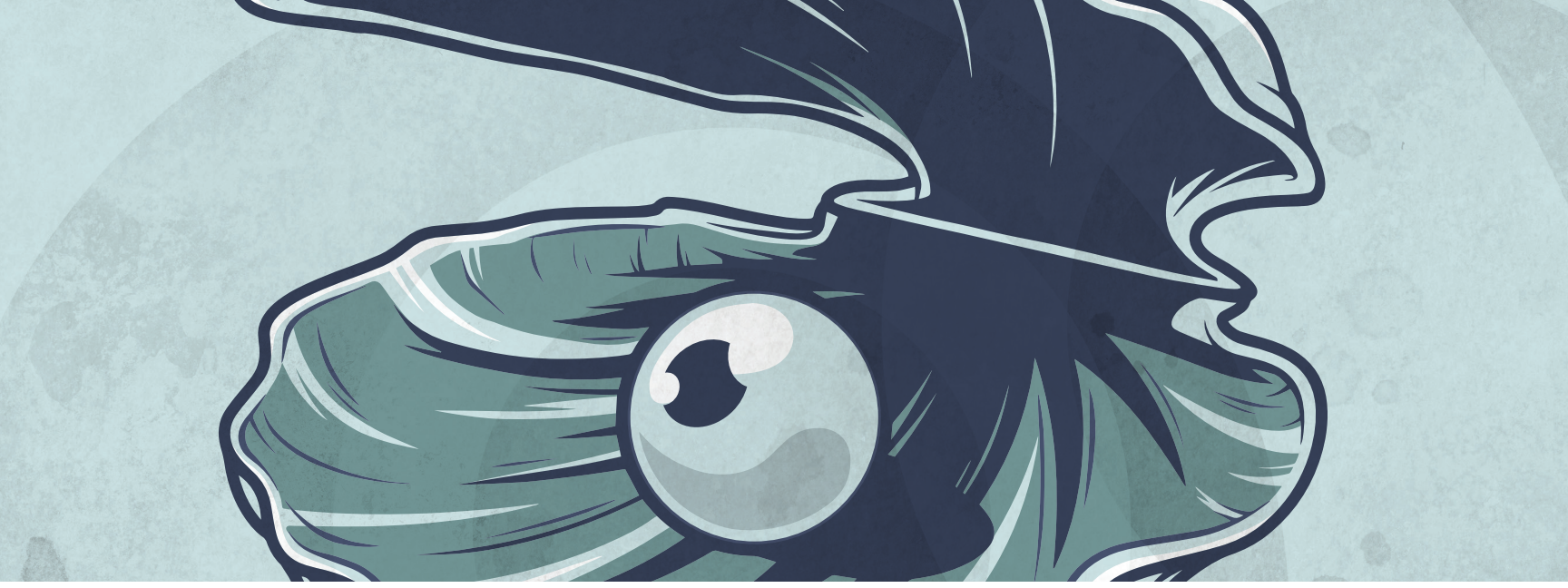

AN ANTI-VEGF TIMELINE

An overview of this form of therapy's early days, how the agents are used today, and what the future may hold.

BY JILL GOTTEHRER, OD, FAAO

Under metabolic stress, the retina and retinal pigment epithelium release vascular endothelial growth factor (VEGF) into the eye.[1] VEGF promotes vascularization by increasing vessel permeability, leading to the growth of new blood vessels.[2,3] Aberrant vessel growth and vessel occlusion can also occur.[2]

The efficacy of anti-VEGF therapy has transformed the treatment of vitreoretinal diseases, including wet age-related macular degeneration (AMD), choroidal neovascularization, diabetic retinopathy (DR), diabetic macular edema (DME), and macular edema secondary to retinal vein occlusion (Figures 1–3). The goal of therapy is to block VEGF, inhibit the growth of abnormal vessels, and reduce vision loss.

