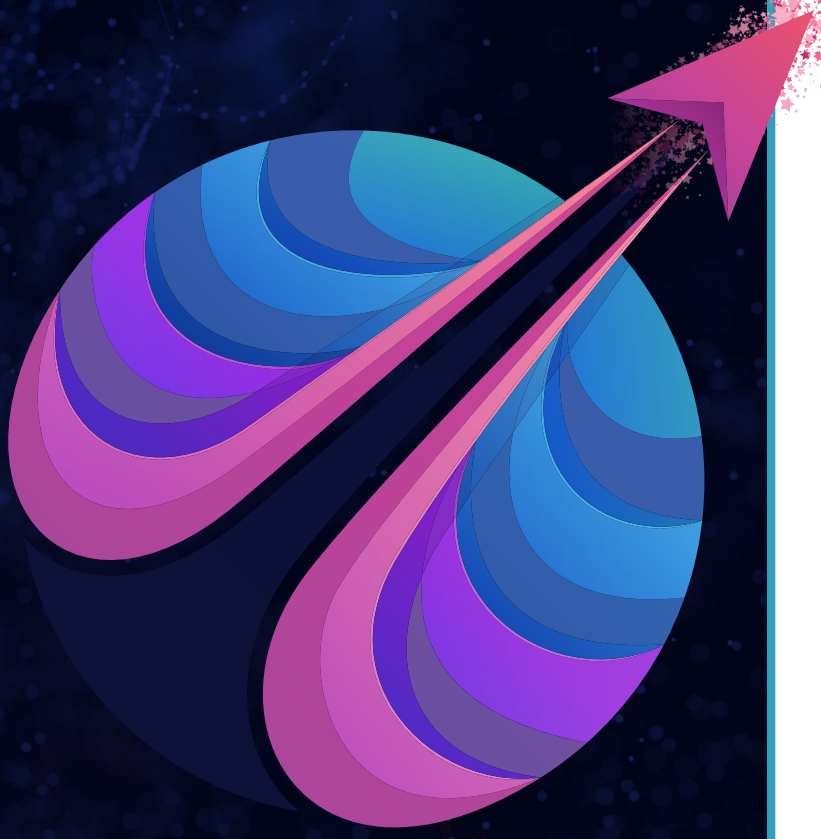

Long-Lasting Anti-VEGF Implants

The treatment landscape is changing.

BY HUY NGUYEN, MD, AND MICHAEL A. SINGER, MD

Care for patients with retinal vascular diseases often includes monthly or bimonthly intravitreal injections. This schedule, combined with possible additional rescue injections and clinic visits for other ocular comorbidities, places a heavy burden on patients. Strong adherence to the injection regimen is required, sometimes indefinitely, to preserve vision. Nonadherence, however, has been reported in 32% to 95% of patients, and up to 50% may be lost to follow-up at 24 months, which can result in significant vision loss.[1] The demand for therapeutics for patients with refractory retinal vascular disease combined with surging patient volume is driving innovation in the form of sustained or alternative drug delivery.

A BRIEF HISTORY OF ANTI-VEGF AGENTS

Neovascular age-related macular degeneration. Anti-VEGF agents have revolutionized the management of retinal vascular permeability and vasoproliferative diseases such as neovascular age-related macular degeneration (nAMD), proliferative diabetic retinopathy, diabetic macular edema (DME), and retinal vein occlusions (RVOs). The molecule responsible for neovascularization was theorized as early as 1948 and received its familiar VEGF name in 1989. The first clinical trials of its inhibitor molecule, bevacizumab (Avastin, Genentech), were conducted a decade later.[2] The drug was approved for the intravenous treatment of colon cancer in 2004, and the agent's off-label use in the vitreous cavity to treat nAMD quickly followed. The vitreous cavity was targeted to limit systemic side effects, setting a precedent for therapies in the pipeline. By the end of 2004, pegatanib (Macugen, Eyetech Pharmaceuticals) became the first US FDA-approved ophthalmic injection for nAMD.

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With the aim of improving drug diffusion through the retina to reach the choroid, Genentech produced a smaller molecule, ranibizumab (Lucentis), by removing the crystallizable fragment (Fc) portion from the full-sized antibody (bevacizumab), reducing the size from 149 to 48 kDa. The smaller molecule achieved faster clearance from the vitreous cavity (half-life of 3.2 vs 5.6 days for ranibizumab and bevacizumab, respectively) but maintained a similar duration of activity.[3]

In 2011, Regeneron added value to the anti-VEGF portfolio by creating a chimeric fusion protein. This protein acts as a VEGF trap by mimicking VEGF receptors 1 and 2 and sequestering VEGF-A (the most targeted isomer in the VEGF family). The protein, aflibercept (Eylea, Regeneron), has binding pharmacokinetics with 100-fold affinity compared to its predecessors.[3] The VIEW trials demonstrated that aflibercept injections delivered every 2 months were noninferior to monthly ranibizumab for the treatment of nAMD.

