CLINICAL TRIALS TARGETING RVO

New therapeutics under investigation are showing promise for the treatment of retinal vein occlusion.

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Retinal vein occlusion (RVO) is a common cause of vision loss worldwide. Its complications, including macular edema, retinal neovascularization, and ischemia, cause anatomic and functional compromise of the retina (Figure). While ischemia and outer retinal damage is difficult to reverse, edema and neovascularization respond remarkably well to current anti-VEGF treatments. However, the treatment burden can be high, and some may experience an incomplete response. Novel agents that are under investigation aim to further improve efficacy and durability to minimize treatment burden while maximizing visual outcomes. In this article, we provide an update on ongoing and recent phase 3 studies.

SEEKING A NEW INDICATION

Faricimab (Vabysmo, Genentech/Roche) is an antibody designed to target both VEGF and angiopoietin-2 (Ang-2), while sparing angiopoietin-1 (Ang-1).[1] Ang-2 is upregulated in disease states and competitively inhibits Ang-1, which results in pericyte death and sensitization to VEGF.[1] Two phase 3 clinical trials are evaluating faricimab for the treatment of macular edema secondary to central RVO (CRVO) or hemiretinal vein occlusion (COMINO) and branch RVO (BRVO; BALATON).[2,3] Patients were assigned to either 6 mg faricimab or 2 mg aflibercept (Eylea, Regeneron) every 4 weeks for a total of 20 weeks followed by faricimab dosed with a personalized treatment interval (PTI) regimen from weeks 24 to 72.[2,3] Both studies met the 24-week primary endpoint of noninferior BCVA gains compared with aflibercept, and the treatment arms experienced a rapid reduction in central subfield thickness.[4]

NOVEL APPROACHES

Tarcocimab (KSI-301, Kodiak Sciences) uses an antibody biopolymer conjugate platform that combines a monoclonal anti-VEGF antibody with a high molecular weight phosphorylcholine-based polymer.[5] The phase 3 BEACON trial is evaluating tarcocimab for the treatment of macular edema secondary to RVO.[6] Patients were assigned to one of two treatment arms: 5 mg tarcocimab at day 1, week 4, and every 8 weeks through week 20 followed by a PTI regimen from weeks 24 to 44 or 2 mg aflibercept every 4 weeks for 20 weeks followed by a PTI regimen from weeks 24 to 44.[6]

Tarcocimab met its 24-week primary endpoint of noninferior visual acuity gains with fewer doses than the average number used in clinical practice.[7] Tarcocimab showed improvement in visual and anatomic outcomes as early as week 1. After 2 monthly loading doses, tarcocimab is dosed every other month and had an average of 3.9 injections through week 24 compared with aflibercept dosed monthly (an average of 5.8 injections).[7] The secondary outcome of avoiding BCVA loss of more than 15 ETDRS letters was also achieved in both groups, and 46% of patients treated with tarcocimab achieved a BCVA gain of 15 or more letters, which was noninferior to patients in the aflibercept group (50%). Tarcocimab had a favorable safety profile with no cases of endophthalmitis, vasculitis, or vascular occlusions.[7]

Aflibercept (Regeneron) is a soluble decoy receptor molecule, which binds to VEGF-A, VEGF-B, and placental growth factor. The efficacy and safety of 2 mg aflibercept

AT A GLANCE

- Phase 3 trials of faricimab (Vabysmo, Genentech/Roche) and tarcocimab (KSI-301, Kodiak Sciences) for the treatment of macular edema in patients with RVO met their primary endpoints.
- The phase 3 SCORE2 trial evaluated bevacizumab (Avastin, Genentech/Roche) for the treatment of macular edema due to RVO.

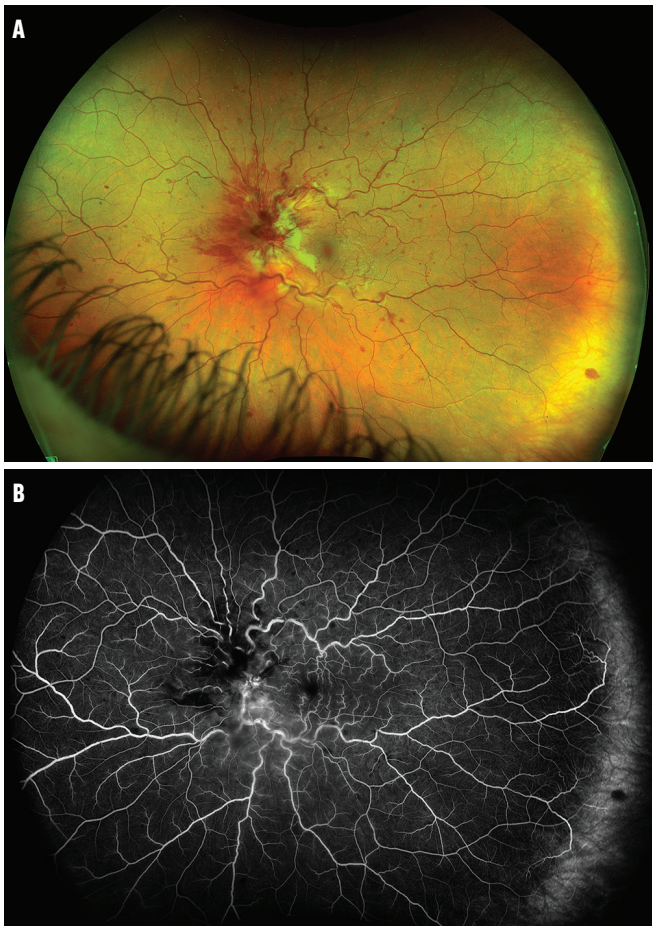

Figure. This 63-year-old man with decreased vision in his left eye presented with diffuse intraretinal and optic disc hemorrhages, cotton-wool spots, and venous dilation and tortuosity, consistent with CRVO (A). Widefield fluorescein angiography shows hypofluorescence due to the blockage caused by the intraretinal and optic disc hemorrhages (B). The angiogram highlights the vascular tortuosity and capillary leakage.