THE EARLY ANTI-VEGF DAYS

Pegaptanib (Macugen; no longer available) became the first intravitreal agent approved for the treatment of wet AMD in 2004. After the FDA approved bevacizumab (Avastin, Genentech) for colon cancer later that year,[4] eye care providers began using the drug off-label to treat retinal diseases such as AMD. Bevacizumab has been found to improve patients' visual acuity as well as their OCT and angiographic findings.[5]

CURRENT PRACTICE

Bevacizumab, ranibizumab (Lucentis, Genentech), and 2 mg aflibercept (Eylea, Regeneron Pharmaceuticals) are the three anti-VEGF medications used most frequently in the United States. Ranibizumab and 2 mg aflibercept are FDA approved for the treatment of wet AMD, DR, and macular edema secondary to retinal vein occlusion; ranibizumab is also approved to treat myopic choroidal neovascularization.[6,7] All three anti-VEGF agents are administered every 1 to 3 months based on the patient's response to treatment.[8]

In recent years, the goal of drug development in this area has been to improve patients' visual outcomes with less frequent treatment.

Brolucizumab

In 2019, the FDA approved brolucizumab-dbll (Beovu, Novartis) for the treatment of wet AMD and DME. Concerns subsequently arose regarding an increased risk of intraocular inflammation with the drug's use. A post-hoc analysis demonstrated an approximately 4.5% risk of intraocular inflammation, delaying this agent's implementation in clinical settings.[9]

When used in select patients to treat DME, brolucizumab is typically administered every 6 weeks for the first five doses, followed by a maintenance dose every 8 to 12 weeks. For wet AMD, brolucizumab is administered every 4 weeks for the first three doses, followed by every 8 to 12 weeks.[10]

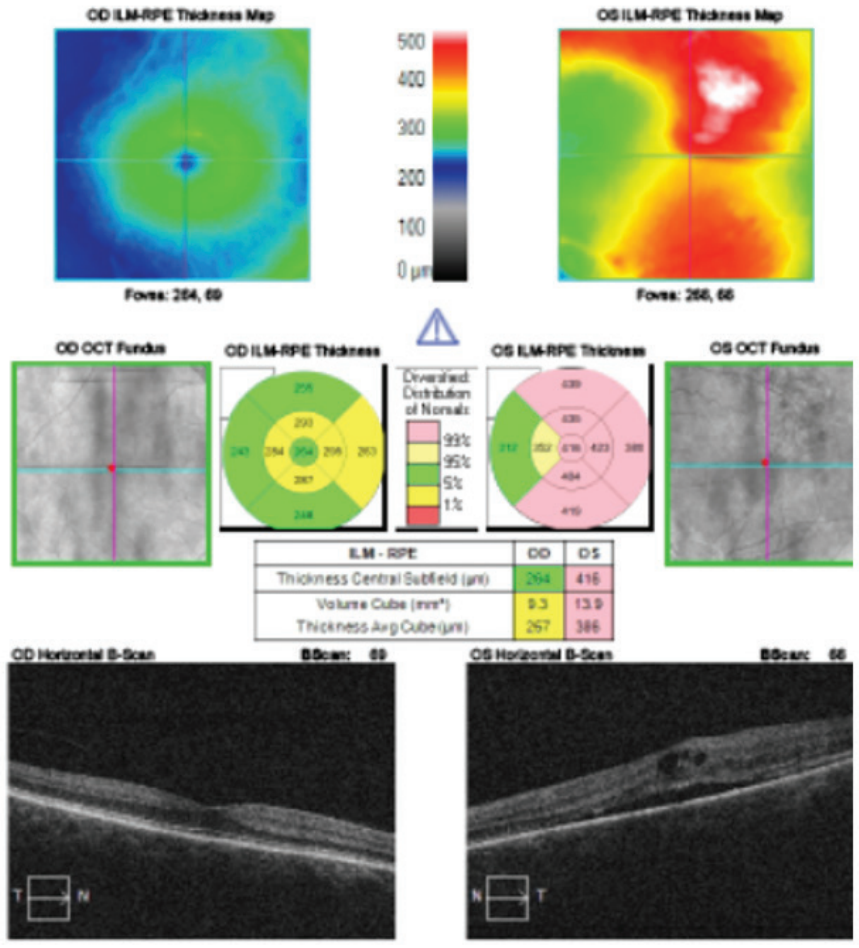

Figure 1. A 67-year-old woman presented with a left branch retinal vein occlusion and macular edema. She was successfully treated with anti-VEGF therapy.

