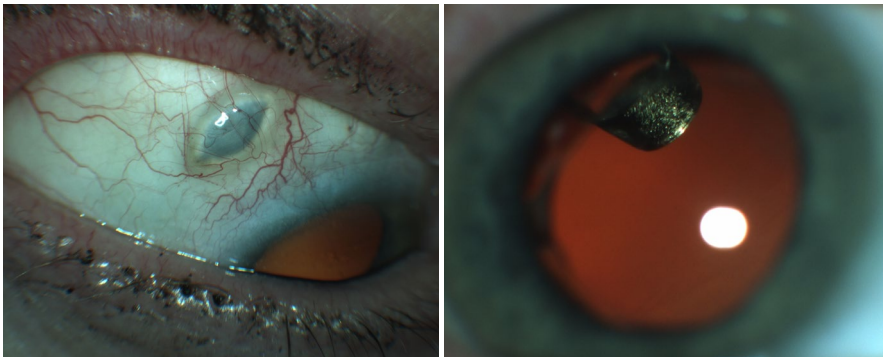
Two New Tools to Treat Wet AMD

Intravitreal anti-VEGF therapy has proved successful in maintaining and often improving VA in patients with neovascular age-related macular degeneration, as well as other conditions including diabetic macular edema (DME). Yet the treatment burden is high, both in cost and frequency of administration.

Now, two recently approved treatments—Vabysmo and Susvimo (both Genentech)—hold promise for reducing this burden.

"If we can consistently give patients three or four months between injections, that will reduce the burden," said Dante Pieramici, MD, at the California Retina Research Foundation in Santa Barbara, California. The most important benefit of longer treatment intervals is that it can be easier for patients to adhere to the regimen and thus may improve long-term, real-world visual outcomes, he said.

Because Vabysmo and Susvimo have been approved for use very recently, retina specialists are proceeding cautiously as they learn which patients are the best candidates and become familiar with the nuances of administering the new therapies.



SUSVIMO. *Right eye of a patient who has a Susvimo implant.*

Novel Compound: Vabysmo

The FDA approved Vabysmo (faricimab-svoa) in January 2022. The drug is a bispecific antibody that blocks both VEGF-A and angiopoetin-2, proteins which lead to leakage and swelling in the eye.

Patient selection. Retina specialists say they turn to Vabysmo for wet AMD patients for whom standard-of-care medications are not working. "I am using it with those who haven't responded to treatment the way I'd like them to," said Purnima S. Patel, MD, at Ophthalmology and Retina Associates in Atlanta. "That means they have fluid, or they still need monthly injections."

"We're hopeful from the phase 3 trials [which compared faricimab with aflibercept] and early clinical experience that we'll be able to dry patients out a little better with faricimab as a more durable and slightly more potent drying agent," said David Eichenbaum, MD, at Retina Vitreous Associates in St. Petersburg, Florida. He has started some patients on Vabysmo if they have been underperforming on Lucentis, Avastin, or Eylea. In his practice, aflibercept patients comprise the bulk of those who switch to Vabysmo. This is because most of the patients in his clinic who have fluid despite high-frequency injections and those who cannot extend have made their way to aflibercept. He noted that the majority of early Vabysmo patients whom he has seen for follow-up visits are doing well—either the retina is drier, if there was fluid, or they are able to go longer between treatments than with standard-of-care therapies.

Dr. Patel also considers each patient's overall health and lifestyle when she is evaluating whether to switch someone to Vabysmo. She pointed out that patients with mobility or transportation challenges may be especially likely to benefit from expanded intervals of treatment.

Treatment. Pivotal studies TENAYA and LUCERNE found that faricimab, administered at intervals up to four months, was noninferior to Eylea (aflibercept) administered at two-month intervals.[1] Two-year data show that the agent is fairly durable, meaning that

BY KATHRYN MCKENZIE, CONTRIBUTING WRITER, INTERVIEWING **DAVID A. EICHENBAUM, MD, PURNIMA S. PATEL, MD,** AND **DANTE PIERAMICI, MD.**

David A. Eichenbaum, MD

nearly 80% of patients [in the phase 3 studies] could go at least three months between injections, and 60% of the patients would get up to four months in treatment with faricimab,[2] said Dr. Pieramici, who was involved in these trials. He added, "I think the anatomical results are better for some of the faricimab patients when you compare them on a head-to-head basis [with Eylea] after the loading doses."

