vascular homeostasis.

Macular degeneration causes the retina to produce pro-angiogenic VEGF.[2] Elevated VEGF-A levels promote vascular leakage and neovascularization. These abnormal blood vessels tend to break and form a scar on the macula, causing severe loss of central vision. Increased Ang-2 signaling sensitizes blood vessels to VEGF-A, resulting in

vascular leakage, inflammation, and vascular permeability.[8] The Ang-2 becomes pro-angiogenic with high levels of VEGF, affecting endothelial cell junction integrity, pericyte drop-off, and angiogenic sprouting.[7] Patients with nAMD had markedly higher Ang-2 levels, compared with controls (57.39±68.78 pmol/ml vs 10.46±5.90 pg/ml, p<0.001).[9] High Ang-2 levels can make blood vessels more susceptible to VEGF, thus limiting the efficacy of anti-VEGF agents.[7] Therefore, targeting Ang-2 may be useful for treating nAMD.

Treatment options for nAMD

Anti-VEGF agents are standard treatment for retinal vascular diseases including nAMD.[10] nAMD is a multifactorial disease with many risk factors and affects the choroidal vessels; neovascularization occurs under the retina and penetrates the photoreceptor layer.[11,12] Anti-VEGF monotherapies include ranibizumab (anti-VEGF-A), aflibercept (anti-VEGF-A and anti-VEGF-B), and brolucizumab (anti-VEGF-A).[6,7] Their effectiveness is limited by the role of VEGF in retinal pathogenesis, and some patients may not respond well to standard anti-VEGF agents.[8,10] Faricimab, a bispecific antibody that inhibits VEGF-A and Ang-2, is a treatment option for nAMD.[6,11] We discuss the mechanism of action, clinical evidence, and treatment recommendations of faricimab for nAMD.

Mechanism of action of faricimab

Faricimab is a first-in-class bispecific antibody targeting both VEGF-A and Ang-2 with long-acting effect.[13,14] Because it targets both VEGF-A and Ang-2, faricimab has long-acting efficacy when treating retinal diseases; additionally, it promotes vascular stability and reduces neovascularization, hyperpermeability, and inflammation, with reduced angiogenesis and less extravasation.[14]

Based on results from the phase III TENAYA and LUCERNE studies, the United States Food and Drug Administration and European Medicines Agency approved faricimab for the treatment of nAMD, with a recommended initial dose of 6 mg by intravitreal injection every 4 weeks for the first four doses, followed by the same 6 mg intravitreal dose every 8 to 16 weeks, depending on disease activity.[15-17]

Clinical data for faricimab

Table 1 shows clinical studies of faricimab. Faricimab (RG7716) is well tolerated with an overall favorable

Table 1. Clinical studies of faricimab for neovascular age-related macular degeneration