Brolucizumab-dbll (Beovu, Novartis) received US FDA approval in 2019. The drug's molecular weight (26 kDa) is the lowest of any anti-VEGF agent ever injected into the eye. Its molecular weight allows high penetration across the retina to reach the retinal pigment epithelium and choroid, making brolucizumab a potent drying agent and a long-acting drug. In the phase 3 HAWK and HARRIER studies, more than half of eyes treated with brolucizumab were maintained at a dosing interval of every 12 weeks after the loading phase. The incidence of intraocular inflammation was higher with brolucizumab than aflibercept (3.6 % vs 0.3%).[4] Postmarket surveillance from Novartis and the American Society of Retina Specialists found incidence of severe intraocular inflammation and prompted the company to release guidelines contraindicating the use of brolucizumab in eyes with active inflammation.

DME and RVOs. In addition to stimulating endothelial migration and replication, VEGF-A decreases vascular stability in eyes with DME and RVOs. The RISE and RIDE clinical trials established ranibizumab for the treatment of DME.[5] In the VIVID and VISTA trials, aflibercept dosed at 2 mg every 4 weeks or 2 mg every 8 weeks after 5 monthly doses showed similar anatomic and visual outcomes, which provided the option of longer intervals between treatments.[6] The BRAVO and CRUISE clinical trials showed the benefit of ranibizumab for RVO, and the GALILEO, COPERNICUS, and VIBRANT trials demonstrated the benefit of aflibercept for RVO.[7]

The Diabetic Retinopathy Clinical Research Network Protocol T, a multicenter randomized clinical trial, compared intravitreal aflibercept, bevacizumab, and ranibizumab for the treatment of DME. When visual acuity loss was moderate or worse, aflibercept was more likely to improve visual acuity in the first year, but the difference in efficacy faded in year 2. Ultimately, all three agents were effective at improving visual acuity. In terms of anatomy, ranibizumab and aflibercept demonstrated superiority to bevacizumab on OCT for reducing fluid in years 1 and 2. The need for rescue laser treatment was lowest with aflibercept.[8]

The phase 3 KITE and KESTREL trials comparing brolucizumab and aflibercept for DME are underway. Preliminary data indicated that approximately half of patients were maintained on brolucizumab with a dosing interval of every 3 months.[9]

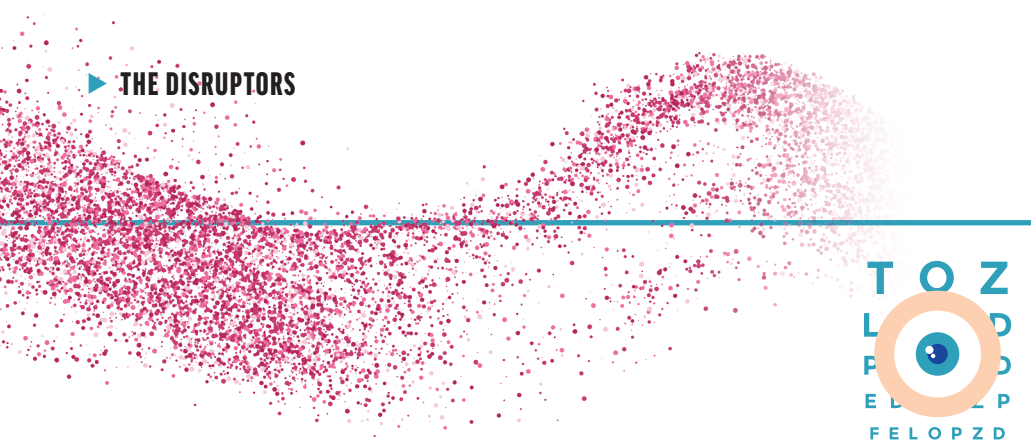
EXTENDING TREATMENT INTERVALS

Investigators are attempting to extend activity duration by increasing the dosage of on-label anti-VEGF agents. The phase 3 PHOTON and PULSAR clinical trials are underway to study high-dose aflibercept administered in 16-week intervals for DME and nAMD.

