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WHAT'S NEXT FOR nAMD?

A FOCUS ON THERAPIES IN THE PIPELINE

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This continuing medical education (CME) activity captures content from a virtual round table discussion.

ACTIVITY DESCRIPTION

Newer classes of drugs are being evaluated to treat age-related macular degeneration (AMD), along with longer duration of currently approved drugs. This supplement reviews the current status of AMD treatments and improved diagnostic technologies, with a focus on therapies in the pipeline.

TARGET AUDIENCE

This certified CME activity is designed for ophthalmologists and retina specialists involved in the treatment and management of patients with retinal diseases.

LEARNING OBJECTIVES

Upon completion of this activity, the participant should be able to:

- **Describe** the differences in real-world clinical outcomes with those from prospective clinical trials.
- **Develop** individualized treatment regimens for patients with AMD who may benefit from treatments with longer duration.
- **Discuss** newer compounds in development or recently approved compounds that are designed to improve visual outcomes while decreasing treatment burden.

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1. Please rate your confidence in your ability to manage patients with age-related macular degeneration (AMD) (based on a scale of 1 to 5, with 1 being not at all confident and 5 being extremely confident).

a. 1
b. 2
c. 3
d. 4
e. 5

2. Please rate how often you apply the latest treatments in AMD (based on a scale of 1 to 5, with 1 being never and 5 being always).

a. 1
b. 2
c. 3
d. 4
e. 5

3. When comparing pivotal trial evidence of anti-VEGF treatment to real-world evidence, which of the following is NOT true:

a. Real-world visual gains are more modest than pivotal trial visual gains
b. Real-world evidence demonstrates fewer injections per year compared to pivotal trials
c. Real-world evidence demonstrates similar visual gains compared to pivotal trials
d. Pivotal trial evidence has demonstrated 7 to 11 letter improvement with anti-VEGF treatment over the course of a year

4. All of the following steps are important for implantation of the port delivery system except:

a. Adequate uveal coagulation
b. Precise wound size
c. No Tenon closure
d. Adequate conjunctiva and tenons closure

5. An 81-year-old man receives ranibizumab injections every 4 weeks for neovascular AMD. He is having difficulty maintaining his office visit schedule and asks about other options. Which of the following is a reasonable option for this patient?

a. Stop ranibizumab therapy
b. Explain the port delivery system and reassure the patient this therapy may become available soon
c. Start bevacizumab therapy
d. Start aflibercept therapy

6. According to the LADDER study, what was the median time to refill for the port delivery system in the high-dose group?

a. 3 months
b. 6.5 months
c. 15.8 months
d. 24 months

7. RGX-314 is gene therapy to turn the eye into an anti-VEGF biofactory. How is this gene therapy delivered?

a. Intravitreally
b. Intravenous delivery
c. Intracamerally
d. Subretinal delivery

8. What percentage of patients remained injection-free with improved visual acuity and stable OCT over 2 years according to phase 1/2a trial data on RGX-314?

a. 20%
b. 30%
c. 40%
d. 50%

9. ADVM-022 is a gene therapy treatment that encodes for aflibercept using a variant of AAV2 as a vector. How is this therapy administered?

a. Intravitreally
b. Suprachoroidal delivery
c. Intracamerally
d. Subretinal delivery

10. A 79-year-old man with neovascular AMD is on monthly aflibercept with well controlled disease. He is interested in discussing the potential for future gene therapy options to treat his disease. He is very reluctant to undergo any procedure in the operating room for treatment. Which potential future options may be the best for this patient?

a. Intravitreal RGX-314
b. Intravitreal ADVM-022
c. Subretinal RGX-314
d. Subretinal ADVM-022

What's Next for nAMD? A Focus on Therapies in the Pipeline

Anti-VEGF treatments have revolutionized the treatment of patients with neovascular age-related macular degeneration (nAMD), improving outcomes and saving the sight of millions.[1] Although anti-VEGF injections are undoubtedly safe and effective, the majority of patients require very frequent treatments.[2] The next treatment revolution for wet, or neovacular, AMD will focus on drug durability. Multiple sustained-release approaches are in development, including implants, microparticles, and gene therapy. Although "not ready for prime time," these emerging treatments could alter the wet AMD landscape if brought to market. The following continuing medical education activity brings together thought leaders in retina to discuss the most promising candidates in the pipeline.

—Arshad M. Khanani, MD, MA — Moderator

THE CURRENT WET AMD ARMAMENTARIUM

Q | ARSHAD KHANANI, MD, MA: There is no doubt that anti-VEGF agents such as bevacizumab, aflibercept, ranibizumab, and most recently brolucizumab, have revolutionized the treatment of patients with nAMD, improving outcomes in terms of vision stabilization or gains. How do you currently manage wet AMD patients? What agents are you using?

CARL D. REGILLO, MD, FACS: For more than a dozen years now, we've had anti-VEGF injectable drugs such as bevacizumab, aflibercept, and ranibizumab—all of which have good, comparable efficacy and safety.[3] Durability, however, is rather limited with these medicines. Most retina specialists use a treat-and-extend approach for managing wet AMD with all three agents in an attempt to achieve the best visual outcomes with the least amount of treatment burden. With this approach, the patient initially is injected monthly until the macula is dry or mostly dry, and then the treatment interval is slowly increased, typically by 2 weeks, until exudation recurs, at which time the treatment interval is then reduced and adjusted accordingly to maintain optimal exudative control and visual acuity (VA).[4,5]

We ultimately determine an exudative-free interval for each patient. It's a spectrum, ranging from some patients who are treated monthly, to others receiving injections every 12 weeks. Studies have shown that in the maintenance phase, these drugs last 8 to 9 weeks, on average.[6-10]

There's some evidence that aflibercept may be slightly more durable than ranibizumab or bevacizumab, but they're all comparable.[11,12] The US FDA approved brolucizumab in 2019 based off results of the pivotal HAWK and HARRIER studies, which showed that it dried the retina better than aflibercept.[13,14] There's some indication that brolucizumab may be a bit more durable than the other agents.[15] It's being used to some degree, but not as often at this time because of safety issues.

Q | DR. KHANANI: Dr. Baumal, you recently published in a case series on brolucizumab complications.[16] What are your thoughts on durability and some of the safety concerns?

CAROLINE R. BAUMAL, MD: While we have come a long way in the past 2 decades, not everyone experiences visual improvements with anti-VEGF therapy.[17] Some people still experience progressive vision loss, and others develop geographic atrophy when exudative AMD resolves.[18,19] There are other patients who cannot maintain their treatment interval because it's too burdensome to come in as often as required.[20,21] Our current treatments are good, but they're not perfect.

The phase 3 HAWK and HARRIER trials found that brolucizumab was noninferior to aflibercept with respect to VA at 48 weeks.[13,14] Also, just over 50% of patients were able to extend to dosing of brolucizumab to every 12 weeks after three loading doses. Patients on brolucizumab were also drier on optical coherence tomography (OCT). Brolucizumab seemed positioned to provide additional benefits of durability with reduced fluid on OCT.[22]

However, a few months after FDA approval, there were reports of occlusive retinal vasculitis noted after its use.[23-26] We reported a retrospective, multicenter series of eyes with varying degrees of retinal vasculitis with retinal artery occlusion and intraocular inflammation after brolucizumab.[16] While intraocular inflammation has been noted following intravitreal injection of the other anti-VEGF agents,[27-31] occlusive retinal vasculitis had not previously been reported in a noninfectious setting after anti-VEGF injection. Most patients had symptoms such as mild floaters, blurred or reduced VA, and ocular discomfort and could present up to 4 weeks after the intravitreal injection. Clinical features included vasculitis initially

affecting the retinal arteries often associated with intraocular inflammation and perivenular hemorrhages. The VA at presentation was related to the location of vasculitis where eyes with optic nerve or macular involvement were more severely affected. This was a new finding after injection of an anti-VEGF agent and it serves to remind us that when new treatments come into the ophthalmology space, it is important to observe for potentially rare events that phase 3 studies may be underpowered to parse out.