Study	Study design	Efficacy	Safety
Chakravarthy et al,[18] 2017	Phase I, open-label, ascending dose study of intravitreal faricimab	Improvement in best-corrected visual acuity: 7 (0-18) letters for single dose and 7.5 (3-18) letters for multidose; reduction in central subfield thickness: 42 (-101 to 10) μm for single dose: and -117 (-252 to -7) μm for multidose	Well tolerated, with an overall favorable safety profile; mild ocular adverse events
Sahni et al,[19] 2020 (AVENUE)	Phase II, randomized, 36-week, multiple-dose regimen (faricimab vs ranibizumab)	Adjusted mean difference (80% confidence interval) in best-corrected visual acuity was 1.6 (-1.6 to 4.7) letters for faricimab 1.5 mg every 4 weeks (p=0.52), -1.6 (-4.9 to 1.7) letters for faricimab 6.0 mg every 8 weeks (p=0.53), and -1.5 (-4.6 to 1.6) letters for faricimab 6.0 mg every 8 weeks (p=0.53), compared with ranibizumab 0.5 mg every 4 weeks.	No new or unexpected safety events
Cheung et al,[20] 2022; Lai et al,[21] 2022; Khanani et al,[22] 2022; Heier et al,[23] 2022 (TENAYA and LUCERNE)	Phase III, randomized, double-blinded, active comparator–controlled, 112-week studies (faricimab vs aflibercept) in treatment-naïve patients	Adjusted mean change (95% confidence interval) in vision gain in year 1 was 5.8 (4.6-7.1) letters for faricimab and 5.1 (3.9-6.4) letters for aflibercept (in TENAYA) and 6.6 (5.3-7.8) letter for faricimab and 6.6 (5.3-7.8) letters for aflibercept (in LUCERNE). >50% of patients were maintained on faricimab every 16 weeks after the loading phase throughout the year. More faricimab-treated patients had no subretinal and/or retinal fluid than aflibercept-treated patients.	Rate of ocular adverse events in year 1 was 36.3% for faricimab and 38.1% for aflibercept (in TENAYA) and 40.2% for faricimab and 36.2% for aflibercept (in LUCERNE). Faricimab had lower rates of intraocular inflammation; no cases of retinal vasculitis or occlusive retinal vasculitis were reported.
		Mean vision gains in year 2 was 3.7 letters for faricimab and 3.3 letters for aflibercept (in TENAYA) and 5.0 letters for faricimab and 5.2 letters for aflibercept (in LUCERNE). Reductions in central subfield thickness in year 2 was -146.5μm for faricimab and -146.2 μm for aflibercept (in TENAYA) and -150.3 μm for faricimab and -141.6 μm for aflibercept (in LUCERNE). Median number of injections was 10 for faricimab every 16 weeks and 15 for aflibercept every 8 weeks.	In year 2, faricimab was well tolerated and had a favorable risk-benefit profile; there were no reported cases of retinal vasculitis or intraocular inflammation associated with retinal occlusion
Sheth et al,[25] 2022 (TRUCKEE)	Real-world efficacy and safety	In 174 patients who switched from aflibercept to faricimab after 44.8 days, there were improvements in Early Treatment Diabetic Retinopathy Study letters of +1.1 letters, reduction in central subfield thickness of -25.7 μm, and reduction in pigment epithelial detachment height of -27.1 μm	Endophthalmitis (n=1), intraocular inflammation (n=0), retinal vasculitis (n=0), retinal artery occlusions (n=0)

safety profile, while improving best-corrected visual acuity (BCVA) and anatomic parameters.[18,19] The phase II AVENUE study confirmed faricimab's safety profile and efficacy to be comparable to monthly ranibizumab intravitreal injections.[19]

In phase III, randomized, double-blinded, aflibercept-controlled, 112-week studies (TENAYA and LUCERNE) [**Figure**],[20-23] patients in the aflibercept (control) group received 3-monthly loading doses before being assigned to an 8-weekly dosing interval, whereas patients in the faricimab (experimental) group received 4-monthly loading doses (at weeks 0, 4, 8, and 12), followed by sham procedures at weeks 16 and 20. Patients were subsequently assigned to 16-weekly, 12-weekly, or 8-weekly dosing intervals based on disease activity at weeks 20 and 24. Faricimab-treated patients without active disease (based on optical coherence tomography (OCT), visual acuity, and clinical examination) at weeks 20 and 24 could immediately extend from 4-weekly to 16-weekly dosing. In the second year of treatment, faricimab was dosed according to a personalized treatment interval, which can be maintained, extended to up to 16-weekly dosing, or reduced to 8-weekly dosing, depending on criteria for central subfield thickness (CST), BCVA, or macular hemorrhage. If any of these criteria is met, the treatment interval is reduced by 4 weeks, and if at least two of these criteria are met, the treatment interval is reduced by 8 weeks.

