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Retina Today

2021 AND BEYOND: WHAT'S ON THE HORIZON FOR WET AMD?

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CONTENT SOURCE

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

ACTIVITY DESCRIPTION

This summary of a discussion among thought leaders in retina highlights the current challenges in managing wet age-related macular degeneration, including compliance issues and nonresponders, and provides insight into the anticipated impact of longer acting treatment options on the field at large.

TARGET AUDIENCE

This certified CME activity is designed for ophthalmologists who treat patients with retinal diseases.

LEARNING OBJECTIVES

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

- **Compare** the challenges faced in management and treatment of patients in clinical practice and **describe** their impact on treatment outcomes.
- **Evaluate** potential advantages of long-acting delivery options for wet age-related macular degeneration.
- **Interpret** how novel pipeline candidates are being developed to address longer treatment intervals.

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PRETEST QUESTIONS

Please complete prior to accessing the material and submit with Posttest/Activity Evaluation/Satisfaction Measures for CME Credit.

- 1. Please rate your confidence in your ability to discuss potential advantages of long-acting delivery options for wet 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. Treatment compliance among patients with wet AMD can be improved by _____. Select ALL that apply.**
 - a. Insisting on a monthly dosing strategy to ensure trips to the clinic
 - b. Establishing a strong physician-patient relationship
 - c. Properly educating the patient on their disease and the purpose of treatment
 - d. Referring patients to retinal specialist within 10 miles of their residence
- 3. A 70-year-old female with cardiovascular disease was referred to your practice. She has 20/25 visual acuity and a blind spot in her central visual field. She is on Medicare. You diagnose her with wet AMD. What does the panel suggest should be your next step for treating this patient?**
 - a. Treat immediately with aflibercept, bevacizumab or ranibizumab
 - b. Provide the diagnosis, but delay treatment until insurance authorization is received
 - c. Observe her to see if her vision worsens
 - d. Treat immediately with brolocizumab
- 4. In the MAPLE study, _____ patients experienced inflammation with abicipar.**
 - a. 15%
 - b. 10%
 - c. 9%
 - d. 7%
- 5. If and/or when should brolocizumab be considered in patients with wet AMD?**
 - a. Brolocizumab should not be considered for any patient with wet AMD due to retinal vasculitis
 - b. Brolocizumab should be used in a the first-line setting in treatment-naive patients due to its superior drying power as compared with other anti-VEGF agents
 - c. Brolocizumab should be used in the second-line setting after starting patients on bevacizumab and switching after insurance approval
 - d. Brolocizumab can be considered in patients who have not responded to other anti-VEGF agents and who have significant intraretinal and/or subretinal fluid
- 6. If the port delivery system is approved, what will need to be considered when implementing it into practice?**
 - a. The rate of inflammation
 - b. The surgical procedure and its potential risks
 - c. The increased rate of geographic atrophy
 - d. Its limited durability
- 7. _____ is a novel antibody biopolymer conjugate that allows for increased durability of action inside the eye.**
 - a. ADVN-022
 - b. KSI-301
 - c. Faricimab
 - d. Port delivery system
- 8. What percentage of patients with wet AMD do not adhere to treatment?**
 - a. 20%
 - b. 31%
 - c. 40%
 - d. 80%
- 9. What is known about the link between anti-VEGF therapy and development of macular atrophy?**
 - a. Macular atrophy is definitely caused by anti-VEGF treatments in wet AMD
 - b. Macular atrophy may part of the natural history of choroidal neovascularization or may be present concurrently at the time of choroidal neovascularization diagnosis
 - c. Eyes with choroidal neovascularization rarely have macular atrophy present
 - d. Patients with wet AMD have preexisting macular atrophy, and no direct link can be made to anti-VEGF treatment

2021 and Beyond: What's on the Horizon for Wet AMD?