The half-life of anti-VEGF intravitreal therapies can also be manipulated by peptide conjugation. Kodiak is using a large antibody binding conjugate (KSI-301) to enhance the durability of its anti-VEGF agent. Phase 1 results in DME, AMD, and RVO were promising: More than 50% of patients were able to go more than 6 months between injections.[10] Several studies of KSI-301 are ongoing: GLEAN and GLIMMER in treatment-naïve patients with DME, BEACON in treatment-naïve patients with RVO, and DAZZLE in treatment-naïve patients with nAMD.

Another interval-spacing strategy currently in a phase 3 clinical trial is a Port Delivery System (PDS) with ranibizumab (Genentech). The PDS is a permanent refillable ocular implant that continuously infuses ranibizumab intraocularly at the pars plana. The phase 2 LADDER trial for nAMD showed promising results and finessed the dosing to 100 mg/mL, with reinjections at a fixed interval of every 6 months (and rescue refills or standard 0.5-mg intravitreal injections for clinically nonresponsive cases).[11] Compared to regular intravitreal injections, the PDS care pathway is a paradigm shift because surgical implantation is required initially. The LADDER study demonstrated that safety depended to some degree on surgical technique. A 3.2-mm slit-knife incision was created, followed by meticulous laser treatment of the choroidal bed to lessen the risk of vitreous hemorrhage and careful surgical closure of Tenon capsule and the conjunctiva to prevent conjunctival retraction, exposure, and infection.[11]

In the phase 3 Archway study, the PDS was refilled in the office every 6 months. The data demonstrated noninferior visual acuity at 72 weeks compared to monthly ranibizumab, and 98% of PDS patients did not need rescue injections. The phase 3 Portal study is investigating the long-term safety and tolerability of the PDS



> “Nonadherence has been reported in **32% to 95% of patients**, and **up to 50% may be lost to follow-up** at 24 months, which can result in significant vision loss.[1] The demand for therapeutics for patients with refractory retinal vascular disease combined with surging patient volume is driving innovation in the form of sustained or alternative drug delivery.”
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for the treatment of nAMD and is anticipated to be completed in 2022.

NEW MOLECULAR TARGETS

New molecular targets, especially angiopoietin-2 (Ang-2), are on the horizon. The Tie-2 receptor found on endothelial cells operates on a different but complementary axis to VEGF to affect vessel formation and stability. The competitive binding of Ang-1 and Ang-2 molecules to the Tie-2 receptor promotes vessel stability or instability, respectively.[12]

Roche introduced faricimab as a novel antibody with dual Ang-2 and VEGF-A binding arms for the treatment of nAMD (phase 3 clinical trials LUCERNE and TENAYA) and DME (phase 3 clinical trials YOSEMITE and RHINE). The phase 2 clinical trial STAIRWAY compared faricimab 6 mg dosed every 12 or 16 weeks to monthly ranibizumab 0.5 mg for nAMD. Phase 3 compared the same schedule of faricimab to aflibercept dosed every 8 weeks. Results indicated that more than 70% of patients could be maintained on faricimab injections delivered every 12 weeks during the first year and that more than 50% could be maintained on a 16-week injection interval.[13] There were similar visual and anatomic improvements between the treatment arms and in both AMD and DME.

GENE THERAPY

Another disruptive strategy is gene therapy to autoproduce anti-VEGF. This form of therapy will be delivered via a subretinal or suprachoroidal route.

RGX-314. This agent produces a ranibizumab-like Fab protein that sequesters VEGF. RGX-314 (Regenxbio) is in phase 2 trials for suprachoroidal delivery for nAMD (AAVIATE) and diabetic retinopathy (ALTITUDE) and a phase 1/2a trial for subretinal injections for nAMD. A phase 1/2a trial of RGX-314 demonstrated that treatment with a single injection was well tolerated by five different dose cohorts. Visual and anatomic status was maintained with few or no rescue injections depending on the cohort.

ADVM-022. This agent produces an aflibercept-like protein. ADVM-022 (Adverum) is in parallel trials, phase 2 for diabetic retinopathy (INFINITY) and phase 2b for nAMD. The phase 1 OPTIC trial of ADVM-022 demonstrated its safety; mild to moderate intraocular inflammation experienced by a subgroup was managed with topical steroids. Preliminary data indicated a preservation of visual acuity and anatomy without the need for a rescue injection.[14]

CONCLUSION

The pursuit of controlled therapeutic release reflects a great unmet need. Current phase 3 clinical trials may extend interval dosing from quarterly to biannually. The increased efficacy and duration of new therapeutics could decrease the individual treatment burden and thus positively disrupt the current burdensome care regimens for patients with retinal vascular diseases. ■

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