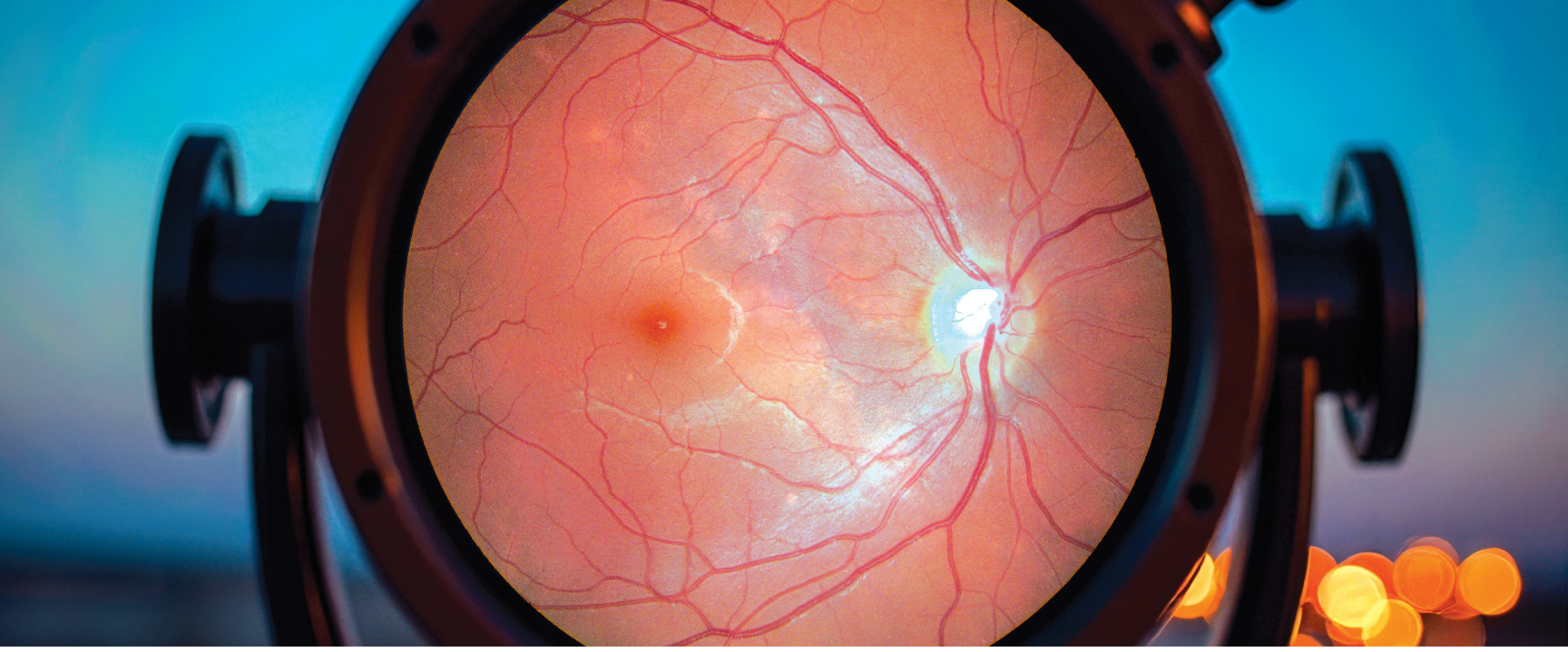
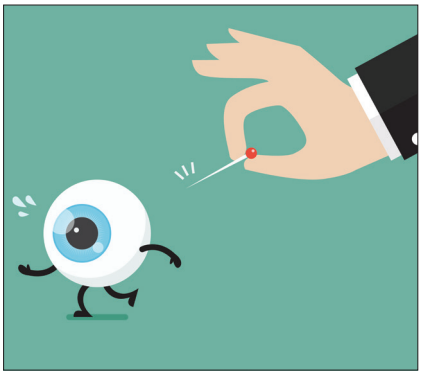


NEW TREATMENTS FOR DIABETIC EYE DISEASE


A rundown of the latest therapy options in clinical trials—and a few in earlier developmental stages.

BY STEVEN FERRUCCI, OD, FAAO, AND BRENDA YEH, OD, FAAO

For almost 50 years, laser photocoagulation has been one of the mainstays of treatment for diabetic retinopathy (DR). Then, a little more than 20 years ago, the treatment landscape was forever changed with the advent of anti-VEGF injections, first for age-related macular degeneration (AMD),[1] then diabetic macula edema (DME), and now DR with or without DME. However, these treatment modalities come with some disadvantages: decreased visual field and loss of visual acuity with laser and the need for frequent, repetitive injections, necessitating compliance and inducing significant patient burden with anti-VEGF injections. Thus, newer treatments



for DR that yield better outcomes, fewer complications, and reduced burden are being investigated. In this article, we take a look at some of these potential treatment options, although this is not an exhaustive listing of all the therapeutic options in clinical trials and in the pipeline.