Treatments in the pipeline with unique mechanisms of action for the treatment of neovascular age-related macular degeneration (AMD) may soon provide patients with longer-acting drugs and sustained drug delivery, thereby lessening patient treatment burden, reducing compliance issues, and enhancing the quality of life while still improving vision. However, for a new therapy to upend the existing treatment paradigm, these approaches must be superior to our current armamentarium of effective, yet imperfect, anti-VEGF therapies. Retinal specialists must be able to appropriately select patients for treatments, balancing the potential risks and benefits to maximize outcomes. The following roundtable discussion brings together thought leaders in retina to discuss the current challenges in managing AMD, including compliance issues and nonresponders, and the expected impact of longer acting treatment options on the field at large.

— Jennifer I. Lim, MD, Moderator

CURRENT CHALLENGES IN TREATING PATIENTS WITH WET AMD

Jennifer I. Lim, MD: A retrospective cohort study of about 9,000 patients with neovascular AMD who received anti-VEGF therapy found that about 20% of patients were lost to follow-up (LTFU).¹ LTFU was defined as receipt of one or more injections with no subsequent follow-up visit within 1 year. The study was performed at Wills Eye Hospital in Philadelphia, an urban retina practice with multiple locations, from April 1, 2012, to January 12, 2016. LTFU rates were greater among patients age 81 or older and patients with an annual income under \$100,000. But patients who lived more than 10 miles from the clinic, those who received unilateral injections, and people of color also seemed to have higher rates of LTFU.

Q | Are you seeing similar trends in LTFU and compliance in your practices?

Karl Csaky, MD, PhD: The COVID-19 pandemic has changed this dynamic pretty significantly.² Somewhere around 40% of US adults have avoided medical care during the pandemic because of infection concerns, including 12% who have avoided emergency care and 31% who have delayed routine care. In ophthalmology specifically, there was an initial 80% drop in appointments at the beginning of the pandemic in March 2020. By June 2020, the number of appointments rebounded but remained 40% lower than normal.³ Given the fear of infection, patients are asking themselves if they really need that follow-up appointment, especially if they have relatively good vision.



"In ophthalmology specifically, there was an initial 80% drop in appointments at the beginning of the pandemic in March 2020."

—Karl Csaky, MD, PhD

Diana Do, MD: I agree with Dr. Csaky that COVID-19 has had a significant impact on follow-up. Patients, especially elderly individuals, are frightened to leave their homes because they are at such high risk. Retinal specialists have taken safety seriously and must continue to reassure patients it is safe to return to the clinic. We don't want them to go blind waiting at home.

Our elderly population has always had challenges with appropriate follow-up because they often rely on family members or caregivers to transport them to appointments. Varano et al conducted a patient and caregiver survey to assess the barriers to AMD care.⁴ Although the primary barriers were the treatment itself and cost, 16% of patients surveyed missed an appointment and said the main obstacle was that a caregiver was unable to take them.

Those missed treatments correspond with poorer outcomes; there is a direct correlation between the number of anti-VEGF injections and outcomes.⁵ Clinical trial outcomes don't translate to the real world, likely due to undertreating active wet AMD.^{6,7} Ciulla et al conducted a retrospective analysis on a large EMR database of nearly 50,000 eyes of patients with treatment-naïve wet AMD. They found a linear relationship between the mean letters gained and mean number of injections.⁸ Hussain et al conducted a large, retrospective analysis of US claims data in 19,000 wet AMD patients and found that over 12 months, patients received an average of 4.6 and 6.9 injections of bevacizumab and ranibizumab respectively, which is much lower than what patients receive on clinical trials.⁹

Dr. Lim: I'm also finding that many of my patients are trying to push that treat-and-extend interval a bit longer. The patients come in at 6 weeks and ask if they can come in at 8 weeks instead. As a result, I'm finding myself trying to extend them faster and further than I normally would because it's hard for them to come back; they're worried about getting sick.

Q | How is the current pandemic impacting compliance?

Nancy Holekamp, MD: I'm a principal investigator on a multinational, qualitative study looking at barriers to treatment adherence that has been accepted at the 2021 Association for Research in Vision and Ophthalmology Annual Meeting. We've found a universal fear of injection across countries. Other barriers to care include a perception of treatment ineffectiveness and travel time to the clinic. In addition, during the past year COVID concerns have also kept patients away from our offices.

