Brolucizumab and faricimab as new treatment options for diabetic macular edema: perspective

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Abstract

Diabetic macular edema (DME) is the leading cause of blindness in the working populations, with patients requiring 10.7 intravitreal injections of anti-vascular endothelial growth factor (VEGF) agents per year. The high rate of non-compliance of anti-VEGF injection in patients with DME and the unmet need in current regimen may result in suboptimal visual outcome. Brolucizumab, an antibody fragment anti-VEGF-A agent, has been approved to treat neovascular age-related macular degeneration, as illustrated in the HAWK and HARRIER trials. Similarly, the KESTREL and KITE DME trials have shown that brolucizumab 6 mg achieves greater improvement in best-corrected visual acuity and greater reduction in central subfield thickness at week 52, compared with aflibercept 2 mg. Fewer patients with brolucizumab have intraretinal and subretinal fluid. Careful monitoring, prompt diagnosis, and timely intervention enable early management of adverse effects including intraocular inflammation and retinal artery occlusion. Moreover, in the BOULEVARD trial, patients with DME on faricimab 1.5 and 6.0 mg have demonstrated greater gain in Early Treatment Diabetic Retinopathy Study letters and greater reduction in central subfield thickness, compared with patients on ranibizumab 0.3 mg. The YOSEMITE and RHINE trials have demonstrated greater improvement in best-corrected visual acuity and two-step Diabetic Retinopathy Severity Scale at week 52 after faricimab 6 mg than after aflibercept 2 mg. Thus, brolucizumab and faricimab are efficacious, durable, and well tolerated, with improved treatment outcome and patient compliance.

Key words: Brolucizumab; Diabetic retinopathy; Faricimab; Macular edema

Introduction

Diabetic macular edema (DME) is the leading cause of blindness in the working populations in developed countries, affecting 12% of people with type 1 diabetes and 28% of people with type 2 diabetes.[1] In 2020, the worldwide prevalence of DME was estimated to be 20 million, which is expected to rise to 30 million by 2045. This imposes an immense burden to the healthcare system.[2]

Current treatment options for DME include primary glycemic control, laser photocoagulation, intravitreal injections of anti-vascular endothelial growth factors (VEGFs), anti-VEGF biosimilars, or corticosteroids, and pars plana vitrectomy. Novel therapies involving cytokine inhibitors, adhesion molecular inhibitors, and Kallikrein-Kinin systemic inhibitors are increasingly popular.[3] The

development of anti-VEGFs revolutionized the medical management of DME. Intravitreal injection of anti-VEGF has a favorable benefit-risk ratio and is more effective than laser photocoagulation on visual improvement and optimization.[4]

Nonetheless, the non-compliance rate of anti-VEGF treatment in patients with DME is high.[5] The most common barrier to follow-up adherence is the long waiting time in clinics, followed by the presence of other medical conditions. Patients with DME typically need to attend 34 medical appointments per year on average.[6] In a survey of European retina specialists in 2014 to 2015, patients with DME had 7.3-fold (95% confidence interval [CI]=6.3-8.6; p<0.0001) increased odds of no showing in appointments than patients with neovascular age-related macular degeneration (nAMD).[5] Missed appointment for anti-VEGF treatment is associated with decreased visual acuity and thus affects both functional and clinical outcomes.[7,8]

Anti-VEGF agents are typically administered every 1 to 3 months. Even with the treat-and-extend regimen, patients still need to receive 10.7 injections per year.[9] There is an unmet need under the current management protocol. According to a survey by the American Society of Retina Specialists in 2017, retinal specialists prefer treatments that require fewer injections and have longer duration of action for patients with DME.[10] Yet, visual outcome positively correlates with the frequency of anti-VEGF treatment; more injections result in better visual acuity.[11] To prevent undertreatment and suboptimal visual outcomes, a new treatment option for DME is needed to lessen the healthcare burden.

In patients with diabetes, hyperglycemia damages small blood vessels in the eye and promotes the release of VEGF. VEGF-A increases neoangiogenic events and vascular permeability.[12] The angiopoietin (Ang) tyrosine kinase endothelial receptor (Tie) pathway plays a role in vascular homeostasis and modulates vascular permeability, inflammation, and angiogenesis.[13] Ang-1 binds to Tie-2, which blocks vascular leakage and proinflammatory cascade in the endothelial cells. However, Ang-2 is an antagonist that destabilizes the vessels and renders them more vulnerable to VEGF. Fluid accumulation disrupts the architecture of the neurosensory unit and leads to retina dysfunction.[14] Both intraretinal fluid and subretinal fluid are associated with DME activity, with intraretinal fluid being more prevalent owing to the disruption of the inner blood-retinal barrier.[15] Over 25% of patients with untreated DME lose ≥2 lines of visual acuity within 2 year, and thus early treatment is important.[16,17] However, up to 40% of patients with anti-VEGF treatment have persistent intraretinal and subretinal fluid accumulation after 3 years.[18] A more effective treatment to dry the macula is needed.

