THE POTENTIAL OF TYROSINE KINASE INHIBITORS

This novel class of drug may one day help to address the growing burden of diabetic eye disease.

By Shawn Kavoussi, MD

Retina specialists caring for patients with diabetic macular edema (DME) currently have three main pharmacologic approaches: anti-VEGF injections, steroids, or a combination of both. Next-generation therapies—such as faricimab (Vabysmo, Genentech/Roche), aflibercept 8 mg (Eylea HD, Regeneron), and the port delivery system with ranibizumab (Susvimo, Genentech/Roche)—now offer more choices, but the limitations remain the same. For example, the Protocol T early analysis showed that up to 35% of patients with DME experience suboptimal responses, gaining fewer than 5 letters at 12 weeks, following monthly aflibercept 2 mg (Eylea, Regeneron) therapy.[1]

Treatment with intraocular steroids, such as the dexamethasone intravitreal implant (Ozurdex, Abbvie) and fluocinolone acetonide intravitreal implant (Iluvien, ANI Pharmaceuticals), comes with the risk for increased IOP and cataract formation.[2,3]

These limitations have led researchers to seek novel mechanisms of action to address DME, several of which are showing promise, including tyrosine kinase inhibitors (TKIs). Here is a look at what TKIs are, where they are in the pipeline, and how they might fit into our treatment paradigm.

A NOVEL MECHANISM OF ACTION

TKIs work by blocking cellular communication and downstream processes through phosphorylation and inhibiting the function of the tyrosine kinase enzyme, which activates cellular signals such as VEGF. When the retina is deprived of oxygen through damage to the vasculature or decreased blood flow, such as in diabetic retinopathy and AMD, VEGF promotes the growth of new, leaky blood vessels. Unlike anti-VEGF medications, which bind to VEGF outside the cell, TKIs block this signaling process within the cell itself. The intracellular mechanism of action blocks all VEGF isoforms, offering the potential for increased durability.[4]

In addition, research shows that retinal thickness

KEY TAKEAWAYS

- The intracellular mechanism of action for tyrosine kinase inhibitors (TKIs) blocks all VEGF isoforms, offering the potential for increased durability.
- Promising TKIs under investigation include EYP-1901 (EyePoint), OTX-TKI (Ocular Therapeutix), and D-4517.2 (Ashvattha Therapeutics).
- TKIs offer the ability to reduce patients' treatment and office visit burden. However, some patients may still require monitoring between injections.

fluctuations with bolus therapy lead to overall worse long-term outcomes and gradual vision decline.[5] Thus, sustained maintenance of consistent drug levels with TKI implants could potentially lead to better visual outcomes.

PROMISING PIPELINE OPTIONS

The vorolanib intravitreal insert (EYP-1901/Duravyu, EyePoint) inhibits VEGFR-1, VEGFR-2, VEGFR-3, and PDGFR-β. Recent radiometric and in vitro assays also demonstrated potent inhibition of JAK1, which tranduces interleukin-6–mediated proinflammatory signaling through the interleukin-6R/gp130 receptor complex.[6]

In the phase 2 VERONA trial, both the 1.34 mg and 2.7 mg doses met the primary endpoint of extended time to first supplemental injection versus aflibercept 2 mg. With the higher dose, BCVA improved by 7.1 letters compared with baseline and central subfield thickness (CST) improved by 75.9 µm compared with baseline—74% more drying in study eyes versus controls.[7] In addition, 73% of eyes in the higher-dose EYP-1901 group were supplement-free versus 50% in the aflibercept group up to week 24. As for safety, the trial reported no treatment-related ocular or systemic serious adverse events.[7]

The company completed enrollment for the phase 3 COMO and CAPRI clinical trials of EYP-1901 for the treatment of DME.[8]