Retinal specialists discuss compliance issues as if there's no solution, but our study found that a strong doctor-patient relationship and patient education all promote compliance. There's other evidence in the literature that confirms this. Kandula et al conducted a prospective, survey-based study on patients' knowledge and perspectives on wet AMD and its treatment, and found that patients were largely unaware of the risk factors and risk-factor modifications for wet AMD.¹⁰ Clinicians hold the key to improving the current dismal compliance statistics through establishing a meaningful doctor-patient therapeutic relationship and through proper education on the disease and the purpose of treatment.



"Clinicians hold the key to improving the current dismal compliance statistics through establishing a meaningful doctor-patient therapeutic relationship and through proper education on the disease and the purpose of treatment."

—Nancy Holekamp, MD

Dr. Lim: That's a great point. It's true that if a patient feels like they're letting down the doctor, they are more likely to return.

Rishi P. Singh, MD: I was a coauthor on a study published recently that explored the consequences of treatment lapses of 3 months or longer with anti-VEGF therapy in approximately

300 patients with AMD.¹¹ We found that even a 3-month lapse caused a significant increase in central subfield thickness, which normalized after treatment was resumed. However, patients who lapsed also lost visual acuity (VA), which did not recover. A short-term lapse in AMD seems to be quite significant; it's critical that they return monthly because if they don't, their vision will decline. We have data on retinal vein occlusion (RVO) and diabetic macular edema (DME) that is different;¹² in those diseases, there is no difference in the final VA in patients LTFU at 1 year. Although there is an anatomical difference at 1 year, there was no difference in the final VA outcome.

Dr. Lim: Dr. Holekamp, you mentioned that patients have a fear of injections. I have found that once patients have their first injection and realize it's not that uncomfortable, they no longer fear it. Do you find that as well?

Dr. Holekamp: Yes. My usual approach is to give people an injection the first time I see them and tell them they need injections. The injections sound much worse than they actually are. The fear of the injection should be secondary to the benefit experienced by patients with AMD. Once a patient has had an injection that is given in a compassionate, careful manner, they find it's not so bad.

Dr. Csaky: In my experience, the reaction of the patient to receiving an injection is related to the degree of vision loss. For example, if someone comes in with a VA of 20/100 or worse, they'll do whatever is needed. On the other hand, if a patient is 20/30 with a little bit of fluid, communicating the need for injections is more challenging. In addition to the fear of a needle in their eye, they worry about side effects. I personalize my dialogue with patients as much as possible and adjust my approach based on the severity of their disease.

Q | Dr. Lim: Has anyone found that financial considerations are barriers to treatment?

Dr. Do: One of the main concerns we have is the initiation of step therapy, which requires the physician to use off-label bevacizumab as the first-line treatment for wet AMD. Before I can switch a patient to a branded drug, bevacizumab has to fail. It's challenging to know which patients will have these types of insurance restrictions because insurance carriers update their policies without telling us. We're almost forced to use bevacizumab in the first-line setting because we don't know if insurance will cover the more expensive US FDA-approved therapies.

Dr. Lim: Is your strategy then to go ahead and treat patients with bevacizumab and try to get the branded drug approved for their next appointment so you're not delaying treatment?

Dr. Do: I like to treat patients on the same day that I diagnose

them because it can be challenging to have them come back a week later. If I have a sample of the branded, FDA-approved drugs, I'll use those. If I don't have samples, I'll use bevacizumab.

Dr. Singh: There is objective data supporting a brief delay in treatment within a reasonable timeframe. In HARBOR, at the time of randomization, it didn't matter if the patient was treated within a day or a week.¹³ Either approach is reasonable; you can treat same-day or wait for insurance approval. I have the same issues with step therapy as Dr. Do. Step therapy is fairly widespread. Any patient with insurance except for Medicare has some sort of step therapy requirement. We are struggling to use branded drugs on our patients, and it becomes quite difficult because there are data showing that branded drugs have a better drying effect than non-branded drugs.¹⁴ In CATT, ranibizumab and bevacizumab had equivalent visual outcomes when injected on the same schedule.¹⁵ But that's not how we treat patients in the real world; we use treat-and-extend. We try to get them as dry as possible, as fast as possible. We need to extend them as quickly as we can. That's where these branded drugs have some advantages over the nonbranded drugs.