Brolucizumab

Brolucizumab is a humanized, single-chain antibody fragment, anti-VEGF-A agent, with a molecular mass of ~26 kDa.[19] It is approved by the United States Food and Drug Administration for treatment of nAMD and DME. In the HAWK and HARRIER phase-3 clinical trials, patients treated for nAMD demonstrated improved best-corrected visual acuity at week 48 (+6.6 letters and +7.6 letters, respectively, both p<0.001).[20] Reduction in central subfield thickness at week 48 was greater after brolucizumab treatment than aflibercept treatment (-172.8 vs -143.7 μm and -193.8 vs -143.9 μm, respectively, both p<0.001), with anatomical outcome favoring brolucizumab.[20] Each 6 mg of brolucizumab results in a 10-fold higher molar dose than aflibercept in the same volume; brolucizumab has more durable efficacy and necessitates less frequent dosing.[19,21] Brolucizumab binds with high affinity to all VEGF-A isoforms and demonstrates similar potency and affinity as aflibercept does.[22,23] Preclinical studies suggest that the small molecular size of brolucizumab facilitates better retina penetration relative to larger VEGF inhibitors.[23,24] Given its longer dosing interval, better tissue penetration, and high binding affinity to VEGF, brolucizumab may help resolve the unmet needs for DME treatment.

In the KESTREL and KITE phase-3 studies that enrolled 926 patients with DME in 36 countries, brolucizumab 6 mg given at 6-week intervals was compared with aflibercept 2 mg given at the standard 4-week intervals during the loading phase.[25,26] Following the loading phase, >50% of patients with brolucizumab (55.1% in KESTREL and 50.3% in KITE) remained on a 3-month interval through year 1 as determined by disease activity assessment, whereas all patients with aflibercept were switch to a 2-month interval.[25] In patients who did not show disease activity after three loading doses of brolucizumab, the likelihood of staying on the 3-month dosing interval through year 1 was 87.6% (95% CI=78.8-93.0) in the KESTREL study and 95.1% (95% CI=87.4-98.1) in the KITE study.[25] Brolucizumab was non-inferior to aflibercept in terms of best-corrected visual acuity at week 52, with >50% of patients maintaining a 3-month dosing interval.[25] In the KITE study, reduction in central subfield thickness was greater with brolucizumab than aflibercept (-187.1 vs -157.7 μm, p=0.001). In the KESTREL and KITE studies, higher proportion of eyes with brolucizumab achieved central subfield thickness of <280 μm at week 52 (Δ13.4% [95% CI=4.9%-23.7%] and Δ16.3% [95% CI=5.7%-25.9%], respectively), and lower proportion of eyes with brolucizumab had intraretinal/subretinal fluid residue at week 52 (Δ-13.2% [95% CI= -23.2% to -3.8%] and Δ-18.4% [95% CI= -28.5% to -8.3%], respectively).[25]

Brolucizumab is well-tolerated. In the KESTREL study, the rates of intraocular inflammation (IOI) were 4.7% (n=9), 3.7% (n=7), and 0.5% (n=1) in patients with brolucizumab 3 mg, brolucizumab 6 mg, and aflibercept 2 mg, respectively. In the KITE study, the rate of IOI was similar in patients with brolucizumab 6 mg and aflibercept 2 mg (1.7% [n=3] vs 1.7% [n=3]), and the rate of IOI and retinal vasculitis was similar to that in the HAWK study and lower than

that in the HARRIER study.[26] The difference is likely due to a longer dosing interval of 6 weeks in the loading phase in the KITE study and differences in disease entity and study design. Most cases of IOI and retinal vasculitis resolved with or without treatment. Nonetheless, the United States Food and Drug Administration reports that there are 4% chance of IOI (anterior uveitis, intermediate uveitis, posterior uveitis, and retinal vasculitis) and 1% chance of retinal artery occlusion.[27] IOI most commonly occurs at 30 days after intravitreal brolucizumab injection, with affected eyes showing segmental sheathing, vascular nonperfusion, cotton wool spots, and sclerotic vessels.[28] At 25 days after brolucizumab injection, adverse effects such as decreased visual acuity, floaters, eye pain, and eye redness may occur.[29]