Faricimab

The FDA approved faricimab-svoa (Vabysmo, Genentech) in 2022 for the treatment of wet AMD and DME. The drug targets both VEGF and angiopoietin-2, another proangiogenic molecule, making faricimab the first bispecific intravitreal anti-VEGF agent. In clinical trials, dosing was extended to every 16 weeks in approximately 50% of patients with wet AMD and DME.[11,12]

High-Dose Aflibercept

In 2023, the FDA approved 8 mg aflibercept (Eylea HD, Regeneron) for the treatment of wet AMD, DME, and DR. The recommended regimen is monthly injections for the first 3 months, followed by treatment every 8 to 16 weeks for wet AMD and every 8 to 12 weeks for DR.

The PULSAR trial evaluated the efficacy of 8 mg aflibercept in patients with wet AMD and found that the higher-dose formulation allowed extended dosing intervals and drying of retinal fluid.[13] The PHOTON study demonstrated the safety and efficacy of extended dosing intervals with 8 mg aflibercept in patients with DME.[14]

Port Delivery System

The port delivery system with ranibizumab (Susvimo, Genentech) is a surgically implanted, refillable intraocular device that can continuously and slowly deliver a high concentration of ranibizumab (up to 100 mg/mL). The system is FDA approved for the treatment of wet AMD and DME. In a phase 3 trial for wet AMD, in-office refills were given every 6 months.[15]

BIOSIMILAR AGENTS

Because bevacizumab, ranibizumab, and aflibercept have been available for more than a decade, their patents are expiring, allowing the development of biosimilars. To gain FDA approval, anti-VEGF biosimilars must have purity, efficacy, and safety equal to that of established anti-VEGF therapy. Unlike a generic drug, biosimilars do not contain the same active ingredients as the approved biologic medications.

No biosimilar agents for bevacizumab are currently FDA approved for ophthalmic use, but several are in development. The FDA has approved ranibizumab-nuna (Byooviz, Biogen) and ranibizumab-eqrn (Cimerli, Sandoz), and other biosimilar agents for ranibizumab are in development. Aflibercept-ayyh (Pavblu, Amgen),[16] aflibercept-jbvf

AT A GLANCE

- Anti-vascular endothelial growth factor (VEGF) therapy has revolutionized the treatment of vitreoretinal diseases.
- The aim of treatment is to inhibit the growth of abnormal vessels and reduce vision loss.
- A goal of current research on anti-VEGF therapy is to ease the burden on patients by reducing the frequency of treatment.

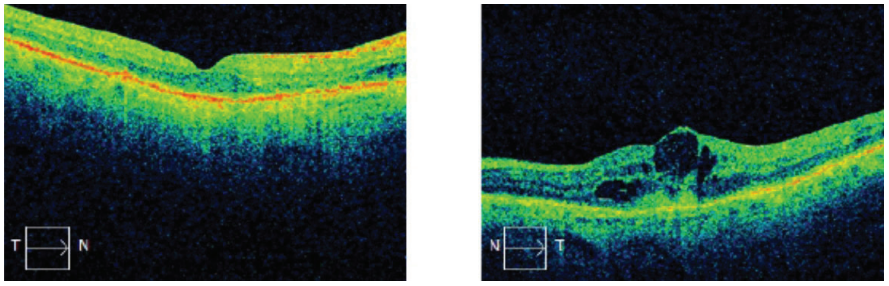

Figure 2. An 80-year-old man with DME was successfully treated with anti-VEGF therapy.