INTRAVITREAL OPTIONS

Vorolanib intravitreal insert (**Durayvu**, Eye Point Pharmaceuticals) is a bioerodible insert of vorolanib, a selective tyrosine kinase inhibitor (TKI), in phase 2 for the treatment of nonproliferative DR (NPDR) and DME.[2] TKI, in turn, effectively blocks all VEGF activity. It has also been shown in animal studies to have neuroprotective properties and to inhibit platelet-derived growth factor, which may lead to antifibrotic benefit, helping with scar formation.

The PAVIA phase 2 clinical trial is a multi-center, randomized, double-masked study comparing two single injection doses of vorolanib against a sham in patients with moderately severe to severe NPDR.[3] The primary

outcome is the percentage of patients with a 2-step or greater improvement in Diabetic Retinopathy Severity Score (DRSS) score at 9 months. Secondary endpoints include a reduction in vision-threatening complications, center-involved DME occurrence, and safety. Preliminary topline results showed that similar proportions of patients treated with vorolanib and sham achieved a 2-step or greater improvement in DRSS at 9 months. However, vorolanib did demonstrate stable or improved disease severity with reduced rates of NPDR regression at 9 months, with 86% of patients in the 3 mg arm and 80% in the 2 mg arm demonstrating stable or improved progression at 9 months versus 70% in the control arm. Further, 0% of patients in the 3 mg arm and 5% in the 2 mg arm worsened 2 steps or more at 9 months versus 10% in the control arm. Overall rates of adverse effects were comparable between treated patients and the control arm, with no cases of endophthalmitis or retinal vasculitis observed. Full results for the phase 2 trial are expected by the third quarter of 2024 for NPDR and the first quarter of 2025 for DME.

Axitinib intravitreal implant (**Axpaxli**, Ocular Therapeutix) is a bioresorbable hydrogen implant of axitinib, a small molecule, multi-target TKI with anti-angiogenic properties.[4] This implant is being evaluated for the treatment of DR, AMD, and other retinal diseases.

The phase 1 HELIOS study evaluated the axitinib intravitreal implant versus a sham control in patents with moderately severe to severe NPDR without DME.[5] Of patients in the treated group, 46.2% experienced a 1- or 2-step improvement in DRSS at 40 weeks compared with 0% in the control group. No patients in the treated group experienced worsening of DRSS at 40 weeks compared with 12.5% in the control group. The axitinib intravitreal implant was generally well-tolerated with no observed inflammation, including no incidence of iritis, vitritis, or vasculitis.[5] Based on these results, Ocular Therapeutix hopes to move directly to a phase 3 study, pending discussions with the FDA.

GENE THERAPY

ABBV-RGX-314 (RegenxBio) is a potential one-time gene therapy being investigated for DR, wet AMD, and other additional chronic retinal conditions treated with anti-VEGF therapy.[6]

ALTITUDE is a multi-center, open-label, randomized, controlled phase 2 study evaluating the efficacy, safety, and tolerability of suprachoroidal delivery of ABBV-RGX-314 in patients with moderately severe or severe NPDR or mild proliferative DR. Two separate doses were evaluated in this study. At 1 year, 100% of patients with baseline NPDR demonstrated stable to improved disease severity with dose level 2 (5 x 1011 genomic copies per eye),[7] while 70.8% achieved improvement in DRSS versus 25.0% in the control group. Additionally, 0% of the treated group worsened 2 steps or greater versus 37.5% in the control group. Of the treated patients, 4.2% developed vision-threatening events versus 37.5% in the control group. The safety profile was favorable, with no cases of chorioretinitis, vasculitis, occlusion, or hypotony reported.

ORAL THERAPY

APX3330 (Ocuphire Pharma) is an orally administered small molecule inhibitor of the transcription factor regulator reduction oxidation effector factor-1 protein (Ref-1) being investigated for the treatment of DR.[8] By inhibiting Ref-1, APX3330 prevents increased VEGF levels, keeping them at a physiological norm and decreasing abnormal activation of angiogenesis and inflammation, both of which play a pivotal role in DR, DME, and other retinal diseases.