During the loading phase (first 12 weeks), more faricimab-treated patients experienced no subretinal fluid and/or intraretinal fluid than aflibercept-treated patients (77% vs 67%, $p<0.05$).[20] First-year data from both TENAYA and LUCERNE studies showed that faricimab-treated patients were non-inferior to aflibercept-treated patients in terms of BCVA change from baseline.[20] In the TENAYA trial,

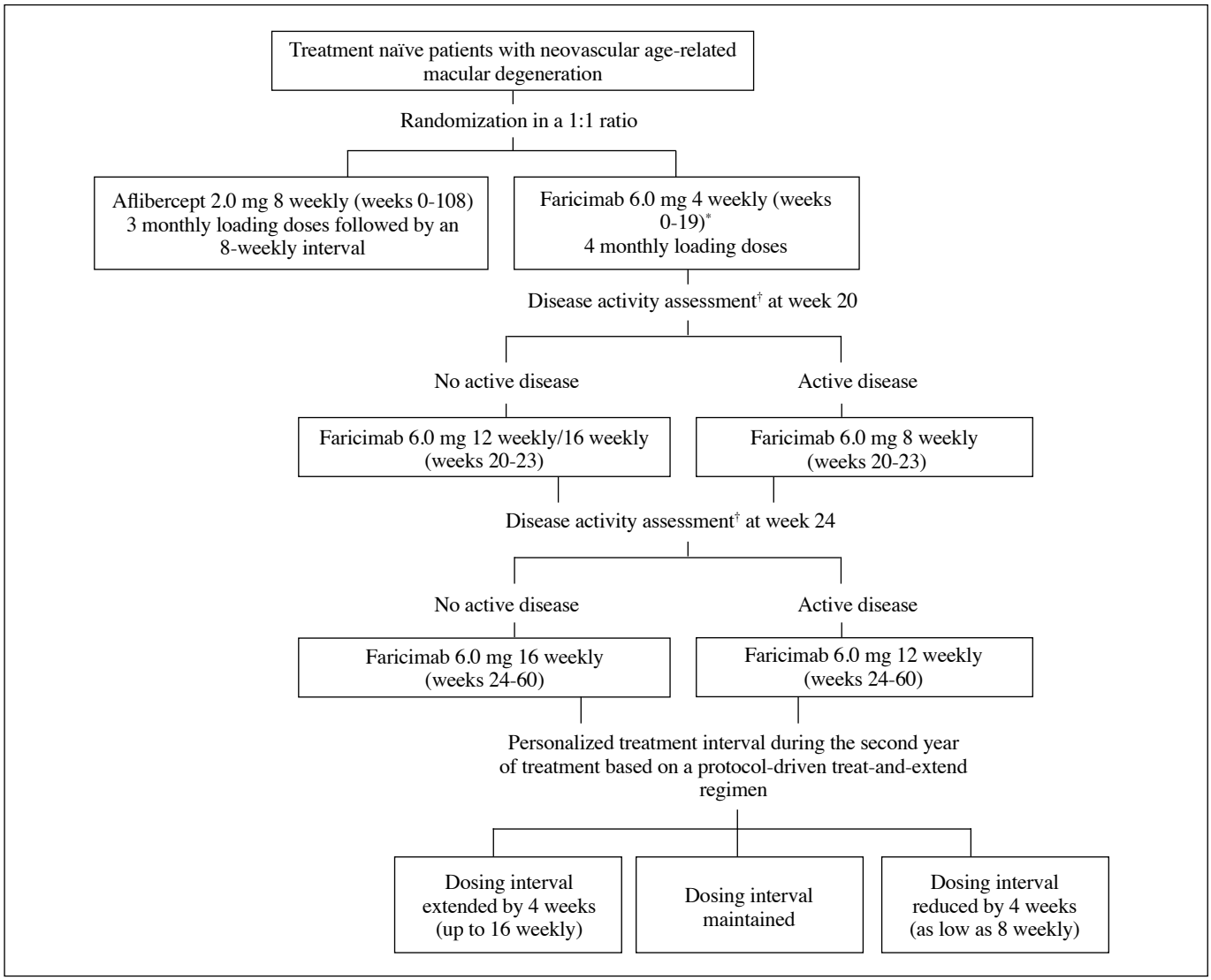

Figure. Study design for the TENAYA and LUCERNE studies[20-22]