Dr. Csaky: Where I practice in Texas, it can take some time to process the insurance paperwork. We start with bevacizumab, but usually the patient is approved for a branded treatment in time for their second visit.

Dr. Holekamp: I like to have a healthy supply of samples for the on-label anti-VEGF agents so I can begin with an approved therapy and treat the same day. When the patient returns in a month, we have determined what their insurance requires regarding step therapy and authorization. I find this to be very effective because I'm not only treating the same day, which more efficient, but it precludes the patient from worrying about the injection. It also makes my staff very efficient in understanding the insurance requirements. I practice in the Midwest. We're lucky in that there are a small number of insurance carriers in the area, so we know which ones requires what. We're able to navigate these waters effectively, but I'm sure there are changes coming in the future.

Dr. Lim: It's interesting to hear all these regional differences. In Illinois, where I practice, only a minority of patients require step therapy. Some of our Medicaid carriers mandate that we use branded drugs, and we start with aflibercept. Our university is prohibited from getting samples, so we don't have that luxury.

CAN LONG-ACTING DELIVERY REVOLUTIONIZE AMD TREATMENT?

Dr. Lim: In 2019, brolucizumab was approved by the FDA for wet AMD based on the strength of HAWK and HARRIER.¹⁶ We've also recently seen data on longer-acting agents and delivery methods in the pipeline, such as ADVM-022, abicipar pegol, and the port delivery system (PDS).¹⁷⁻²⁰ I think we're on the brink of some new therapies with extended durability.

Q | What are your expectations of long-acting delivery? Do you expect better outcomes, better adherence, and less variability on the optical coherence tomography (OCT)? What do you think will be the main advantages of some of these longer-acting duration drugs?

Dr. Singh: Long-term data is really quite poor for many of these studies. You see registration studies that have extended patients beyond 2 to 4 years, and they all have detrimental outcomes. For abicipar, MAPLE had a 9% inflammation rate down from the 15% rate in CEDAR and SEQUOIA, but the inflammation reduction wasn't enough to gain FDA approval.^{19, 21} FDA rejected abicipar for wet AMD treatment due to the unfavorable risk-benefit profile.²²

Potentially increased treatment adherence is great, but we can't tolerate inflammation. We're seeing signals of inflammation in brolucizumab, abicipar, and ADVM-022, despite the durability.²⁰ Brolucizumab has had significant issues with retinal vasculitis and inflammation and now contains a black box warning.²³⁻²⁸ I don't think these are acceptable alternatives for what we have. I'd rather forego the durability and continue to use anti-VEGF agents without the risk of inflammation.



"Potentially increased treatment adherence is great, but we can't tolerate inflammation."

—Rishi P. Singh, MD

Dr. Do: I do think improved adherence combined with increased durability could translate to better vision outcomes in the long term. As we know from Dr. Holekamp's work, patients in the real world receive approximately five or fewer injections during a 1-year period for their active wet AMD than patients on clinical trials.⁶ If we had a drug with a longer duration of action, we could control the disease for longer periods without the patient coming to the clinic for treatment.

Dr. Holekamp: With our current anti-VEGF treatment paradigm, we risk undertreating patients because of the treatment burden. It's very easy for retinal specialists to quantify a complication like intraocular inflammation, but it's difficult to compare

that complication rate to the rate of undertreatment. Real-world patients are not experiencing the VA gains seen in clinical trials. If we actually have safe, long-acting drug delivery, then we'll be able to replicate clinical trial results in the real world. I think better VA outcomes for large groups of real-world patients will be the biggest impact of long-acting delivery.

Dr. Csaky: Anti-VEGF therapies have had a remarkable impact on AMD patients, but they don't address the biology of the disease. We push for durability because anti-VEGF doesn't fully address the underlying pathology, be it vessel instability or whatever is driving the fluid and potential hemorrhaging. It's critical to understand that just making an anti-VEGF more durable will not change the pathology of the disease. We need better agents that can address the full pathologies of neovascular AMD.