Adverse effects. However, he is still watching for any adverse effects, particularly in light of the problems with Beovu (brolucizumab).[3] "Is Vabysmo going to be more inflammatory than standard-of-care medications? The truth is we just don't know." Phase 3 data suggest that faricimab may have slightly more potential for inflammation,[1] but that inflammation will be mild to moderate, he said. So far, the incidence of "real-world inflammation" likewise appears to be low, he added.

Treat-and-extend. Dr. Eichenbaum describes himself as an "ardent treat-and-extender" with patients who are on Lucentis, Eylea, and Avastin. He was also involved in the Vabysmo clinical trials and plans to use treat-and-extend with Vabysmo as he sees how his patients respond to the new medication. "I am gradually extending my Vabysmo patients out with a goal of achieving four-month extension for a lot of them. I hope to see a proportion of four-month extenders similar to the proportion that we see in the Vabysmo pivotal trials."

Practice. Injecting Vabysmo is a little different from current standard-of-care drugs in that it is not yet available in a preloaded syringe, said Dr. Pieramici. Because there is not a lot of the drug in the vial, he said, "you have to be careful when drawing it up. Otherwise, you're going to have a lower volume and thus a lower dose of the drug."

Both Dr. Pieramici and Dr. Eichenbaum note that the drug tends to be more viscous and takes slightly more force to inject. Dr. Pieramici recommends using a 30-gauge needle rather than a 32-gauge. Dr. Eichenbaum uses a Luer-lock syringe to prevent the needle from popping off during the injection, and he typically injects with a 33-gauge needle.

New Delivery System: Susvimo

Approved in October 2021, Susvimo is a refillable reservoir the size of a grain of rice. It is loaded with ranibizumab in the operating room before implantation and provides continued delivery of the drug. Refills of the device are carried out in the clinic. The implant is designed to last the life of the patient.[4]

Patient selection. Patients who are highly intolerant of injections or those who require frequent injection even on Vabysmo would make good candidates for Susvimo, said Dr. Eichenbaum.

Dr. Pieramici foresees Susvimo as an alternative for a small number of patients who are currently receiving frequent injections. He said that he thinks the rate of adoption will be low because Vabysmo is also an option, and he believes most patients would opt for a more durable injection rather than surgery. Among those who are good Susvimo candidates, Dr. Pieramici looks for motivated patients who have healthy conjunctiva.

Procedure. Intraocular implantation is done as outpatient surgery under local anesthesia and takes less than an hour. "The procedure is relatively straightforward but requires very meticulous surgical technique," said Dr. Pieramici, who was involved in the Susvimo LADDER clinical trials. Steps in the surgery include a conjunctival peritomy, a precisely measured scleral cut-down, external laser cautery, pars plana incision, and placement of the implant,[5] with a meticulous conjunctival closure to prevent erosion or retraction around the implant. He recommends that ophthalmologists who want to learn to implant the device study the procedure carefully and take advantage of additional training provided by Genentech, with a surgical device specialist if necessary.

Dr. Eichenbaum, who was also involved in clinical trials for Susvimo, noted that there is a "learning curve" with implantation. "I think it's something, essentially, that all retina surgeons can do; they just need appropriate coaching and training to do it safely and efficaciously."

Bilateral implantation? To date, Dr. Eichenbaum has not implanted Susvimo bilaterally; however, he has one patient who is interested. He noted that, at least for now, he would wait at least one month, maybe two, before implanting the device in the second eye. This, he said, is because "we saw more adverse events clustered relatively soon after implantation in the phase 2, phase 3, and extension trials." Before performing second eye surgery, he would watch for quiescence of the first eye and "good, stable conjunctival coverage of the implant."

Post-op. After the implant procedure, patients should protect their eyes and avoid heavy jarring exercise during the first week after the implant. "I had a patient who was punched in that eye shortly after the procedure. He did fine, the implant did fine, but it was a wake-up call [about the importance of post-op eye safety]," said Dr. Pieramici. He recommends safety goggles for those who play sports.