* *The four monthly doses were administered at weeks 0, 4, 8, and 12. At weeks 16 and 20, a sham procedure was administered*

† *Best-corrected visual acuity loss ≥5 letters (vs mean) or ≥10 letters (vs highest recorded); or central subfield thickness increase ≥50 μm (vs mean) or ≥75 μm (vs highest recorded); or presence of new macular hemorrhage.*

the adjusted mean change was 5.8 letters (95% confidence interval [CI]=4.6-7.1) for faricimab and 5.1 letters (95% CI=3.9-6.4) for aflibercept.[22] In the LUCERNE trial, the adjusted mean change was 6.6 letters for both faricimab (95% CI=5.3-7.8) and aflibercept (95% CI=5.3-7.8).[23] The second-year data showed that faricimab up to 16-weekly dosing (3 injections) was comparable to aflibercept 8-weekly dosing (6 injections) in terms of vision improvements.[22] In the TENAYA study, the mean vision gain from baseline was +3.7 eye chart letters for faricimab and +3.3 letters for aflibercept.[22] In the LUCERNE trial, the mean vision gain from baseline was +5.0 letters for faricimab and +5.2 letters for aflibercept.[22] By week 108, patients on faricimab up to 16-weekly dosing had a lower median number of injections than patients on aflibercept 8-weekly dosing (10 vs 15).[22]

Patients on faricimab (up to 16-weekly dosing) had rapid meaningful CST reductions in the initial dosing phase, and these were sustained throughout the maintenance phase.[22] Similarly, approximately 45% of patients treated with faricimab 16-weekly dosing exhibited an early reduction in CST that was stable throughout the maintenance phase, albeit with fewer injections.[22] Both the TENAYA and LUCERNE studies showed reduction in CST: -146.5 µm with faricimab up to 16-weekly dosing versus -146.2 µm with aflibercept 8-weekly dosing, and -150.3 µm with faricimab up to 16-weekly dosing versus -141.6 µm with aflibercept 8-weekly dosing, respectively.[22]

At week 112, faricimab showed long-acting disease control: maintenance of vision gain, CST reduction, and BCVA improvement.[22] In the TENAYA study, the proportion of patients on faricimab 16-weekly dosing increased from 45.7% at week 48 to 59.0% at week 112.[22] In the LUCERNE study, the proportion of patients on faricimab 16-weekly dosing increased from 44.9% at week 48 to 66.9% at week 112. The proportion of patients on extended dosing intervals (12-weekly and 16-weekly) remained similar over years 1 and 2 in both trials.[22] Maintenance of vision gain can be attributed to the vascular stability achieved by targeting both the VEGF-A and Ang-2 pathways.[7] The TENAYA and LUCERNE studies found promising results for longer intervals between dosing, highlighting the potential for individualized treatment regimens and reduced treatment burden.[21] By week 108, the median number of injections was 10 for faricimab and 15 for aflibercept. In personalized treatment interval by week 60, the median number of injections was 3 for faricimab up to 16-weekly dosing and 6 for aflibercept 8-weekly dosing.[22]

Faricimab is well tolerated with a favorable risk-benefit profile. The TENAYA and LUCERNE trials showed that faricimab and aflibercept had acceptable and comparable safety profiles during the first and second years of treatment.[21,22] The rates of intraocular inflammation were low, and no cases of retinal vasculitis or occlusive retinal vasculitis were reported.[21,22] The Hong Kong Retina Expert Panel provides recommendations for treat-and-extend regimen for managing nAMD.[24]

Real-world data for faricimab

The TRUCKEE study investigated the outcome of intravitreal faricimab in treatment-naïve patients and patients with persistent disease activity.[25] Patients who switched from aflibercept to faricimab were followed up after a mean of 44.8 days; all had better visual acuity, reduction in CST, and pigment epithelial detachments. There were no cases of intraocular inflammation, retinal vasculitis, or retinal artery occlusions after the use of faricimab.