These reports led Novartis to commission a Safety Review Committee (SRC) to review the HAWK and HARRIER imaging data, noting the combined incidence of intraocular inflammation in the 3-mg and 6-mg brolucizumab groups at 4.6%, with a 2.1% incidence of occlusive retinal vasculitis in the eyes with intraocular inflammation.[32,33] Using imaging data from the HAWK and HARRIER studies, the SRC found that incidence of intraocular inflammation with brolucizumab treatment was 4.6%, which is close to what was reported in the trials (4.4%). Despite a low overall incidence (<1%) of at least moderate vision loss related to intraocular inflammation, the SRC found that the incidences of both retinal vasculitis and retinal vascular occlusion were higher than what was reported by the study investigators. From 1,088 eyes treated with brolucizumab, 23 (2.1%) eyes had intraocular inflammation with retinal vasculitis and retinal vascular occlusion; approximately, From this subpopulation, seven eyes (30%) developed at least moderate vision loss (defined as ≥15 ETDRS letter loss) and five eyes (22%) developed severe vision loss (≥30 ETDRS letter loss). While reports of intraocular inflammation and occlusive retinal vasculitis were higher in brolucizumab treated eyes, the overall rates of moderate to severe visual loss were similar between brolucizumab and aflibercept treated eyes.[32,33]

MANAGING PERSISTENT FLUID: THE GREAT DEBATE

Q | **DR. KHANANI:** What is your target for anatomical success in a patient with exudative (wet) AMD, and how much fluid do you tolerate in your patients?

CARL C. AWH, MD: I prefer to see complete resolution of intraretinal fluid. Complete resolution of subretinal fluid is preferable, but we know that patients with persistent subretinal fluid can maintain quite good vision.[34] For example, in HARBOR, at 1 and 2 years, patients with residual subretinal fluid (SRF) were just as likely to have a best corrected visual acuity (BCVA) of at least 69 letters as patients whose fluid resolved.[34] The VIEW study also showed little difference in visual gains between arms, even though there was a significant difference in the number of patients who were dry versus those with persistent fluid.[10] Recently, the FLUID study looked at this phenomenon directly.[35] Researchers concluded that VA was comparable between patients who "tolerated" fluid and those who didn't, and the fluid-tolerant group had fewer injections overall.

Therefore, I'm not particularly aggressive in my treatment of small stable amounts of SRF in patients with good VA while receiving monthly injections. I do have a few patients where the SRF seems to accumulate rapidly, with an associated loss of vision. I'll treat those patients more aggressively, even at intervals of 2 or 3 weeks.

One of my partners, Eric Schneider, MD, presented the TRISTAR study during the 2020 American Society of Retina Specialists Virtual Annual Meeting. He treated a series of patients with refractory AMD with aflibercept every 2 weeks.[36] Patients experienced a regression of the SRF and a modest improvement in vision.

Although it's probably better to have less fluid, this potential benefit must be balanced against the risk and expense associated with each injection. These concerns have been heightened by the COVID-19 pandemic, when we don't want our elderly patients leaving their homes and coming to medical offices any more than necessary.

Q | **DR. KHANANI:** I agree. We always want to dry the intraretinal fluid (IRF) completely, as that is associated with worsening vision and increasing rates of macular atrophy,[37,38] but we have a bit more tolerance for SRF if it persists despite frequent injections. There has been some discussions about SRF being "protective," what are your thoughts?

DR. REGILLO: The goal should still be resolution of exudation. We should interpret these retrospective subgroup analyses from studies like CATT, IVAN, VIEW, and HARBOR with some caution.[10,39-42] I find it difficult to believe that SRF is protective or advantageous, even though there have been some reports of improved visual outcomes correlated with the presence of SRF.

As Dr. Awh mentioned, a small sliver of fluid that doesn't go away or fluctuate in a patient with very good VA is probably well tolerated. But when it fluctuates, when I see it increase, when I see vision affected, I don't believe that it is good for the patient in the long run. There's new evidence suggesting that fluctuations, in terms of degree and frequency, are detrimental to visual outcomes.[43] We must be cautious. I think it's best to keep signs of exudation, including SRF, to a minimum.

DR. KHANANI: Dr. Baumal, you're an imaging expert. How are you using OCT and OCT-angiography (OCTA) to manage patients with persistent fluid?

DR. BAUMAL: OCT and OCTA are invaluable to manage our patients. I use OCTA in most patients to evaluate for choroidal neovascularization (CNV).[44] The flow overlay feature, which places the OCTA flow data onto the structural OCT, can demonstrate if a retinal pigment epithelial detachment (PED) is vascularized.[45] OCTA is helpful to confirm the presence of CNV while fluid on OCT helps to determine CNV activity. It is important to assess the OCT line scans for IRF, SRF, and changes in retinal volume and thickness on the cube scan. The CATT study showed that IRF had a more deleterious effect on vision than SRF.[46] If there is residual persistent SRF, I try to see the patient a week after an anti-VEGF injection to see if the SRF is anti-VEGF responsive.

OCT imaging can help exclude retinal disorders that mimic nAMD but do not respond to anti-VEGFs. Indocyanine green angiography has utility to assess for polypoidal choroidal vasculopathy in eyes with incomplete response to anti-VEGFs and I might combine photodynamic therapy with my anti-VEGF injection

in these eyes.[47,48] As clinicians, we tend to lump all patients with nAMD together but it may be a heterogeneous disease with variable patient responses. In the future, imaging and machine learning may be helpful to distinguish AMD subtypes, and this may help to direct our treatment decisions.

DR. KHANANI: I agree that we need to learn more about the patient subtypes. I don't use OCTA every time because it can be time-consuming in a busy clinic, but it is clearly beneficial in patients who either don't show much leakage on fluorescein angiography (FA).

SUSTAINED-RELEASE THERAPIES: A GAME CHANGER IN WET AMD MANAGEMENT

Implants

Q | DR. KHANANI: Dr. Awh, you've been involved with the port delivery dystem (PDS) with ranibizumab from the start, presenting the first results from the LADDER trial.[49,50] Can you tell us about the PDS technology and what did LADDER and ARCHWAY tell us about it?

DR. AWH: The PDS is a permanent, refillable, intraocular implant that is surgically implanted at the pars plana and filled with a customized, concentrated formulation of ranibizumab. Ranibizumab is released at therapeutic concentrations into the vitreous for many months. In LADDER, we saw that a significant number of patients went more than a year before needing a refill exchange, with a median time to first refill of 15.0 months. The refill exchange is an office-based procedure using a special dual-lumen needle that exchanges the contents of the PDS with new ranibizumab solution.[49] LADDER helped us refine the implantation and refill procedures and learn how the PDS worked at different drug concentrations, which informed the design of the phase 3 ARCHWAY study.[51,52]

Top-line data from ARCHWAY showed that the PDS, using 100 mg/mL of ranibizumab and refill exchanges every 6 months, achieved equivalent visual outcomes and similar anatomic outcomes as monthly injections of standard-dose ranibizumab.[51,52] These are exciting data because real-world experience has consistently demonstrated that patients treated with intravitreal injections fail to achieve the results obtained in pivotal clinical trials. There are many reasons for this, but we know that treatment burden is a major impediment to achieving ideal outcomes for our patients.[53]

As Dr. Baumal astutely pointed out earlier, we shouldn't expect to understand the full spectrum of risks and benefits of a new drug or device until after it's released into the market. With ARCHWAY, we found the type of complications one should expect with a surgical procedure. In my opinion, the complication rate was acceptable, particularly given that the surgeries were performed by investigators for whom this was a completely new procedure. Mild vitreous hemorrhage was observed in about 5% of eyes. These hemorrhages cleared in every case without surgical intervention.

