

A Timely Debut for Extended-Release Polymer Technologies



A look at sustained-release therapeutics in the retina pipeline.

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Even though most retina practices across the country have been preoccupied this year with changes brought on by the coronavirus pandemic, 2020 is still an exciting year because of the potential of new ophthalmic treatments in the pipeline. In this article, we discuss some of these potential new developments in retina, focusing on extended-release polymer technology. As is the case with many emerging therapeutics, some of these treatments have not yet released peer-reviewed data and should be evaluated with caution.

OCULAR THERAPEUTIX

OTX-TKI (axitinib intravitreal implant, Ocular Therapeutix) is a sustained-release tyrosine kinase inhibitor (TKI) implant targeting VEGF-induced retinal leakage, delivered through intravitreal injection for the treatment of exudative macular degeneration. Using a bioresorbable hydrogel, this injectable is designed to deliver its drug for up to 12 months. In a preclinical study, Dutch belted rabbits ($n = 9$) were dosed bilaterally with OTX-TKI, then challenged with VEGF at 2, 3, and 6 months. Compared with control eyes ($n = 4$), OTX-TKI significantly suppressed leakage at all challenge points.¹ In a follow-up study, OTX-TKI was evaluated for 12-month dosing.² Using a similar setup, 15 rabbits were bilaterally dosed and then challenged with VEGF injections at 3, 6, 9, and 12 months. Leakage was significantly suppressed at all

challenge points in comparison with control eyes ($n = 4$). Ocular Therapeutix began recruiting for a phase 1 clinical trial outside the United States in 2018 evaluating safety, durability, and tolerability in individuals with wet AMD. Completion is anticipated in November 2021.³

GRAYBUG VISION

GB-102 (sunitinib maleate, Graybug Vision) is an injectable intravitreal TKI suspended in polymer microparticles (MP). Due to concerns regarding the possibility of MPs blocking the visual axis, GB-102 was modified to promote aggregation

AT A GLANCE

- ▶ A number of sustained-release polymer implant technologies with potential therapeutic applications in retina are undergoing clinical evaluation.
- ▶ Several of the drugs deployed by these implants are inhibitors of tyrosine kinase or other kinases, and one is a drug-polymer conjugate.
- ▶ Results for most of these potential therapeutics have not undergone peer review and should be evaluated with caution.

of the MPs to form a depot after intravitreal injection; the MPs later biodegrade to form lactic acid and glycolic acid.⁴ The drug inhibits multiple intracellular tyrosine kinases, thereby inhibiting VEGF receptors 1, 2, and 3. It also inhibits platelet-derived growth factor receptors A and B, stem-cell growth factor receptor, and colony stimulating factor. A study using a murine model for type 2 neovascularization (NV) found that 10 µg of MPs injected intravitreally significantly reduced incidence of NV for 24 weeks.

Of note, subconjunctival injection of GB-102 was also explored in murine models. Histologic examination revealed significant differences for 2 µg and 20 µg MP dosing compared with empty MP injection. The noninjected fellow eye was also examined and found to have no significant difference compared with empty MP injection, suggesting little systemic spread of the compound. The follow-up time for subconjunctival injection was minimal, and this route must be further explored. Additionally, the study appeared to support neuroprotective effects of GB-102, with significantly greater outer nuclear thickness and higher rhodopsin kinase levels in comparison with free aflibercept (Eylea, Regeneron).⁴

In results announced in a press release by Graybug Vision, the ADAGIO phase 1/2a multicenter trial, including 32 patients with wet AMD who had previously responded to anti-VEGF therapy, met its primary endpoints of safety and tolerability. According to the company, GB-102 was “well-tolerated with no dose limiting toxicities, drug-related serious adverse events or inflammation” in the trial. Graybug Vision also reported that, in a secondary endpoint, 88% and 68% of participants in the trial were maintained on a single dose of GB-102 at 3 and 6 months, respectively.⁵ These results are cause for cautious optimism, although a well-powered study will be necessary to verify these unrefereed results.

