

THE DIABETIC EYE DISEASE PIPELINE IN 2021



The future remains bright with many clinical trials reporting promising data.

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Continued advancement in the treatment of diabetic eye disease is critical as the global burden of diabetes increases. Intravitreal injections of ranibizumab (Lucentis, Genentech), aflibercept (Eylea, Regeneron), and bevacizumab (Avastin, Genentech) have a long history of efficacy and safety for the treatment of diabetic macular edema (DME), with increasing use for diabetic retinopathy (DR). Still, unmet needs remain for more durable agents and improved efficacy. To manage the shortcomings of current anti-VEGF therapies, new agents and novel delivery systems are under investigation.

ANTI-VEGF ADVANCES

Faricimab (Genentech/Roche) is an investigational bispecific antibody designed as an intravitreal injection to neutralize both the angiotensin-2 (Ang-2) and VEGF-A pathways.¹ Under pathologic conditions, Ang-2 is upregulated and blocks angiotensin-1, a vascular stability factor, from binding to the Tie-2 receptor. This competitive inhibition results in endothelial cell destabilization, pericyte destruction, upregulation of inflammatory cytokines, and sensitization of the vasculature to the effects of VEGF-A.¹

YOSEMITE and RHINE are two identical, fully enrolled, pivotal phase 3 trials evaluating 6 mg faricimab for the treatment of DME.²⁻⁴ A total of 1,891 treatment-naïve patients were randomly assigned to one of three treatment arms: every 8 weeks after six monthly loading doses; a personalized treatment interval (PTI) regimen after four monthly loading doses; or every 8 weeks after five monthly loading doses.

The trials met their primary endpoints at 1 year with both faricimab arms offering noninferior/equivalent visual gains

compared with aflibercept with at least a 10-letter gain in each treatment arm.²⁻⁴

As for secondary endpoints, more than 70% of faricimab PTI patients were in the 12- or 16-week treatment interval group at the end of the first year.¹

Faricimab was well tolerated without any unexpected safety

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HOW IT STARTED

The first issue of *Retina Today* included an article detailing the latest pharmacologic treatments for diabetic macular edema (DME), with the understanding that laser photocoagulation was the standard.¹ Most of today's therapies, including steroid injections and implants, were still under investigation.¹ Anti-VEGF therapy with pegaptanib (Macugen, Bausch+Lomb), already FDA approved for wet AMD, was in phase 2 trials for DME with promising data; phase 3 was recruiting.²

After Philip Rosenfeld, MD, PhD; Andrew Moshfeghi, MD, MBA; and Carmen Puliafito, MD, first published on the use of intravitreal bevacizumab (Avastin, Genentech) in wet AMD in 2005, several retina specialists began exploring the benefits of its off-label use for DME.³ By March 2006, Dante J. Pieramici, MD; Robert L. Avery, MD; and others were offering patients with advanced disease a single intravitreal injection of 1.25 mg bevacizumab; they noted that, in some cases, the treatment resulted in rapidly reduced DME and increased vision.⁴

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4. Pieramici DJ, Avery RL. Bevacizumab in the treatment of ocular disease. *Retina Today*. 2006;1(1).

signals or cases of occlusive retinal vasculitis. The 2-year results are expected by early 2022, and the phase 3 extension study RHONE-X will follow patients for an additional 2 years.⁵

The FDA accepted faricimab's biologics license application in July 2021, and the EMA accepted faricimab's marketing authorization application.

Brolucizumab (Beovu, Novartis) is a humanized single-chain fragment that binds to VEGF-A, administered by intravitreal injection.⁶ Compared with other VEGF-A inhibitors, brolucizumab is smaller with a molecular weight of 26 kDa, allowing for a higher molar concentration per injection and possibly more anti-VEGF effect than current treatments.⁶

The phase 3 KITE and KESTREL trials evaluated 6 mg or 3 mg brolucizumab, respectively, for patients with center-involving DME. Patients in the treatment arms received injections every 6 weeks for five loading doses followed by maintenance injections every 12 weeks for 1 year, with an option to adjust to every 8 weeks. The comparator arm received aflibercept every 8 weeks after five monthly loading doses.^{7,8}