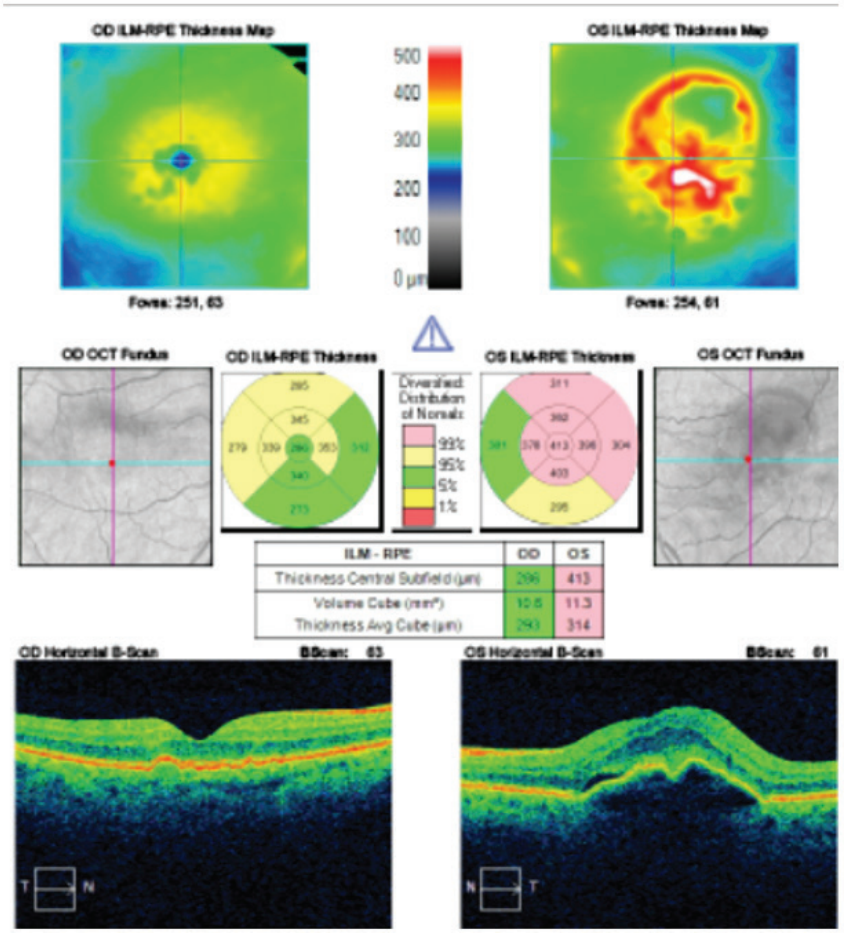

Figure 3. A 73-year-old man with wet AMD of the left eye began anti-VEGF injections.

(Yesafili, Biocon Biologics), and aflibercept-yszy (Opuviz, Biogen) have received FDA approval but are not yet available in the United States.

GENE THERAPY

Recombinant adeno-associated virus-mediated gene therapy is being explored for the treatment of wet AMD and DME. The use of a viral vector that expresses an anti-VEGF protein allows long-term transgene expression following a single intravitreal, suprachoroidal, or subretinal injection. ABBV-RGX-314 (Regenxbio/Abbvie), ixo-vec (ixoberogene soroparvovec, Adverum Biotechnologies), and 4D-150 (4D Molecular Therapeutics) are all in phase 3 clinical trials, with several other drug candidates in earlier phases of investigation. The goal is to reduce the frequency of treatment compared with currently available options.

OPTOMETRISTS' ROLE IN TREATMENT

Although optometrists do not perform anti-VEGF injections, they play a pivotal role in providing guidance to patients regarding how the procedure is performed and any complications that may arise. More importantly, optometrists encourage patients to adhere to prescribed anti-VEGF therapy to optimize their visual outcomes and quality of life. ■

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