Another trial evaluating GB-102 in patients with diabetic macular edema (DME) and retinal vein occlusion (RVO) was recently completed, but no results had been announced at the time of the writing of this article.⁶ A phase 2b trial in individuals with AMD has concluded patient enrollment and is ongoing.⁷

KODIAK

KSI-301 (Kodiak) is an anti-VEGF–biopolymer conjugate being examined for use in wet AMD, DME, and RVO to rapidly reduce VEGF burden and provide extended durability. KSI-301 uses an antibody–biopolymer conjugate platform that is 950 kDa in size, compared to 48 kDa for ranibizumab (Lucentis, Genentech) and 115 kDa for aflibercept. Results of clinical trials to date are available only via meeting presentations,⁸ so caution is advised in their interpretation until they have been peer-reviewed.

In a phase 1b study in patients with wet AMD, DME, or

RVO, participants were given three baseline injections of KSI-301 at 1-month intervals, then monitored with protocol-guided treatment from 12 to 148 weeks, with mandated injections at least every 6 months for AMD patients.

KSI-301 was deemed to be well tolerated in 546 total doses given to 130 participants. Intraocular inflammation was seen after 0.37% of injections (2 of 546) with either trace or 1+ vitreous cell. Both cases had complete resolution of inflammation without vasculitis or retinitis. The adverse event profile was considered consistent with intravitreal anti-VEGF agents.

According to data from the phase 1b trial presented this year, preliminary results in AMD (n = 51) indicate that BCVA improved by 5.8 letters from baseline at 44 weeks. The first retreatment was given before 3 months, at 4 months or longer, at 5 months or longer, or at 6 months for 18% (9), 82% (40), 66% (27), and 49% (20) of patients, respectively.

Preliminary results in DME (n = 35) indicate that BCVA improved by 6.6 letters from baseline at 44 weeks. The first retreatment was given at or before 3 months, at 4 months or longer, at 5 months or longer, or at 6 months or longer for 24% (8), 76% (25), 70% (23), and 67% (22) of patients, respectively. At 44 weeks, 45% (15) of patients had yet to require a retreatment.

Preliminary results in RVO (n = 35) indicate that BCVA improved by 22.4 letters from baseline at 44 weeks. The first retreatment was given at or before 2 months, at or before 3 months, or at 4 months or longer for 33% (11), 44% (14), and 56% (18) of patients, respectively. At least once during follow-up, 71% (24) of patients achieved a treatment interval of greater than 4 months.

Kodiak is recruiting for phase 3 trials for patients with wet AMD, DME (two separate trials), and RVO.⁹⁻¹²

AERIE PHARMACEUTICALS

AR-13503 (Aerie Pharmaceuticals), an inhibitor of rho kinase and protein kinase C (PKC), is a sustained-release implant being investigated for the treatment of wet AMD and DME. Suspended in a bioerodible polymer, AR-13503 provides controlled release of its active ingredients. Preclinical studies of AR-13154, a precursor molecule to AR-13503, demonstrated reduction of choroidal neovascularization of 35% ($P < .001$), and a significantly superior effect when used in combination with aflibercept (57%, $P < .005$).¹³ Initial reports have shown linear drug release in vitro for more than 100 days. In rabbits, concentrations of AR-13503 were sustained at or above therapeutic levels established by an in vitro study for 5 months, followed by gradual decline in month 6. Drug concentrations in nontherapeutic regions (cornea, lens, vitreous) never exceeded 20% of those seen in the retina, retinal pigment epithelium, and choroid.¹⁴ Phase 1 clinical trials have

finished recruitment, and completion is anticipated in September 2021.¹⁵

AR-1105 (Aerie Pharmaceuticals) is a bioerodible dexamethasone implant being investigated for use every 6 months in individuals with DME, RVO, or uveitis. In a pharmacokinetics and tolerability study in cynomolgus monkeys, therapeutically relevant dexamethasone concentrations were detected in the retina, choroid, and vitreous for at least 6 months with minimal anterior chamber and systemic exposure. Additionally, there was no implant-related effect on IOP.¹⁶ In a September 2020 press release, Aerie reported results of a recently completed phase 2 multicenter study of 49 patients. The implant “demonstrated positive and sustained treatment effects with both formulations as shown by increases in best corrected visual acuity and reductions in macular edema,” according to the company.¹⁷ At the time of this writing, no statistics are available for review, and no timeline for phase 3 trials has been made public.

LOOKING AHEAD

Therapeutic approaches to the range of retinal vascular diseases continue to evolve. Although currently available treatments provide far greater benefit than was conceivable 15 years ago, we have much to look forward to with drugs and implants now in the pipeline, including the possibility that they will offer enhanced efficacy and durability. ■

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