There were four cases of endophthalmitis among the 248 patients who were randomized to the PDS. One of those four cases occurred in a patient who cleaned out a septic tank and got endophthalmitis with *Enterococcus faecalis*, a highly virulent organism that resulted in irreversible vision loss for that patient. The other three patients had good outcomes with a return of VA to baseline in each case. Each of these three cases was associated with conjunctival retraction.

Given this association of conjunctival retraction and endophthalmitis, I think we can reduce the risk of endophthalmitis with careful attention to the surface of the eye. We can significantly reduce the likelihood of a conjunctival retraction with meticulous management of the conjunctiva and Tenon capsule during the implantation surgery. We'll also have to identify and address early evidence of conjunctival retraction or erosion during the postoperative period. With these steps, I think we can lower the complication rate. We should also keep in mind that although the rate of endophthalmitis will likely remain higher for a surgical procedure than for a single intravitreal injection, the risk to vision associated with intravitreal injections is more from irreversible vision loss associated with delayed or missed injections than from endophthalmitis.

DR. KHANANI: Monthly ranibizumab is the gold standard and sets a very high bar in terms of efficacy. Having the PDS be equivalent and noninferior shows this technology has the potential for good visual outcomes in the real-world setting. Dr. Regillo, you are also very involved in the PDS program. Do you have anything to add to Dr. Awh's summary?

DR. REGILLO: I agree with Dr. Awh's assessment that LADDER and ARCHWAY demonstrated tremendous results in terms of durability, efficacy, and anatomic outcomes. In ARCHWAY, more than 98% of patients in the PDS arm went from baseline to the first refill without needing supplemental intravitreal ranibizumab injections.[52] This tells us that we're achieving excellent durability in the vast majority of our patients.

I also agree that the side-effect profile is acceptable and can be improved upon. The surgery itself is straightforward, and any vitreoretinal surgeon can easily adopt it into practice. It does take some special attention to certain unique steps in the operation in order to minimize postoperative complications. For example, exact scleral incision size is critical; the full thickness scleral incision must be precisely 3.5 mm. If it's more, you potentially risk the device moving or dislocating. If it's less, you may increase the risk of vitreous hemorrhage postoperatively.

Good cauterization of the exposed pars plana uveal tissue with an endolaser probe applied externally at the time of surgery is very important to keep the rates of vitreous hemorrhage low. This modification from the original procedure used at the start of the LADDER study tremendously improved the rates of postoperative vitreous hemorrhage going forward in the clinical trial program. Not only did the rate of hemorrhage drop, the degree also lessened from phase 2 to phase 3. In ARCHWAY, the hemorrhages were mild to moderate and resolved spontaneously. The vitreous hemorrhage

problem improved as we learned more about these important aspects of the surgical procedure.

Lastly, you must carefully manage the conjunctiva and Tenon capsule in an optimal fashion to minimize postoperative erosion or retraction. I can recall in LADDER using only one or two absorbable sutures to close the conjunctiva and Tenon capsule. It's a relatively large 6 x 6 mm conjunctival-Tenon opening to expose the superotemporal quadrant in order to make your scleral incision and insert the port. But in ARCHWAY, we emphasized more secure closure of both conjunctiva and Tenon capsule layers by adding more sutures.

We should be able to decrease the rates of conjunctival retraction even further going forward in practice based on what we have learned from the clinical trials. That's a complication glaucoma surgeons very rarely ever see with glaucoma surgery because their closure is very meticulous. We are learning the best conjunctival closure practices from our glaucoma colleagues, which should help the retraction problem and keep the risk of both retraction and endophthalmitis as low as possible.

As for the refill-exchange procedure performed in the office, it is pretty straightforward, too, but it is very different from the standard intravitreal injection we do with our current anti-VEGF agents. The refill requires a special dual-bore 34-gauge needle. The soft silicone diaphragm on the device which needs to be penetrated with the needle to perform the refill exchange is very small and entry into the device requires a high degree of precision to enter without bending the rather small needle. Using lighted loupes helps to localize the center of the device diaphragm. The angle of approach with the needle is also important. It has to be perpendicular to the plane of the diaphragm. Lastly, it takes a bit of force to insert it, typically more than what's needed for an intravitreal injection through the sclera. None of this is particularly difficult, but it's a different experience requiring a bit more attention to detail and precision.

DR. BAUMAL: One thing that's unique about the PDS program is the use of virtual reality to train surgeons on the PDS insertion and refill techniques and the different surgical scenarios that may be encountered. This standardized virtual approach is something that can be used in the future to teach new surgical procedures and reduce complications. As we gain more experience with the PDS, there will be additional methods to enhance surgical success.

An important consideration is how our colleagues in medical retina will approach the PDS device. Most patients who have received it are very happy and enjoy not having to come to the office as much.

DR. AWH: In ARCHWAY, the average PDS patient had about five intravitreal injections before the implantation procedure, so they were familiar with the injection experience.[52] More than 90% of patients with the PDS preferred it over intravitreal injections. Given the demonstrated vision and anatomic outcomes provided by the PDS, our ability to reduce and manage associated risks will greatly influence its use. The risks are manageable and, as I discussed earlier, can be minimized. The treatment benefit of the PDS, with drug refill exchange every 6 months, are obvious and compelling. In my opinion, the PDS implantation should be done by retina specialists who can perform the surgical technique well. Ongoing monitoring and care of patients with the PDS can be done by retina specialists who are well versed in the management of AMD.

DR. REGILLO: We had fairly extensive training on the PDS surgical and refill techniques in the trials. We also had a surgical liaison during the trial to help guide both the surgical implant and refill exchange procedures. The liaisons were right over your shoulder, going through all the steps with you. In clinical practice, the training will require a mix of modalities, including surgical videos, in-person wet labs, virtual platforms, and the use of a surgical liaison for the first few procedures.

Patient satisfaction was very high in ARCHWAY. We're running some survey research right now with our patients getting injections, and asking them about the pros and cons of continued injections versus the PDS. The PDS is very attractive to patients who receive frequent injections. Physicians are also more likely to offer the PDS to patients who receive injections every 4 to 8 weeks than with patients receiving injections every 10 to 12 weeks. The benefits of the long-acting delivery we're seeing are numerous. It's convenient and it has the potential to improve long-term visual outcomes.

DR. KHANANI: Excellent points. We have also participated in LADDER and ARCHWAY trials and my experience has been similar. There is clearly a learning curve for PDS implantation and the refill-exchange procedure but with advanced surgical training and surgical liaison's input, it can be easily mastered. Also, the patient satisfaction with PDS has been very high in my practice. As far as the trial design is concerned, there has been a lot of criticism about the supplemental ranibizumab treatment criteria in the ARCHWAY trial, where more than 100 µm of fluid was tolerated. Dr. Awh, please provide some insight into this issue.