The axitinib intravitreal insert (OTX-TKI/Axpaxli, Ocular Therapeutix) embeds axitinib within a bioresorbable polyethylene glycol hydrogel depot that is injected intravitreally. The hydrogel gradually dissolves while the medication is released over the course of several months, targeting all VEGF receptors and PDGFR. The phase 1/2a clinical study demonstrated sustained intraocular axitinib delivery with an approximately 89% to 90% reduction in annualized anti-VEGF injection burden compared with each patient's historical pre-enrollment treatment frequency. Approximately one-third of patients required no rescue injections through 12 months while maintaining stable BCVA and CST.[9]

The phase 3 Helios-3 trial is evaluating OTX-TKI dosed every 12 months in patients with nonproliferative diabetic retinopathy versus sham. In the phase 3 SOL-1 trial in patients with wet AMD, treatment with OTX-TKI demonstrated superiority over aflibercept for a durability-based endpoint for wet AMD.[10]

Migaldendranib (D-4517.2, Ashvattha Therapeutics) is delivered subcutaneously through a nanoparticle hydroxyl dendrimer carrier. Early phase 1 studies demonstrated favorable safety and biological activity.[11] The TEJAS phase 2 trial was the first randomized clinical study evaluating subcutaneous D-4517.2 in patients with neovascular AMD and DME. The study was designed to assess the safety, tolerability, pharmacokinetics, and preliminary efficacy of repeated subcutaneous dosing compared with intravitreal aflibercept. Multiple subcutaneous doses were safe and well-tolerated and provided a > 69% reduction in treatment burden in study eyes and a > 67% reduction in fellow eye treatment in patients with bilateral disease.[12]

TKI UPDATE IN THE NEWS

EyePoint recently announced the results from the phase 3 LUGANO study in wet AMD. While the primary endpoint was not achieved in the full dataset, the vorolanib intravitreal insert (EYP-1901/Duravyu) was noninferior to on-label aflibercept (Eylea, Regeneron) control (nominal *P*-value = .0096) in an ad hoc analysis excluding 9 of 211 patients who experienced ≥ 15-letter vision loss unrelated to wet AMD.[1]

In the trial, key secondary endpoints were met, including a reduction in treatment burden, increased supplement-free rates, safety with redosing, and strong anatomic control through week 56 compared with aflibercept.[1]

EYP-1901 continued to be safe and well tolerated with repeat dosing, including no observed events of insert migration, anterior chamber opacities, free-floating drug particles, retinal vasculitis, or severe intraocular inflammation.[1]

1. EyePoint announces topline data from LUGANO, the first of two pivotal phase 3 clinical trials for Duravyu 2.7mg in wet AMD [press release]. EyePoint. August 17, 2026. Accessed August 19, 2026.investors.eyepoint.bio/news-releases/news-release-details/eyepoint-announces-topline-data-lugano-first-two-pivotal-phase-3

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FITTING INTO THE TREATMENT PARADIGM

Given their novel approach, TKIs hold promise as adjuncts to our current therapeutic approaches, or, for select patients, first-line treatment. For example, patients newly diagnosed with mild-to-moderate DME might respond to a primary monotherapy with a TKI, significantly minimizing the treatment burden compared with anti-VEGF monotherapy. For more severe disease

where the CST is greater than 400 µm, patients may benefit from a loading phase of anti-VEGF therapy followed by combination therapy. Overall, TKIs offer the ability to reduce treatment and office-visit burden. However, these patients may still require monitoring between injections.

In addition to monitoring concerns, each of the TKIs under investigation come with potential complications due to their sustained delivery method as implants.

For example, the implant procedures will introduce an initial learning curve, as each one has it's own unique injection technique and applicator. In addition, clinicians must educate patients on the potential for visual floaters and set that expectation. Residual material in the vitreous cavity may also affect the treatment decisions to redose patients after 6 to 9 months for some implants.

IMPROVING DME CARE

As the prevalence of diabetes continues to rise, clinicians must seek novel approaches to care for patients presenting with DME. Investigational TKIs may soon provide a novel approach with the promise of reduced treatment burden. Phase 3 trial data and real-world experience will eventually determine the safety and efficacy of TKIs, in addition to clarifying their role in managing our patients with DME. ■

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