were demonstrated for CRVO in the COPERNICUS and GALILEO trials, and for BRVO in the VIBRANT study.[8,9] In an attempt to further improve outcomes and potentially increase durability, a high-dose 8 mg agent is currently being evaluated, with promising initial results presented for wet AMD (PULSAR) and diabetic macular edema (PHOTON).[10] An RVO study is also under consideration.

STALLED RESEARCH

Brolucizumab (Beovu, Novartis) has variable domains of its monoclonal antibody that are joined by a short flexible linker stabilization peptide. Its lack of an Fc region allows it to have a small molecular size.[11] RAPTOR and RAVEN were terminated phase 3 clinical trials evaluating brolucizumab for the treatment of macular edema in patients with BRVO and CRVO, respectively.[12,13] Participants were randomized into one of two treatment arms: 6 mg brolucizumab or 2 mg aflibercept every 4 weeks for six injections, followed by 48 weeks of individualized flexible treatment. The studies were terminated early due to increased adverse events, including retinal vasculitis and retinal vascular occlusions, in patients who had more than three doses of the study drug.[12]

HOPE FOR THE FUTURE

We are hopeful that these anti-VEGF agents under investigation will improve upon the efficacy and durability of current treatments. The future remains promising in our quest to improve outcomes for patients with vision loss from RVO. ■

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COMPARING CURRENT THERAPIES

Bevacizumab (Avastin, Genentech/Roche), is a humanized monoclonal antibody that directly inhibits all active isoforms of VEGF. It was originally engineered to prevent angiogenesis in solid tumor cancers, and although it is a pillar of treatment for patients with retinovascular disease, bevacizumab remains an off-label option in the ophthalmic space.[1] SCORE2 was a phase 3 National Eye Institute-sponsored clinical trial that included 362 patients with macular edema due to central retinal vein occlusion (CRVO) or hemiretinal vein occlusion.[2] Patients were randomized to 1.25 mg bevacizumab every 4 weeks or 2 mg aflibercept (Eylea, Regeneron) every 4 weeks for 6 months.

The primary outcome was visual acuity letter score (VALS) at the 6-month follow-up.[2] Scores ranged from 0 to 100 with higher scores indicating better visual acuity.[3] The primary analysis findings from SCORE2 showed that the mean VALS were the same for both groups (69.30, P = .001), meeting the criteria for noninferiority.[3] Secondary outcomes included the change in central subfield thickness (CST) from baseline to 6 months, and both treatment groups showed similar decreases in CST.[3]

There have been several secondary analyses from the SCORE2 clinical trial. One study followed VALS and CST outcomes of patients who responded well to the SCORE2 treatment arms. These patients received monthly injections or treat-and-extend regimens from months 6 to 12.[4] At 12 months, the mean CST in both groups improved, and there was no significant change in VALS from baseline between the treatment groups, although the sample sizes were limited.[4]

In another study examining 24-month outcomes, VALS and CST worsened at 24 months compared with 12 months in both groups.[5] At 60 months, VALS significantly improved from baseline, but were less than the improvement observed at 12 months.[6]

A follow-up study was conducted to evaluate VALS and CST at 12 months for patients who responded poorly to anti-VEGF treatments at 6 months in SCORE2.[7] Of the 49 poor responders, 35 patients did not respond to bevacizumab and were switched to aflibercept. The mean changes from 6 to 12 months in VALS and CST were 10.27 (P < .001) and -125.4 µm (P < .001), respectively. Fourteen patients did not respond to aflibercept and were switched to dexamethasone, and their mean changes in VALS and CST from 6 to 12 months were 2.65 (P = .37) and 46.00 µm (P = .46), respectively.[7]

Another secondary study from SCORE2 examined patient-reported visual function at 6 months between the two treatment arms using the 25-item National Eye Institute Visual Function Questionnaire (NEI VFQ-25) composite and subscale scores.[8] Among the 346 participants, both the bevacizumab (P < .001) and aflibercept groups (P < .001) significantly improved in NEI VFQ-25 composite score from baseline.[8]

Because CRVO can be associated with glaucoma, one secondary study examined IOP-related events at 60 months in SCORE2 to evaluate the risks and benefits of therapy in both good responders and poor responders to anti-VEGF who were switched to an alternative treatment.[9] There were 312 patients who met inclusion criteria: 25 (8%) had IOP elevation greater than 10 mm Hg over baseline, and five (1.6%) had IOP higher than 35 mm Hg. The results supported continued monitoring of IOP in eyes with CRVO treated with anti-VEGF therapy.[9]

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