DR. AWH: Given the results of the phase 2 LADDER trial and the pharmacokinetics of the PDS, the designers of ARCHWAY thought that 100 µm of fluid was a reasonable amount to tolerate. I understand why some would question this threshold, but the excellent outcomes suggest that this appropriately balanced the need to protect vision with the desire to reduce treatment burden. Fewer than 2% of patients received supplemental treatment before the planned refill exchange.

DR. REGILLO: All studies that try to assess durability allow for some recurrent exudation. It may or may not be what we do in practice, but it's different here. The PDS is not a treatment that wears off quickly, such is the case with an intravitreal bolus injection of currently used anti-VEGF agents, nor are we getting recurrences at a high frequency. In LADDER, there was recurrence once every 14 to 18 months on average and that's much less likely to be detrimental to VA than if 100 µm or so of exudation recurs more frequently such as every 4 to 8 weeks.

Microparticles

Q | **DR. KHANANI:** GB-102 is a tyrosine kinase inhibitor (TKI) and is delivered as a microparticle depot formulation of sunitinib malate via an intravitreal injection. Dr. Baumal, can you tell us about GB-102 and the data you've seen so far? What is your take on its safety and efficacy?

DR. BAUMAL: In order to achieve longer durability and visual efficacy, medications that have different mechanisms of action or a combination of medications may be necessary. GB-102 is an intravitreal injectable depot formulation of sunitinib malate that blocks multiple angiogenesis pathways including VEGF receptors 1, 2, and 3. It also blocks all VEGF signals, including VEGF-A, -B, -C, and -D.[54] Interestingly, it works at a different level in the cascade, prior to the VEGF effect. It might have more of a pan-VEGF inhibition. GB-102 is attractive because of its different mechanism of action and because it is a TKI. Oral TKIs have been evaluated in diabetic retinopathy in the past, and they had systemic effects.[55] That's why GB-102 is being evaluated intravitreally.

DR. REGILLO: ADAGIO was a phase 1/2a study, designed in many ways like LADDER: previously treated patients, similar rescue criteria, and a single intravitreal injection of GB-102.[56] It was a dose-escalating study with four dose cohorts (0.25 mg, 0.5 mg, 1 mg, and 2 mg), and patients were followed for 8 months. The trial met its primary endpoints of safety and tolerability. There were no dose-limiting toxicities, serious treatment-related adverse events, or inflammation. Sixty-eight percent of patients went 6 months without needing a rescue and 88% were maintained on a single dose at 3 months.

ADAGIO gave us a hint of biologic effect and the durability that we're hoping for, but there were some problems with particle dispersion and migration into the anterior chamber in 28% of patients. Such migration didn't turn out to be harmful, but it did affect vision temporarily. It may have also reduced efficacy or durability.

A modified version of GB-102 that should help limit particle dispersion is being evaluated in a phase 2b study called ALTISSIMO (NCT03953079). Enrollment is complete, and results are expected in the first half of 2021.[57]

DR. KHANANI: I agree. There was a clear durability signal seen in the ADAGIO trial but safety needed to be addressed. The new optimized GB-102 was then developed for better microparticle adhesion and was tested in the macular edema safety study in patients with diabetic macular edema and retinal vein occlusion (NCT04085341). The study showed significant improvement in particle dispersion in the 1-mg group but 2-mg group still had a significant number of particle dispersion. Hence, the 2-mg dose was discontinued in the ADAGIO study and 1-mg dose was continued.

Dr. Awh, there are clearly cases of particle migration in earlier studies with GB-102. Most of them resolved over time without intervention. However, some patients required anterior chamber washout. If you have a patient who needs a sustained-delivery approach that can last 4 to 6 months and is delivered via intravitreal injection in clinic, would you use GB-102 given the risk of particle migration and floaters?

DR. AWH: The idea of small particles floating around in the anterior chamber concerns me. I can easily think of adverse effects beyond decreased vision and floaters. If a phase 3 study shows that a treatment that can be administered in the office can be as effective and as safe as a treatment that requires a trip to the operating room, that would be very appealing. Let's hope for the best as studies proceed for GB-102 and similar therapies.

DR. REGILLO: Particles should not be visible to the patient. GB-102 or any microparticle-based delivery product won't be well received by patients if it causes significant floaters or obscures vision.

DR. KHANANI: At the end of the day, we have to assess the risks and benefits. There appears to be durability benefit of GB-102 in wet AMD based on the ADAGIO data. Let's hope it continues to show promise and reaches the clinic. What are some other molecules that you are excited about that can address durability when it comes to treating wet AMD?

DR. REGILLO: There are other promising products in the pipeline that might give us 3, 4, or more months of durability. Faricimab is in phase 3 (NCT0382330 and NCT03823287). KSI-301, a novel anti-VEGF antibody biopolymer conjugate, is in a pivotal study (NCT04049266).[58,59] Both faricimab and KSI-301 are looking more durable than what we have currently and would potentially be preferred over current anti-VEGF injections if the durability is consistently greater.

DR. BAUMAL: Our anti-VEGF treatments are very effective, even though frequent injections are required. The next phase of treatment will need to have a high bar to surpass with minimal side effects. If it does have side effects, the treatment benefit and the visual advantage or the reduction in number of treatments would have to be significant to outweigh that.

DR. KHANANI: Faricimab data from the STAIRWAY trial is clearly promising in terms of durability.[60] KSI-301 phase 1b trial has also shown excellent durability in patients with wet AMD.[59] Both of these molecules appear to have safety profile similar to current agents but I agree with Dr. Baumal that the safety bar is very high, and we need more efficacy and safety data from the pivotal trials to confirm these findings.

Gene Therapies

Q | **DR. KHANANI:** RGX-314 is a one-time subretinal gene therapy that requires a vitrectomy. It uses a NAV-AAV8 vector containing gene encoding for a monoclonal antibody fragment that blocks VEGF activity, thereby preventing neovascularization and exudation. It's in phase 1/2a, which is fully enrolled with 42 patients.

The data so far looks promising. We just saw 2-year data from the earlier cohorts where we see continued protein production, as well as maintenance of OCT and vision. There were some retinal pigmentary changes in higher-dose group that we need to learn about but otherwise there were no safety concerns.[61] RGX-314 delivered via in-clinic suprachoroidal injection is also being investigated in ongoing trials.

Dr. Awh, the surgery for RGX-314 is very similar to the tissue plasminogen activator (tPA) technique that you pioneered, but here you are going into an attached retina and making a bleb. From your perspective, how difficult is the surgery? Can vitreoretinal specialists in private practice do this procedure?

DR. AWH: I think it's within the skill set of any well-trained vitreoretinal surgeon to do a subretinal injection with a microcannula. My concern is the level of precision that will be necessary in terms of the location and volume of the agent that's being injected, as well as the need to limit egress of the agent during and after the injection. Surgical injection of tPA or balanced salt solution beneath the retina doesn't require us to control those variables.

DR. REGILLO: The RGX-314 program looks very promising. The phase 1/2a trial had five dosing cohorts, and the gene product was increased with each dose. The ability to control the exudation was quite good, starting around cohort 3, with cohort 5 looking the best. In cohort 5, the majority of patients went 9 months without needing rescue, and researchers had no tolerance for recurrent exudation in the study. At 9 months of follow-up, there were 11 patients in cohort 5 and only three required rescue injections.[61]

RGX-314 has great durability. These are patients who required injection monthly or every other month and went nearly a year without needing treatment. That's very impressive. There's no intraocular inflammation when you inject the product subretinally via vitrectomy, and they had a very good safety profile with the drug itself.

RGX-314 could potentially give many of these patients a one-and-done scenario with little to no treatment for the rest of their lives. It's still early, but by the time we get into pivotal studies we'll have 5-year data on some patients.