Using faricimab to treat nAMD in clinical practice

Assessment and diagnosis

Early diagnosis and timely treatment of nAMD are crucial to prevent vision deterioration.[26] Diagnosis may be delayed because of lack of symptoms and unawareness of visual changes.[26] nAMD should be suspected in patients with distorted or reduced vision, particularly when there are other related risk factors.[4,27] Various guidelines recommend that older patients aged ≥50 years with visual problems should undergo eye investigations such as the Amsler grid and visual acuity tests.[4,26,28,29] Although both tests are readily accessible, operators should be aware that sensitivity can vary for the Amsler grid and is not specified for visual acuity tests.[30] OCT or fundus fluorescein angiography should be considered.[1,4] OCT can detect intra- and sub-retinal fluid and is supplementary to fundus fluorescein angiography,[30] which should be performed if OCT does not indicate any abnormalities but visual acuity is reduced.[4]

Treatment and monitoring

Intravitreal injection of faricimab 6 mg every 4 weeks for four doses should be used to treat nAMD. Treatment response and disease status should be assessed using OCT and visual acuity tests.[16] Subsequent doses of faricimab can be given at longer intervals of every 8 to 16 weeks.[15] Patients without active disease by weeks 20 and 24 can immediately switch from 4-weekly to 16-weekly dosing.[20,21]

Both the National Institute for Health and Care Excellence and the Australian Pharmaceutical Benefits Advisory Committee recommend faricimab for nAMD.[11,31] Faricimab is registered for use in Hong Kong.[32] Faricimab should be administered if the patient has a BCVA between 6/12 and 6/96, no permanent structural damage to the central fovea, a lesion with the greatest linear dimension of ≤12-disc areas, and signs of recent disease progression.[11] Faricimab has

Table 2. Annual dosage of faricimab and aflibercept for neovascular age-related macular degeneration[22]

Anti-vascular endothelial growth factor agents	Median No. of injections throughout the 2 years	Median No. of injections in the second year of treatment
Faricimab 6 mg	10	3
Aflibercept 2 mg	15	6

comparable efficacy and safety to aflibercept.[31] Faricimab 6 mg and aflibercept 2 mg are equally cost-effective for the treatment of nAMD.[31] Cost-effectiveness may vary according to the study setting and/or design. The TENAYA and LUCERNE studies demonstrated that treatment with faricimab necessitated a lower median number of injections in the first year than treatment with aflibercept (**Table 2**).[22] More than 78% of patients receiving faricimab could be dosed once every 12 weeks or at longer intervals.[25]

Conclusions

The VEGF and Ang-2 pathways play an important role in the pathogenesis of nAMD. Faricimab is a novel bispecific antibody that inhibits both the VEGF and Ang-2 pathways. Clinical and real-world data suggest that faricimab treats nAMD as effectively as aflibercept with a similar safety profile but requires fewer injections. Therefore, faricimab offers potential long-term cost savings by reducing the number of medical visits and hence treatment burden.

Contributors

The author designed the study, acquired the data, analyzed the data, drafted the manuscript, and critically revised the manuscript for important intellectual content. The author had full access to the data, contributed to the study, approved the final version for publication, and takes responsibility for its accuracy and integrity.

Conflicts of interest

Roche paid AKHK honorarium as the chairman of the College of Ophthalmologists of Hong Kong Annual General Meeting in 2022 and an advisor at the Hong Kong DME advisory board meeting.

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Data availability

All data generated or analyzed during the present study are available from the corresponding author on reasonable request.

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