UNDERSTANDING NOVEL MECHANISMS OF ACTION OF TREATMENTS IN THE PIPELINE

Dr. Lim: There are numerous drugs in the pipeline or recently approved with different mechanism of action including brolucizumab, abicipar, conbercept, the PDS with ranibizumab, and faricimab.²⁹⁻³³

Q | Dr. Csaky, you have a science background. Would you discuss their mechanisms of action, starting with faricimab?

Dr. Csaky: We have an enormous repository of preclinical data that supports the role of Ang2 expression in these disease states, both in diabetes and in choroidal neovascularization.³⁴ When you combine Ang2 with VEGF, it's synergistic in its ability to cause instability of the vasculature.^{35,36} When we look at the biology of choroidal neovascularization, we can clearly show in animal model and even in vitreous levels, Ang2 is present. The question is if combination anti-Ang2 and anti-VEGF is better than anti-VEGF alone. We'll know shortly.

However it is important to remember that in some cases, pre-clinical data did not always translate to improvements in clinical outcomes. PDGF was a good example of that; pegpleranib did not add any value to anti-VEGF alone.³⁷ But clearly, Ang2 appears to drive a certain degree of inflammation. It appears that ICAM, a marker of inflammation, was decreased in the clinical trials with faricimab, but not with ranibizumab. This suggests that anti-Ang2 may have an additional, specific anti-inflammatory capabilities. We know that inflammation plays a role, to some degree, in AMD. We know macrophages are there in the disease by histology.

Dr. Lim: Is there any possibility that decreasing inflammation would decrease fibrosis or decrease atrophy?

Dr. Csaky: The preclinical data on the anti-fibrotic aspects of anti-Ang2 has been shown in various skin models.³⁸ We know from CATT that anti-VEGF alone is marginally effective as an anti-fibrotic agent. There's still a quarter of patients who develop

fibrosis despite intensive anti-VEGF.¹⁵ We're entering into this era where very intelligent science is being applied in the clinic, and faricimab could be anti-fibrotic. It remains to be seen what the efficacy is; it might take 2 years to fully demonstrate that capability.

Q | Dr. Lim: Let's move onto ADVM-022, a potential gene therapy for AMD. What are the pros and cons of ADVM-022's mechanism of action?

Dr. Singh: I think, in general, gene therapies can be a step up for patients who can't adhere to monthly, bi-monthly, or quarterly therapy. There are also a subset of patients who still experience vision loss and complications with monthly therapy.³⁹ Gene therapy might be an area where we see a higher dose with a more continuous delivery model versus the peaks and troughs we see in other therapies. However, we don't know all the mechanisms around macular atrophy, and studies indicate that, in the long term, AMD patients who lose vision are losing it from macular atrophy.^{40,41} Now, whether that's anti-VEGF related or not, it's hard to say; you can't tease away the mechanisms right now.

There's been some discussion for the Diabetic Retinopathy Clinical Research Retina Network to do a study on continuous therapy versus noncontinuous therapy in relation to macular atrophy. They are still discussing these trials, but this is an area that needs to be investigated before we say *okay* to gene therapy. We don't know how much it will cost or how to turn it off. But, if there is a link between macular atrophy and gene therapy, that would be potentially the end of that paradigm regardless of the mechanism of delivery.

Dr. Lim: Two recent studies addressed the idea of macular atrophy and anti-VEGF. On a reanalysis of IVAN, they could not link macular atrophy and anti-VEGF.⁴² Another group looked at the HARBOR data posthoc and concluded that the macular atrophy was not associated with anti-VEGF or the number of anti-VEGF injections, per se.⁴³ Could it be that the macular atrophy was already present? When you analyze AREDS data, a significant proportion of patients—40%—already had some macular atrophy (seen with fundus autofluorescence) when the choroidal neovascular membranes (CNVM) were diagnosed.⁴⁰ Another larger proportion developed macular atrophy during CNV treatment. Was the macular atrophy pre-existing, a side effect of anti-VEGF, or just the natural history of CNVM running its course?