DR. BAUMAL: More information is needed before we can assess the efficacy of the procedure. We need long-term results to look for systemic effects. There don't appear to be any currently, but it's still gene therapy. Many of our patients are elderly and frail, and this is a surgical procedure so it has to be safe. For this reason, alternative modes of drug delivery are being evaluated.

DR. REGILLO: The vitrectomy surgery may not be necessary to administer RGX-314. Regenxbio has launched the phase 2 AAVIATE trial (NCT04514653), which is evaluating the efficacy, safety, and tolerability of suprachoroidal delivery of RGX-314 using a proprietary microinjector device as an office-based procedure.[62] The hope is it will be just as effective as subretinal administration.

DR. KHANANI: The efficacy looks promising, but gene therapy is a paradigm shift when it comes to treatment of wet AMD and we need long term safety data. Another gene therapy program that looks very promising is in-clinic, intravitreal injection of ADVM-022. This agent uses a .7m8 vector to deliver a gene encoding for aflibercept. Preclinical data showed long-term expression of aflibercept after a single injection of ADVM-022 and levels of aflibercept seen were similar to a bolus intravitreal aflibercept injection.[63,64] OPTIC (NCT03748784) is a phase 1 dose-ranging trial that is evaluating the safety and tolerability of a single intravitreal administration of ADVM-022 in patients with wet AMD who are responsive to anti-VEGF treatment.[65] There are four cohorts. Patients in cohorts 1 and 4 receive a high dose of ADVM-022 (6 x 10^11 vg per eye) and patients in cohorts 2 and 3 receive a low dose (2 x 10^11 vg per eye). Patients in cohorts 3 and 4 received topical steroids for 6 weeks, while cohorts 1 and 2 received oral steroids for 13 days.

We have topline data from all four cohorts, which was presented at EURETINA.[65] Cohort 1 saw phenomenal efficacy. Fifteen patients across cohorts 1 and 4 have required no retreatments, with some patients maintaining on a single injection for 15 months or longer. Few patients in cohorts 2 and 3 have required rescue.

Some patients treated with ADVM-022 did get inflammation after the steroids were stopped or tapered, but it was mild in most cases and responded well to topical steroids in all patients. Early data from cohort 4 is consistent with cohort 3, suggesting that topicals lead to fewer adverse events and less inflammation.

Dr. Awh, what are your thoughts on ADVM-022, which is an in-office procedure, versus RGX-314, which requires surgery but obviously there were differences in inflammation?

DR. AWH: The idea of effective gene therapy achievable with a single intravitreal injection is tremendously appealing. Mild inflammation controllable with a limited course of topical steroids is a reasonable trade-off to avoid surgery in the operating room. The decision, should we be lucky enough to have both treatments approved and available, will depend on efficacy and complication rates revealed in larger trials. On the surface, ADVM-022 is certainly promising.

DR. BAUMAL: One of the big benefits of ADVM-022 is that the single in-office injection would be in line with the intravitreal injection procedures that we're are accustomed to doing. It would be easy to incorporate ADVM-022 into our treatment paradigm, and patients would likely be agreeable to the procedure. However, more clinical and imaging information from a larger trial is necessary to characterize the inflammation and determine safety. As a cautionary tale, the rate of intraocular inflammation was 4.4% after brolucizumab in the HAWK and HARRIER studies; however, the vasculitis really did not become apparent until after the study, highlighting the need for long-term safety data.

DR. REGILLO: Dr. Baumal is absolutely right. The attraction here is that the high dose is providing excellent exudative control with a single injection. Fortunately, the inflammation seen so far is mild to

moderate and controllable. However, inflammation that is an active management issue for more than a few months may lessen the attraction of this approach for some patients. We need more information on the degree, chronicity, and duration of the inflammation along with how much treatment is needed to control it.

It's still early. We need to see data from all cohorts over at least 1 year out to see how long patients need tropical drops. The oral steroid regimen used in cohorts 1 and 2 may have been tapered off too quickly, which is why the study was amended to use topical steroids instead of oral steroids prophylactically from the beginning in cohorts 3 and 4. Some patients did need to be restarted or kept on topicals longer. Again, additional follow-up from all cohorts will be needed to sort this all out and know how to best prevent or manage any inflammation associated with the therapy.

DR. KHANANI: The key is to characterize the inflammation now and learn how to treat it. We also need to determine which patients develop inflammation and why. There's lots of learning left to do, but these gene therapy programs seem promising. We're not there yet, but we could be in 3 to 5 years.

MANAGING RESIDUAL FLUID IN THE REAL WORLD

Case 1: Switching Agents May Resolve Lingering Fluid

DR. BAUMAL: A 67-year-old woman who had been receiving monthly anti-VEGF injections for 2 years presented to our office. Despite this, she has more signs of exudation. Her VA was good at 20/25, but she is symptomatic, complaining of blurred vision and a small gray scotoma (Figure 1). She could not be extended beyond her 4-week interval of injections or the SRF would worsen. Her OCTA revealed a flat fibrovascular PED with evidence of CNV on the flow overlay.

In order to check the efficacy of the anti-VEGF agent, I gave her an anti-VEGF challenge and had her return a week after the injection to evaluate for clinical effect. At that time, the fluid had completely resolved (Figure 2). This informs me the anti-VEGF agent was working, but its effect was not sustained for the 4-week interval between injections. Where do we go from here?

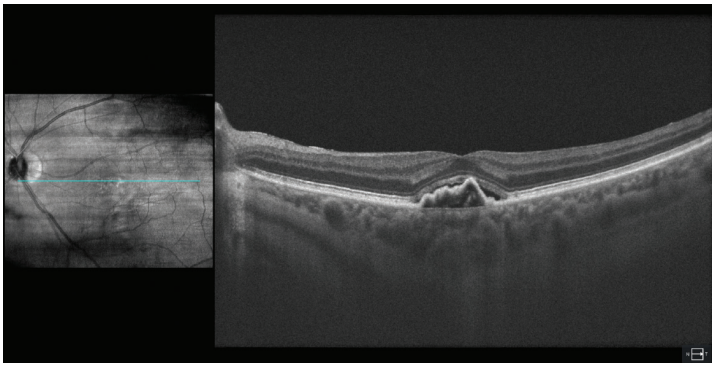

Figure 1. Case 1: A 67-year-old female 4 weeks after anti-VEGF injection.

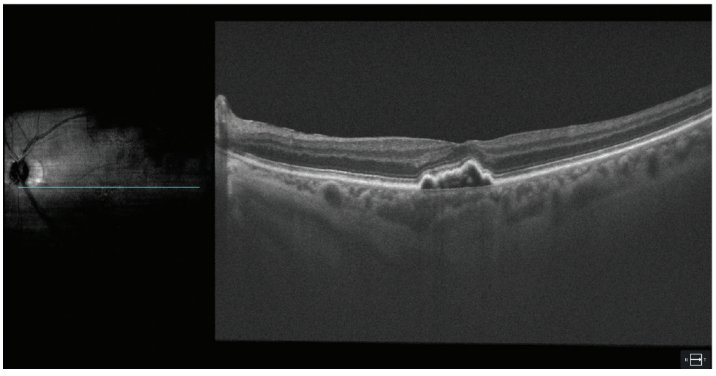

Figure 2. Case 1: A 67-year-old female 1 week after anti-VEGF injection.

DR. AWH: What is the vision of the fellow eye?

DR. BAUMAL: The fellow eye is 20/20, with good vision and intermediate AMD.

