Beyond anti-VEGF: can faricimab reduce treatment burden for retinal disease?

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Conflict of Interest Statement

MC reports no relevant disclosures. PAK has acted as a consultant for DeepMind in automated analysis of retinal imaging with deep learning, for Roche in personalised health care, for Novartis in personalised health care, for Apellis in automated analysis of geographic atrophy, and for BitFount in privacy protecting machine learning. He is an equity owner in Big Picture Medical, an Australian small and medium-sized enterprise focused on telemedicine. Big Picture Medical are not involved in any pharmaceutical or products relevant to the topic of this Comment. He has received speaker fees from Heidelberg Engineering, Topcon, Allergan, and Bayer.

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The introduction of anti-vascular endothelial growth factor (VEGF) medications has had a revolutionary impact on the practice of ophthalmology. For many patients with blinding eye conditions like neovascular ("wet") age-related macular degeneration (nAMD) and diabetic macular edema (DME), intravitreal anti-VEGF agents provided the first hope for meaningful visual recovery.[1,2]

Despite their impact, anti-VEGF medications are not without significant drawbacks. For nAMD, patients often require 50 or more injections, sometimes for 10+ years or the remainder of their lives.[3] For DME, patients typically require 12-15 injections in the first three years, at which time loss to follow-up is close to one-third.[4] Treatment burden is thought to be a key reason why the benefits of anti-VEGF in clinical trials have never fully translated to clinical practice.[2] Given the ageing population and growing obesity epidemic, both nAMD and DME are projected to increase significantly in the future.[5,6] A key question for researchers has therefore evolved – how can we improve the durability of drug therapy?

One promising avenue is the potential for new drug targets to produce a more sustained effect. On this background, two reports in *The Lancet* investigate the treatment of nAMD[7] and DME[8] with faricimab, a novel dual-ligand inhibitor. In addition to binding VEGF-A, faricimab targets angiopoietin-2, a ligand operating distinct from the VEGF pathway that regulates vascular destabilisation and inflammation.[7] These multi-centre, randomised, double-masked, non-inferiority trials, compare the safety and efficacy of faricimab with aflibercept, an existing anti-VEGF drug that is widely used.[9]

Heier and colleagues[7] report week 48 results of the identical TENAYA/LUCERNE trials for nAMD. In total, 1,329 nAMD patients (60% female, 87% white) were randomised to: (1) faricimab at an interval between 8-16 weeks, or (2) aflibercept 8-weekly (in both cases preceded by 4-weekly loading doses). The trials met their primary endpoints of non-inferior

best-corrected visual acuity (BCVA) gains (TENAYA: +5·8 [4·6–7·1], +5.1 [3·9–6·4], LUCERNE: +6·6 [5.3–7.8], 6·6 [5.3–7.8] letters [95% confidence interval (CI)] for (1) and (2) respectively). The faricimab arm achieved dosing intervals of ≥12 weeks and 16 weeks in ~80% and ~45% of patients respectively. Anatomic outcomes defined by optical coherence tomography (OCT) and adverse events were comparable between groups.

Similarly, Wykoff and colleagues[8] present one-year results of the identical YOSEMITE/RHINE trials for DME. In total, 1,891 DME patients (40% female. 79% white) were randomised to: (1) faricimab 8-weekly, (2) faricimab at a treat-and-extend interval of 4–16 weeks, or (3) aflibercept 8-weekly (in all cases preceded by 4-weekly loading doses). Both faricimab arms met the primary endpoint of non-inferior BCVA gains (YOSEMITE: +10·7 [9·4–12·0], +11.6 [10·3–12·9], +10·9 [9·6–12·2]; RHINE: +11·8 [10·6–13·0], +10·8 [9·6–11·9], +10·3 [9·1–11·4] letters [97.52%CI] for (1), (2), and (3) respectively). The faricimab treat-and-extend arm achieved dosing intervals of ≥12 weeks and 16 weeks in ~70% and ~50% of patients respectively. Authors report improved OCT-defined anatomic outcomes for faricimab over aflibercept, however there was a degree of subjectivity in the authors' interpretations. It was unclear whether the decision to average central subfield thickness across three visits was pre-specified, and the remaining anatomic outcomes did not have a pre-specified time point. Of four reported anatomic outcomes, only one outcome in one trial (YOSEMITE) showed significant differences favouring faricimab at week 52. Of note, serious ocular adverse events were higher in faricimab arms compared to aflibercept (YOSEMITE:1·9%, 2·9% vs 0·6%; RHINE: 2·8%, 3·1% vs 1·9%), although total adverse events were comparable.

What do these results mean for patients and their treating teams? As with most promising new therapies, a cautiously optimistic approach seems prudent. The key findings showed enhanced durability of faricimab beyond previous anti-VEGF trials, with non-inferior BCVA gains compared with a widely used anti-VEGF. Both papers share numerous strengths, most

notably a rigorous randomised study design with sham injections, blinding of outcome assessors, and similar baseline characteristics. An important limitation was a high rate of major protocol deviations for all trials of 39–47%, in part driven by the coronavirus pandemic. In this regard, authors commendably performed several sensitivity analyses to consolidate primary findings. Other limitations include the absence of a comprehensive published protocol and the industry-funded nature of the trials.

Further research is necessary to build confidence in the safety and efficacy of faricimab. The need for caution is exemplified by the emergence of safety concerns[10] following the publication of phase 3 trials for brolucizumab, another anti-VEGF that has been studied for enhanced durability.[11] Two-year results of the ongoing TENAYA/LUCERNE and YOSEMITE/RHINE trials will provide longer-term safety and durability data, whilst exploring the potential for improved functional and anatomic outcomes. Importantly, it has not been established whether faricimab would show improved durability in a direct comparison with variably-dosed aflibercept. Although pivotal aflibercept trials utilised a fixed-dose regimen,[12] most retinal specialists favour a variable-dose method,[9] suggesting that trials reflecting the real-world use of aflibercept are needed. Despite many unanswered questions, these trials present a promising step forward for the millions of patients reliant on vision-preserving anti-VEGF medications.

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