Both trials achieved their primary endpoints showing noninferiority to aflibercept at 1 year with a comparable 9 to 10 letters of improvement; patients in KITE received a lower number of total injections at longer intervals for brolucizumab-treated eyes.^{9,10}

KINGFISHER, a separate DME trial that enrolled 517 participants randomly assigned to 6 mg brolucizumab or aflibercept every 4 weeks, also met its primary endpoint of noninferiority to aflibercept at 1 year.⁹

In KITE, 2.2% of participants receiving brolucizumab experienced intraocular inflammation (IOI) compared with 1.7% of patients receiving aflibercept, and no events of retinal vasculitis were seen in either arm. Retinal vascular occlusions occurred at a rate of 0.6% in both groups and were not associated with inflammation or vasculitis.⁹ In KINGFISHER, IOI was seen in 4% of brolucizumab-treated eyes and 2.9% of aflibercept eyes, and retinal vasculitis was seen in 0.9% of brolucizumab eyes and 0.6% of aflibercept eyes. Retinal vascular occlusions were reported in 0.3% of brolucizumab eyes and 0.6% of aflibercept eyes and were not associated with inflammation or vasculitis in either group.⁹

OPT-302 (Opthea Limited), a 'trap' agent that binds to and neutralizes VEGF-C/-D, is being explored as an adjuvant intravitreal injection for patients undergoing standard anti-VEGF therapies. A multicenter phase 1b/2a trial evaluated OPT-302 in combination with aflibercept for refractory DME.¹¹ The phase 1b was a nine-patient dose escalation study where OPT-302 was given with aflibercept, and phase 2a randomly assigned 144 participants 2:1 to aflibercept with 2 mg OPT-302 or aflibercept monotherapy.⁹ Of patients treated with combination therapy, 53% achieved the primary endpoint of ≥ 5 letter gain at week 12 compared with baseline, which was greater than the predefined success measure of 38%.¹¹ In a subgroup of patients with a prior history of

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aflibercept treatment, the mean change in BCVA at week 12 was +6.6 letters after switching to the combination therapy and +3.4 letters for those continuing on monotherapy.¹¹

KSI-301 (Kodiak Sciences) is an intravitreal anti-VEGF biologic built on a proprietary antibody biopolymer conjugate platform.⁶ This feature, combined with its large molecular weight, may allow for a longer intraocular half-life.¹² It is designed to have a duration of approximately 6 months. A phase 1a single-dose escalation study of nine patients with severe previously treated DME showed rapid improvement in vision and anatomy as early as 1 week after injection without any drug-related adverse events.¹³ This was maintained 12 weeks after injection across all dose levels.¹³

The phase 1b trial was an open-label exploratory study that evaluated treatment-naïve patients with wet AMD, retinal vein occlusion, or DME over 72 weeks.^{13,14} Patients received three monthly loading doses of either 2.5 mg or 5 mg KSI-301 followed by subsequent doses per retreatment criteria.¹⁴ At 24 weeks, there was a mean gain of 5.9 letters and a 58 μm reduction in central subfield thickness.^{13,14}

GLEAM and GLIMMER, pivotal phase 3 trials enrolling 450 participants with treatment-naïve DME, are comparing KSI-301 with aflibercept. The primary endpoint will be visual acuity change from baseline at 1 year with 2-year follow-up.¹⁵

The port delivery system (PDS) with ranibizumab (Susvimo, Genentech/Roche), approved by the FDA for the treatment of wet AMD, remains under investigation for DME.¹⁶ The fully enrolled phase 3 PAGODA trial of 545 DME patients is comparing the PDS (with refill exchanges at 6-month intervals) with monthly 0.5 mg ranibizumab. The primary endpoint is the visual acuity change from baseline averaged over weeks 60 and 64.¹⁷

The phase 3 PAVILION trial of moderately severe or severe nonproliferative diabetic retinopathy without DME is evaluating the percentage of participants with ≥ 2 -step letter improvement at 1 year.¹⁸ The 160 patients will be randomly assigned to either two monthly intravitreal injections of ranibizumab followed by the PDS with fixed refills every 36 weeks or observation with as-needed monthly injections

of 0.5 mg ranibizumab until crossing over to the PDS arm.¹⁸

High-dose 8 mg aflibercept (Regeneron) is being investigated as an alternative to the standard 2 mg aflibercept dose for DME. PHOTON is a fully enrolled (660 patients) phase 3 noninferiority trial evaluating the efficacy and safety of 8 mg aflibercept at intervals of 12 or 16 weeks compared with 2 mg aflibercept dosed every 8 weeks for DME.¹⁹