DR. AWH: I think injections every 4 weeks and 20/25 VA with a tolerable scotoma is reasonable, particularly given the good vision of the fellow eye. If the patient were dissatisfied with their vision, I'd consider a trial of every 2 to 3 week injections. The patient would need to be willing to assume the inconvenience, cost, and risk associated with more frequent treatments. This is

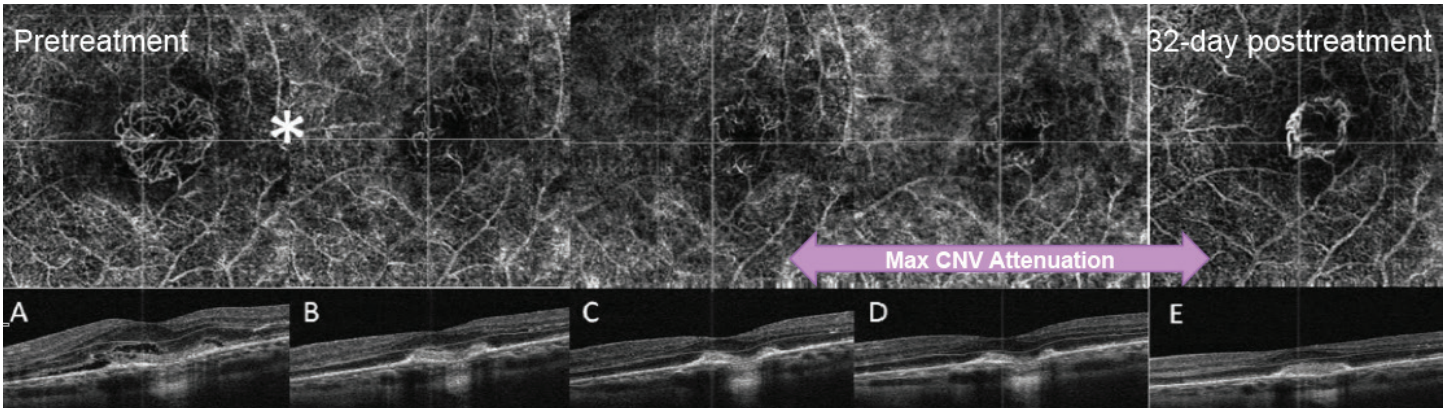

Figure 3. Case 2: How the neovascular membrane reacts to anti-VEGF.[66]

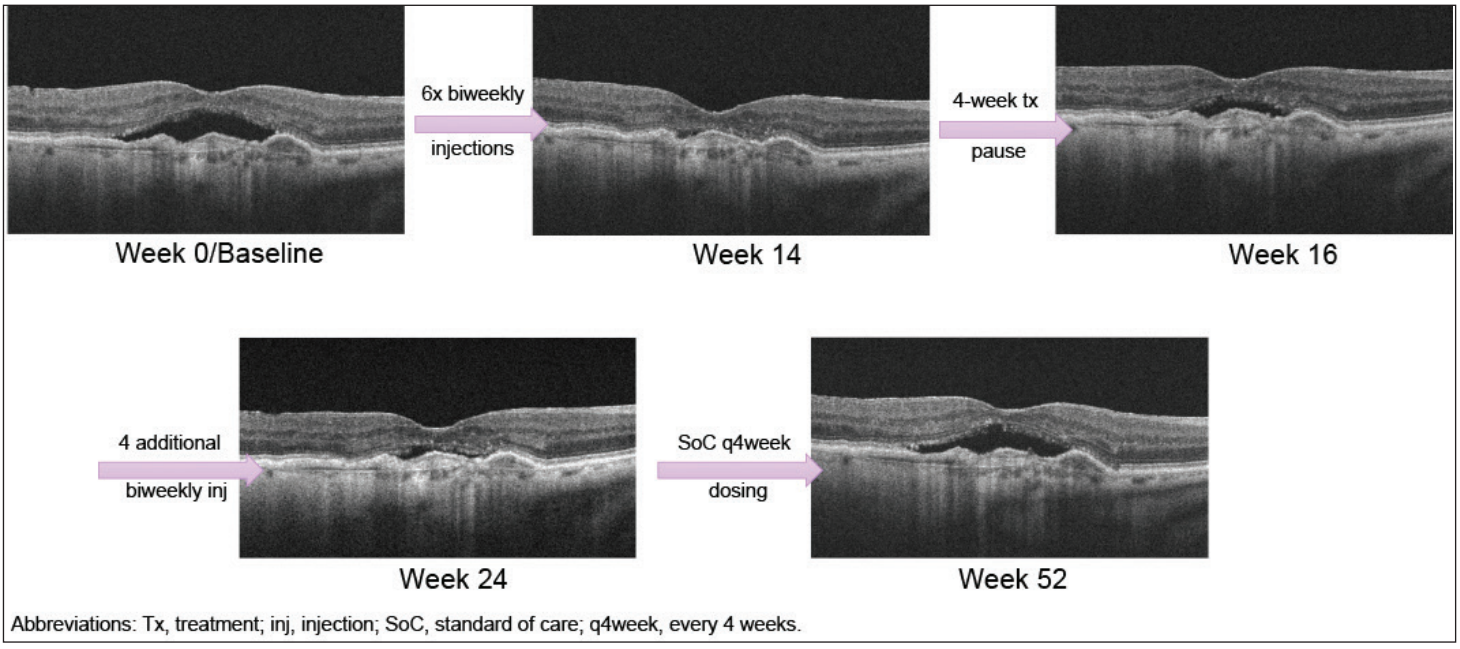

Figure 4. Case 2: Persistent SRF in a TRISTAR study patient.[36]

an option I'd consider if there had been no improvement with switching agents.

DR. REGILLO: You've nicely demonstrated that she is anti-VEGF responsive, and that her symptoms improve shortly after treatment. If the patient was tolerating her vision and the sliver of SRF for 2 years, I'm inclined to keep her at the 4-week interval. That said, we have four anti-VEGF agents at our disposal. When I see patients who want greater durability, I consider switching agents. Aflibercept may give patients on bevacizumab or ranibizumab an additional week or 2. I've had some patients who couldn't go beyond 4 weeks, even with aflibercept. I was able to extend the interval with brolucizumab.

Some of our colleagues may be hesitant to use brolucizumab in a patient with such good vision, in case a rare vascular event occurred. I'd consider brolucizumab an option for this patient as long as they were aware of and comfortable with the potential risks.

DR. BAUMAL: I did try different agents in this patient and there was no difference in effect. Her fluid always recurred before 28 days. She was treated early on with brolucizumab and the fluid completely resolved, but this was prior to reports of occlusive vasculitis. After the issues related to inflammation and vasculitis became apparent, I decided to switch her back to her prior anti-VEGF agent. She was disappointed as she felt that her symptoms had markedly improved after brolucizumab, but she agreed that the risk appeared to outweigh the benefits as she had relatively good VA from the start. She did not want to be injected more frequently than every 4 weeks, so she remains on monthly aflibercept tolerating a small amount of SRF.

DR. KHANANI: This case clearly highlights the unmet need for more durable agent to treat patients with wet AMD.