Treatment. Dr. Pieramici said that patients who have the device "love it" because it eliminates the need for frequent injections. "We're seeing with the Susvimo implant that there are patients who come in at six months who don't appear to need it refilled, and they can go potentially longer—as we saw in the LADDER trial." The Velodrome study[6] currently under way in Europe is focused on refills being done every nine months, he noted.

Adverse effects. Conjunctival retraction and erosion were issues that occurred in 4% to 5% of patients in Susvimo trials, so these are not infrequent, said Dr. Pieramici.[7] However, he suggested that these figures reflect older data and that better surgical technique should help mitigate these issues. Retraction and erosion are risk factors for infections; in clinical trials, 2% of patients experienced at least one episode of endophthalmitis after receiving the implant,[7] which is higher than postinjection endophthalmitis rates.[8]

In response to those in the retina community who have expressed concern that the reservoir could become infected, erode, or extrude, Dr. Eichenbaum said, "These are certainly risks of the device. The most important thing is to be well-versed in the benefit-risk

profile, as well as how to monitor for and manage exposure of the implant. We have developed robust techniques for salvaging exposed implants in the clinical trials, and I think we will continue to improve our Susvimo safety as a community over time."

Practice. Currently, Dr. Pieramici is checking patients' implants every two months, with refills every six months. He's inclined to extend the implant checks to every three months if there are no other problems such as conjunctival erosion or retraction around the device.

Refills. Good visualization, illumination, and magnification are key to successful Susvimo refills, said Dr. Eichenbaum, who uses loupes for precise perpendicular targeting of the center of the implant. It is vital to train staff to have the necessary items ready, including an eyelid speculum, topical anesthetic, a cotton-tipped applicator, and refill materials.

"It's very important to position the patient correctly," said Dr. Pieramici, who typically has the patient lie back in the chair. He uses the slit lamp first to visualize the implant septum. Then he puts on a headset with magnification and lighting and makes sure that the refill needle enters the septum perpendicularly. It is important to stand on the side of the patient opposite the implant to position the needle properly, he said.

Clinical Decision-Making

Should ophthalmologists adopt new drugs or protocols if the ones they are now using with patients are working well, and if treat-and-extend regimens with standard-of-care treatments are proving successful? At this early stage, the current thinking seems to be that patients may be switched if standard-of-care treatments are not satisfactory or if patients are seeking to potentially increase the intervals between their treatments. However, for those who require less frequent visits, said Dr. Patel, "It's going to be life-changing, and if we can get better outcomes with the patients that we couldn't dry up [with standard-of-care treatments], that's great too."

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4 Ranade SV et al. *Drug Deliv.* 2022;29(1):1326-1334.
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6 A Study of the Efficacy, Safety, and Pharmacokinetics of a 36-Week Refill Regimen for the Port Delivery System With Ranibizumab in Patients With Neovascular Age-Related Macular Degeneration (Velodrome). clinicaltrials.gov/ct2/show/NCT04657289.
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8 Li T et al. *JAMA Ophthalmol.* 2021;139(10):1080-1088.

Dr. Eichenbaum is director of research for Retina Vitreous Associates and collaborative associate professor of ophthalmology at the Morsani College of Medicine in St. Petersburg, Fla. *Relevant financial disclosures: Genentech: C,I,S; Kodiak: C,I; Regeneron: C,S.*

Dr. Patel is founder of Ophthalmology and Retina Associates in Atlanta. *Relevant financial disclosures: None.*

Dr. Pieramici is director of the California Retina Research Foundation and partner in California Retina Consultants of Santa Barbara, Calif. He was principal investigator for the Archway, Ladder, and Portal trials. *Relevant financial disclosures: Genentech: C,S; Regeneron: C,S.*

See disclosure key, page 8. **For full disclosures,** see this article at aao.org/eyenet.

ABOUT COST. For a recent study about Susvimo costs, see "Anti-VEGF Cost Analysis: Implant Versus Injections," in the Journal Highlights section on page 21.

Don't miss **Retina Subspecialty Day, Section XI: Neovascular AMD. When:** Saturday, Oct. 1, 9:25-10:56 a.m. **Where:** Arie Crown.