ZETA-1 was a randomized, double-masked, placebo-controlled phase 2 trial designed to evaluate the safety and efficacy of APX3330 in patients with diabetes.[8] In the trial, APX3330 did not meet the primary endpoint of percentage of patients with a 2-step or greater improvement in DRSS score at 24 weeks. However, APX3330 did demonstrate statistically significant reduction of disease at 24 weeks, at which point no treated patients had a binocular 3-step or greater worsening of DRSS from baseline compared with 16% for the control group. Furthermore, visual acuity was stable in the treated group, with fewer treated patients losing 5 or more letters of distance vision (6%) compared with patients taking the placebo (19%). There were no treatment-related serious adverse events and no changes noted in liver, kidney, or heart function. Further analysis of the trial data is ongoing, with additional results expected to be reported at several upcoming ophthalmology meetings.

Several other systemic treatments are in early developmental stages, including an oral rho kinase inhibitor (**OPL-0401**, Valo Health)[9]; a guanylate cyclase inhibitor

runcaciguat (**BAY1101042**, Bayer Pharmaceuticals)[10]; a cannabinoid receptor 2 agonist vicasinabin (**RG-7774**, BioWorld MedTech); a connexin43 hemichannel blocker (**Tonabersat**, MedChemExpress); an oral, small molecule plasma kallikrein inhibitor (**RZ402**, Rezolute)[11]; and a novel, oral small molecule inhibitor of the pathological Cx43 hemichannel (**Xiflam**, InflammX Therapeutics).[12]

DROPS

Nesvategrast (**OTT166**, OcuTerra) is a novel selective Arg-Gly-Asp (RGD) integrin inhibitor in eye drop form.[13] RGD integrins play a role in angiogenesis, vascular leakage, fibrosis, and inflammation. Nesvategrast was studied in the phase 2 Diabetic Retinopathy: Early Active Management clinical trial as a treatment for DR.[14] With a goal of earlier, convenient, and noninvasive treatment, this medicated eye drop was designed with the intention of allowing patients to self-administer it in the comfort of their own home. The study failed to meet its primary endpoint, a statistically significant improvement on the DRSS scale compared with the control group. Furthermore, it did not meet an important secondary endpoint of having a significant effect on disease progression, as measured by the DRSS scale. There was, however, a statistically significant finding of preventing visually threatening events in patients with moderately severe and severe NPDR by week 24.[14] Additionally, nesvategrast was shown to be safe and well-tolerated. OcuTerra is planning to reevaluate its strategic plans moving forward.

OCS-01 (Oculis) is an OptiReach formulation of high-concentration dexamethasone eye drop developed to treat the retina. The OptiReach solubilizing formulation technology improves the solubility of lipophilic drugs, increasing the residence time on the ocular surface, thereby enabling drug passage from the ocular surface to the posterior segment of the eye. Positive findings from stage 1 of the DIAbetic Macular edema patients ON a Drop (DIAMOND) program, which was announced in the second quarter of 2023, have led to enrollment in the DIAMOND-1 and DIAMOND-2 trials.[15] The double-masked, randomized, multi-center phase 3 studies will evaluate the efficacy and safety of OCS-01 eye drops in patients with DME. Oculis aims to enroll 350 patients in each of these pivotal trials who will be randomized 1:1 to receive OCS-1 or vehicle six times daily for the 6-week induction phase and then three times daily through week 52 for the maintenance phase. The primary endpoint is change in BCVA ETDRS letter score at week 52. Secondary endpoints include percentage of patients with 15 or more letters gained in BCVA and change in central subfield thickness, both at week 52.

THE FUTURE IS PROMISING, BUT THE WORK IS NOT YET DONE

As the global incidence of diabetes increases,[16] so too will its complications, including potential blindness. Although new therapies, such as anti-VEGF injections, have greatly expanded our ability to care for patients with diabetic eye disease, there remains a need for additional safe, effective, and durable treatments for diabetic eye disease. It is impossible to predict which of these therapies may be the next breakthrough; thus, it is imperative that research continues in the quest to find better treatments for our patients with diabetes. ■

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STEVEN FERRUCCI, OD, FAAO
- Chief of Optometry, Sepulveda VA, North Hills, California
- Professor, Southern California College of Optometry, Marshall B. Ketchum University, Fullerton, California
- Member, *Modern Optometry* Editorial Advisory Board
- steven.ferrucci@gmail.com
- Financial disclosure: None

BRENDA YEH, OD, FAAO
- Assistant Chief of Optometry, Sepulveda VA, North Hills, California
- Assistant Professor, Southern California College of Optometry, Marshall B. Ketchum University, Fullerton, California
- Financial disclosure: None