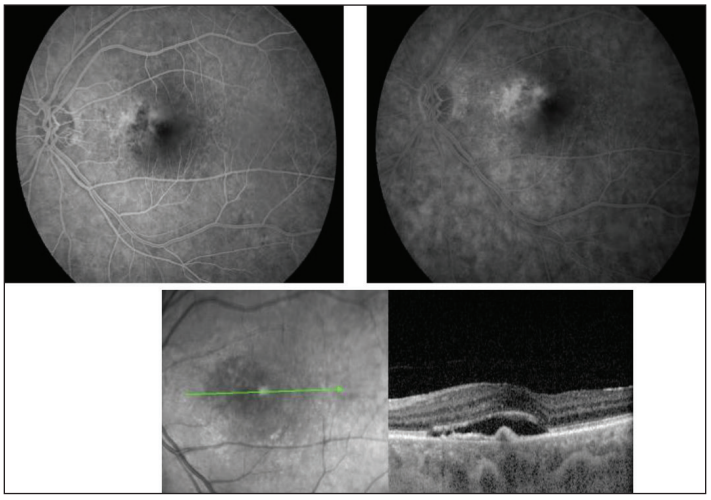

Figure 5. Case 3: A 77-year-old woman with distortion OS at presentation with fluorescein angiographic features of active, leaking choroidal neovascularization and OCT findings of SRF. The patient's VA was 20/60.

Case 2: TRISTAR Study Illustrates Efficacy of Biweekly Injections for Persistent Fluid

DR. AWH: I will discuss the TRISTAR study, which was conducted in our practice. Dr. Eric Schneider, the lead investigator, studied patients with persistent SRF after at least 1 year of monthly anti-VEGF injections. Patients were treated with six consecutive biweekly aflibercept injections, followed by a 4-week interval until their next treatment. Patients were then randomized to receive either four additional biweekly injections or two monthly injections, then all patients were returned to monthly injections. Dr. Schneider found that biweekly injections caused significant improvement or resolution of SRF and a slight improvement in vision,

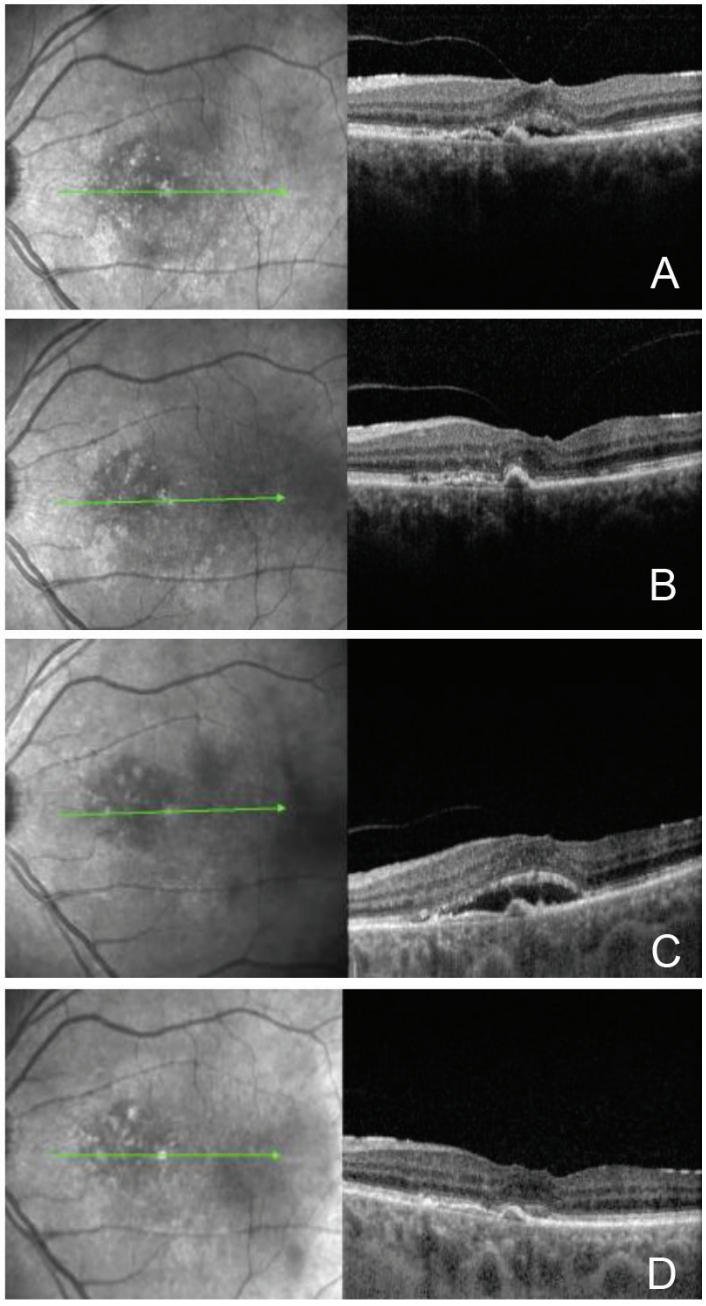

Figure 6. Case 3: A 77-year-old woman with SRF on anti-VEGF treatment with aflibercept. There is complete resolution of SRF with treatment intervals of 4 weeks and recurrent SRF and decreased vision with an attempt to extend the treatment interval to 6 weeks (A-D).

but that the patients regressed to prebiweekly status following return to monthly injections. Persistent SRF is very common.[36]

Figure 3 is from a series by Lumbroso et al, showing the effect on the neovascular membrane after an intravitreal anti-VEGF injection.[66] The regression on OCTA of the membrane is greatest immediately after the injection, with the membrane reappearing on OCTA well before the 1-month visit.

Figure 4 shows one of the patients from Dr. Schneider's study with a typical picture of persistent SRF.[36] The SRF significantly decreased after six biweekly injections, returned during the 4-week "pause," decreased when the biweekly injections resumed, then reaccumulated when the patient returned to monthly injections. This demonstrates the potential benefits of more frequent injections but, more importantly, suggests that other means of delivering continuous anti-VEGF treatment, like the PDS or gene therapy, could be particularly beneficial for the subset of patients with persistent SRF.

DR. REGILLO: Long-term results will determine how aggressive we need to be in treating persistent SRF. Fluctuating fluid is always more concerning than a small sliver of fluid that persists and never changes. In those patients, we may be able to extend safely over time.

DR. BAUMAL: There are patients who may benefit from injections more frequently than monthly, but a 2- to 3-week treatment interval is extremely difficult to sustain.

DR. REGILLO: I agree. I've had very few patients getting treatments more frequently than monthly, mainly because the benefits to their vision seem to be marginal.

DR. KHANANI: Very impressive study but as everyone suggested, it is not feasible to treat patients every 2 weeks. This case highlights the unmet need for more powerful drying agents with better durability.

Case 3: Determining Active Exudation

DR. REGILLO: Figure 5 shows a 77-year-old female with distortion in her left eye for 3 weeks. She was 20/60 with SRF and leaking, occult CNV on the angiogram at presentation. After two courses of monthly aflibercept, her vision improved to 20/30. I extended the interval to 6 weeks and there was some recurrent SRF and decreased vision to 20/50, so I returned to the 4-week interval with recovery of vision and resolution of SRF (Figure 6).

Finally, I have one last important point. Not all cysts represent active exudation. We need to ensure we don't misinterpret cysts over fibrosis, cysts over atrophy, or outer tubulation as active exudation.

DR. BAUMAL: It is important to examine our patients clinically, as well as look at all features and multiple levels on the OCT. Vitreomacular traction may also mimic exudation.

DR. REGILLO: That's absolutely right. We need to strike a balance between overtreatment and undertreatment. The key to success in managing patients with wet AMD is early detection. When the lesion is small and their vision is good, you can keep their VA stable. In fact, when VA at baseline is 20/40 or better, about 80% or so of patients will maintain 20/40 or better VA after 2 years on a treat-and-extend regimen.[67] Even in the CATT 5-year data, half of the eyes were 20/40 or better.[39] Early detection and keeping on top of the disease are key.