In management of nAMD, injection of three doses of brolucizumab at 4-week intervals is recommended.[30] Patients should be followed up at 8 weeks after the third dose (week 16) to assess the drug effect and any adverse outcomes. Subsequent follow-up should be extended to 12 weeks if the disease is stable with no intraretinal/subretinal fluid accumulated. However, treatment should maintain at an 8-week interval if the disease is active with intraretinal/subretinal fluid accumulated. Patient-centered dialogue, patient information booklet, and procedure-specific consent form should be provided to patients. Patients should understand risk factors of IOI including old age, female, history of diabetes, neutralizing antibodies, and prior IOI.[31] Regular monitoring by self and doctors is vital for early detection of IOI. Patients with symptoms of floaters and ocular discomfort for >2 days ought to be evaluated for IOI.[32] Ophthalmological examination should be performed at baseline, 3 months after the loading phase, and 6 or 9 months. Examination should include beam slit lamp assessment of the anterior chamber, dilated fundoscopy assessment of the anterior and posterior vitreous, central and peripheral retina, and pars plana, color fundus photography, and optical coherence tomography. Topical corticosteroid drops should be used for anterior uveitis, whereas systemic corticosteroids should be used for intermediate uveitis, posterior uveitis, and retinal vasculitis.[32] Careful monitoring, prompt diagnosis, and timely intervention are the key of managing adverse effects of brolucizumab.[33]

Faricimab

Faricimab is a 150 kDa-size, bispecific antibody for treatment of DME, nAMD, and retinal vein occlusion.[13] It acts by binding to both VEGF-A and Ang-2 to block vascular leakage and pathological growth of abnormal vessels. In the BOULEVARD phase-2 trial, 229 patients with DME were randomly assigned to receive intravitreal injection of faricimab or ranibizumab.[34] Patients with faricimab 6 mg and 1.5 mg had a mean improvement in visual acuity of 13.9 (80% CI=12.2-15.6) and 11.7 (80% CI=10.1-13.3) letters of ETDRS (Early Treatment Diabetic Retinopathy Study) after 24 weeks, respectively, whereas 72.1% (80% CI=62.9%-79.8%) and 60.6% (80% CI=51.6%-68.9%) of patients had improvement of ≥10 ETDRS letters, respectively. Reduction in central subfield thickness was -225.8 (80% CI= -242.5 to -209.1) μm and -217.1 (80% CI= -233.0 to -201.2) μm, respectively. In addition, 38.6% and 27.7% of patients had more than two-step improvement in Diabetic Retinopathy Severity Scale, respectively. Compared with faricimab 6 mg, ranibizumab 0.3 mg only achieved a mean improvement in visual acuity of 10.3 ETDRS letters, with a mean difference of 3.6 (80% CI=1.5-5.6, p=0.03), and the mean difference in reduction in central subfield thickness was -21.1 (80% CI= -38.7 to -3.5) μm.

In the YOSEMITE and RHINE phase-3 trials, 1891 patients with DME were randomly assigned to receive faricimab 6 mg every 8 weeks (n=315 and n=317, respectively), faricimab 6 mg at a personalized treatment interval (n=313 and n=319, respectively), or aflibercept 2 mg every 8 weeks (n=312 and n=315, respectively).[35] In the YOSEMITE study, the mean best-corrected visual acuity improvement was 10.7 and 11.6 ETDRS letters in the two faricimab groups, respectively. In the RHINE study, the mean best-corrected visual acuity improvement was 11.8 and 10.8 ETDRS letters in the two faricimab groups, respectively, compared with 10.3 ETDRS letters in the aflibercept group. In the YOSEMITE and RHINE studies, >70% of the patients in the two faricimab groups received injection every 12 weeks or longer during year 1, and 68% and 64% of patients in the respective studies showed no significant interval reduction during year 1. In the YOSEMITE study, the adjusted mean reduction in central subfield thickness was -206.6 (95% CI= -214.7 to -198.4) μm and -196.5 (95% CI= -204.7 to -188.4) μm in the two faricimab groups, respectively. In the RHINE study, the reduction in central subfield thickness was -195.8 (95% CI= -204.1 to -187.5) μm and -187.6 (95% CI= -195.8 to -179.5) μm in the two faricimab groups, respectively. In the YOSEMITE study, 46.0% (95% CI=38.8%-53.1%) and 42.5% (95% CI=35.5%-49.5%) of patients in the two faricimab groups achieved more than two-step improvement in Diabetic Retinopathy Severity Scale at week 52. In the RHINE study, the proportions of patients were 44.2% (95% CI=37.1%-51.4%) and 43.7% (95% CI=36.8%-50.7%), respectively. In the YOSEMITE and RHINE studies, 2% and 1% patients with faricimab had IOI, respectively, and two patients in each study had endophthalmitis, but no patient had retinal vasculitis (unlike cases that result from brolucizumab treatment). Overall, faricimab is well tolerated with a good safety profile.

Conclusion

Brolucizumab 6 mg and faricimab 6 mg are viable treatment options for DME; they are efficacious, durable, and well tolerated, with improved treatment outcome and patient compliance and hence decreased healthcare burden.

Contributors

All authors designed the study, acquired the data, analyzed

the data, drafted the manuscript, and critically revised the manuscript for important intellectual content. All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

All authors have disclosed no conflicts of interest.

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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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