GENE THERAPY UPDATES

ADVM-022 (Adverum) uses an AAV.7m8 vector carrying the coding sequence for aflibercept and is administered via intravitreal injection.²⁰ Adverum unmasked all patients in the phase 2 INFINITY trial after an unexpected serious adverse reaction of hypotony was noted in a participant who received a single high dose of the study drug.²¹ After further review, the company announced that it will not pursue DME as an indication for future ADVM-022 trials.²²

RGX-314 (Regenxbio) is an AAV8 vector carrying an anti-VEGF monoclonal antibody fragment. The phase 2 ALTITUDE trial is looking at patients with DR without DME who are treated with a single dose of RGX-314, delivered suprachoroidally.²³ Positive 3-month interim data from cohort 1, treated with a single injection at a dose level of 2.5×10^{11} genomic copies per eye, show that treatment is well tolerated and 33% of patients had a ≥ 2 -step improvement from baseline on the ETDRS-DRSS compared with 0% of patients in the control arm.²⁴

STEROID DEVELOPMENTS

OCS-01 (1.5% ophthalmic suspension, Oculis), a topical formulation of dexamethasone, uses the company's proprietary soluble nanoparticle technology. The phase 2 clinical trial met its primary endpoint at week 12, showing a mean central macular thickness of $-53.6 \mu\text{m}$ in the treatment group compared with $-16.8 \mu\text{m}$ in the control arm.²⁵ In addition, the mean change in BCVA at week 12 was higher in the OCS-01 group ($+2.62$ letters) compared with the control arm ($+1.04$ letters). The study found no significant differences in tolerability between the two groups, but did note that IOP increases were more common in the treatment arm, consistent with the known effects of steroids.²⁵ Oculis announced the beginning of the phase 3 trial for DME at AAO 2021.

AR-1105 (Aerie) is a bioerodible intravitreal implant (manufactured using PRINT technology) that releases dexamethasone. The phase 2 trial evaluated two formulations of AR-1105 in 49 patients with macular edema associated with retinal vein occlusion. Topline results at 6 months demonstrated increased BCVA and reduced macular edema, with one formulation reaching peak efficacy earlier than the other; however, the slower-acting formulation demonstrated a longer overall duration—up to 6 months. Both formulations of AR-1105 were well tolerated with no unexpected safety findings. The company is preparing for phase 3 studies in DME.²⁶

NOVEL MOLECULAR TARGETS

THR-149 (Oxurion) is a plasma kallikrein inhibitor given in the form of an intravitreal injection. In a phase 1 safety trial, 12 patients had an average improvement of 6.4 letters at 90 days after one injection.²⁷ No dose-limiting toxicity or drug-related adverse events were seen.²⁷ The KALAHARI phase 2 trial is currently enrolling 122 patients and will randomly assign them to three monthly injections of THR-149 or aflibercept. The primary outcome measure will be mean change in vision from baseline at 3 months.²⁸

UBX1325 (Unity Biotechnology) is a Bcl-xL inhibitor currently under investigation in a phase 1 study of patients with DME or AMD for whom anti-VEGF therapy was not considered beneficial.²⁹ The 24-week data released in November demonstrated that 50% of patients receiving UBX1325 had a ≥ 10 letter gain and 62.5% experienced a ≥ 5 letter gain. Additionally, a majority of the patients did not meet rescue criteria after a single UBX1325 injection through week 24.

A phase 2a study is currently enrolling 62 patients with DME who will be randomly assigned to a single intravitreal injection of UBX1325 or sham therapy.³⁰ The primary outcome measures are ocular and systemic safety and tolerability over 24 weeks.³⁰

IN SUMMARY

Many novel treatments under investigation have the potential to improve durability and/or efficacy of current therapy for DME and DR. The recently encountered safety hurdles remind us to tread cautiously, as new complications may accompany novel therapies. However, the future remains promising in our quest to improve the therapeutic landscape for patients with DME and DR. ■

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