DR. KHANANI: Another great case highlighting the efficacy of currently available agents but the limitation of durability. To summarize our discussions, especially now during the COVID-19 pandemic, we need agents and delivery systems that are more durable. Our hope is that sustained delivery will decrease the treatment burden for patients who need frequent injections and lead to better real-world outcomes. I want to thank all of you for your expertise and your time discussing therapies in the pipeline for wet AMD. ■

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WHAT'S NEXT FOR nAMD? A FOCUS ON THERAPIES IN THE PIPELINE

Release Date: November 2020
Expiration Date: December 2021

INSTRUCTIONS FOR CREDIT

To receive credit, you must complete the attached Pretest/Posttest/Activity Evaluation/Satisfaction Measures Form and mail or fax to Evolve Medical Education LLC; 353 West Lancaster Avenue, Second Floor, Wayne, PA 19087; Fax: (215) 933-3950. To answer these questions online and receive real-time results, please go to http:// evolvemeded.com/online-courses/2008-supplement2. If you experience problems with the online test, please email us at info@evolvemeded.com. Certificates are issued electronically, therefore, please provide your email address below.

Please type or print clearly, or we will be unable to issue your certificate.

Name _____

Phone (required) _____ ❑ Email (required) _____

Address _____

City _____ State _____ Zip _____

License Number _____

OE Tracker Number _____

DEMOGRAPHIC INFORMATION

Profession
___ MD/DO
___ OD
___ NP
___ Nurse/APN
___ PA
___ Other

Years in Practice
___ > 20
___ 11-20
___ 6-10
___ 1-5
___ <1

Patients Seen Per Week (with the disease targeted in this educational activity)
___ 0
___ 1-15
___ 16-30
___ 31-50
___ 50+

Region
___ Northeast
___ Northwest
___ Midwest
___ Southeast
___ Southwest

Setting
___ Solo Practice
___ Community Hospital
___ Government or VA
___ Group Practice
___ Other
___ I do not actively practice

Models of Care
___ Fee for Service
___ ACO
___ Patient-Centered Medical Home
___ Capitation
___ Bundled Payments
___ Other

LEARNING OBJECTIVES

DID THE PROGRAM MEET THE FOLLOWING EDUCATIONAL OBJECTIVES?	AGREE	NEUTRAL	DISAGREE
Describe the differences in real-world clinical outcomes with those from prospective clinical trials.	_____	_____	_____
Develop individualized treatment regimens for patients with AMD who may benefit from treatments with longer duration.	_____	_____	_____
Discuss newer compounds in development or recently approved compounds that are designed to improve visual outcomes while decreasing treatment burden.	_____	_____	_____

POSTTEST QUESTIONS

Please complete at the conclusion of the program.

1. Based on this activity, please rate your confidence in your ability to manage patients with age-related macular degeneration (AMD) (based on a scale of 1 to 5, with 1 being not at all confident and 5 being extremely confident).

a. 1
b. 2
c. 3
d. 4
e. 5

2. Based on this activity, please rate how often you apply the latest treatments in AMD (based on a scale of 1 to 5, with 1 being never and 5 being always).

a. 1
b. 2
c. 3
d. 4
e. 5

3. When comparing pivotal trial evidence of anti-VEGF treatment to real-world evidence, which of the following is NOT true:

a. Real-world visual gains are more modest than pivotal trial visual gains
b. Real-world evidence demonstrates fewer injections per year compared to pivotal trials
c. Real-world evidence demonstrates similar visual gains compared to pivotal trials
d. Pivotal trial evidence has demonstrated 7 to 11 letter improvement with anti-VEGF treatment over the course of a year

4. All of the following steps are important for implantation of the port delivery system except:

a. Adequate uveal coagulation
b. Precise wound size
c. No Tenon closure
d. Adequate conjunctiva and tenons closure

5. An 81-year-old man receives ranibizumab injections every 4 weeks for neovascular AMD. He is having difficulty maintaining his office visit schedule and asks about other options. Which of the following is a reasonable option for this patient?

a. Stop ranibizumab therapy
b. Explain the port delivery system and reassure the patient this therapy may become available soon
c. Start bevacizumab therapy
d. Start aflibercept therapy

6. According to the LADDER study, what was the median time to refill for the port delivery system in the high-dose group?

a. 3 months
b. 6.5 months
c. 15.8 months
d. 24 months

7. RGX-314 is gene therapy to turn the eye into an anti-VEGF biofactory. How is this gene therapy delivered?

a. Intravitreally
b. Intravenous delivery
c. Intracamerally
d. Subretinal delivery

8. What percentage of patients remained injection-free with improved visual acuity and stable OCT over 2 years according to phase 1/2a trial data on RGX-314?

a. 20%
b. 30%
c. 40%
d. 50%

9. ADVM-022 is a gene therapy treatment that encodes for aflibercept using a variant of AAV2 as a vector. How is this therapy administered?

a. Intravitreally
b. Suprachoroidal delivery
c. Intracamerally
d. Subretinal delivery

10. A 79-year-old man with neovascular AMD is on monthly aflibercept with well controlled disease. He is interested in discussing the potential for future gene therapy options to treat his disease. He is very reluctant to undergo any procedure in the operating room for treatment. Which potential future options may be the best for this patient?

a. Intravitreal RGX-314
b. Intravitreal ADVM-022
c. Subretinal RGX-314
d. Subretinal ADVM-022

ACTIVITY EVALUATION

Your responses to the questions below will help us evaluate this CME activity. They will provide us with evidence that improvements were made in patient care as a result of this activity.

Rate your knowledge/skill level prior to participating in this course: 5 = High, 1 = Low _____

Rate your knowledge/skill level after participating in this course: 5 = High, 1 = Low _____

This activity improved my competence in managing patients with this disease/condition/symptom. ____ Yes ____ No

Probability of changing practice behavior based on this activity: _____ High _____ Low ____No change needed

If you plan to change your practice behavior, what type of changes do you plan to implement? (check all that apply)

Change in pharmaceutical therapy ____

Change in nonpharmaceutical therapy ____

Change in diagnostic testing _____

Choice of treatment/management approach ____

Change in current practice for referral _____

Change in differential diagnosis _____

My practice has been reinforced _____

I do not plan to implement any new changes in practice ___

Please identify any barriers to change (check all that apply):

____ Cost

____ Lack of consensus or professional guidelines

____ Lack of administrative support

____ Lack of experience

____ Lack of time to assess/counsel patients

____ Lack of opportunity (patients)

____ Reimbursement/insurance issues

____ Lack of resources (equipment)

____ Patient compliance issues

____ No barriers

Other. Please specify: _____

_____

_____

The design of the program was effective for the content conveyed. ___ Yes ___ No

The content supported the identified learning objectives. ___ Yes ___ No

The content was free of commercial bias. ___ Yes ___ No

The content was relative to your practice. ___ Yes ___ No

The faculty was effective. ___ Yes ___ No

You were satisfied overall with the activity. ___ Yes ___ No

Would you recommend this program to your colleagues? ___ Yes ___ No

Please check the Core Competencies (as defined by the Accreditation Council for Graduate Medical Education) that were enhanced through your participation in this activity:

____ Patient Care

____ Practice-Based Learning and Improvement

____ Professionalism

____ Medical Knowledge

____ Interpersonal and Communication Skills

____ System-Based Practice

Additional comments:

_____

____ **I certify that I have participated in this entire activity.**

This information will help evaluate this CME activity; may we contact you by email in 3 months to see if you have made this change? If so, please provide your email address: _____

_____