Dr. Csaky: During the 2020 53rd Virtual Retina Society Annual Meeting, Glenn Jaffe, MD, presented an analysis of LADDER data that showed the PDS implant did not increase the rate of geographic atrophy (GA).⁴⁴

Dr. Holekamp: It seems as though the fluid compartment matters because these posthoc analyses showed that subretinal fluid was protective against GA.^{15,45,46} Intraretinal fluid and cystic changes within the retina were more correlated with GA. I think

the best evidence for me that anti-VEGF therapy is not associated with macular atrophy is the use of anti-VEGF agents in RVO and diabetes. If atrophy was being caused by the anti-VEGF agent, we'd see atrophy in those two conditions, and we don't.

Q | **Dr. Lim:** Are you excited then about the possibility of gene therapy?



"It seems as though the fluid compartment matters because these posthoc analyses showed that subretinal fluid was protective against GA."

—Nancy Holekamp, MD

Dr. Holekamp: I am very excited about gene therapy. While gene therapy is evolving and the clinical trials have a long runway, I believe gene therapy will ultimately be successful. I favor an intravitreal or suprachoroidal injection over having to perform surgery for viral vector delivery. Surgery is a barrier that is undesirable. Gene therapy promises a continuous release of anti-VEGF that is possibly better than the current pulsatile, peak and trough delivery that we're currently using. I also think that there is potential for continuous anti-VEGF therapy to be disease-modifying.

The inflammation concerns are valid. About two-thirds of the patients in the highest dose cohort of the phase 1 ADVM-022 clinical trial had low-grade inflammation that could be controlled with topical corticosteroids given once or twice a day.^{20,47} The inflammation seen with ADVM-022 is not the same inflammation we're seeing with brolucizumab and abicipar. I can say with confidence that science will be able to engineer a viral capsid that doesn't create inflammation. I think we have the potential to overcome inflammation. I'm excited about this field and where it's heading.

Dr. Singh: The only point I disagree with is the assumption that anti-VEGF isn't causing macular atrophy because we're not seeing it in diabetic retinopathy, DME, or RVO. Those are diseases of the middle or inner retina and not a disease of the outer retinal structures as with AMD. In addition, CATT 2-year data clearly showed a higher rate of progression to GA in patients without it at baseline, with higher rates in the monthly treatment groups

that in the as-needed groups.¹⁵ I don't think that we can say conclusively, based upon other disease states, that anti-VEGF therapy is not contributing the development of macular atrophy.

Q | **Dr. Lim:** I'd like to move on to KSI-301. Dr. Do, what can you tell us about this new molecule?

Dr. Do: KSI-301 is an intravitreal VEGF inhibitor.⁴⁸⁻⁵⁰ It's built on a novel antibody biopolymer conjugate (ABC) platform that allows for increased durability of action inside the eye. The molecule has a larger molecular weight than the current anti-VEGF agents, but yet the ABC platform allows it to penetrate the retina and the choroid with ease to block VEGF. Most interestingly, Kodiak Sciences conducted a large phase 1b trial in treatment-naïve eyes that had wet AMD, DME, and macular edema associated with RVO. The results to date have been very promising, showing that KSI-301 is safe, well-tolerated, with a potential durability of 4 to 6 months inside the human eye.⁴⁸ This enhanced durability is exciting data. KSI-301 is now in late-stage, phase 3 clinical trial development in wet AMD, RVO, and DME (NCT04611152, NCT04592419, and NCT04049266).⁵¹⁻⁵³ I think this is a very promising intravitreal biologic that could potentially give retinal physicians and patients enhanced durability with a clinic-based treatment.

Dr. Lim: It's promising that one injection lasts 6 months.



"I don't think that we can say conclusively, based upon other disease states, that anti-VEGF therapy is not contributing the development of macular atrophy."

—Rishi P. Singh, MD

Dr. Do: The first study included three loading doses, followed by as-needed treatment according to protocol-defined disease activity state.⁵⁰ They found that more than 60% of eyes could have a treatment-free interval of at least 6 months. They've reported no drug-related serious adverse events. They've had no episodes of retinal vasculitis or occlusive disease, which are those severe events that we saw with brolucizumab and abicipar. The adverse

events reported with KSI-301 are in line with what's seen with aflibercept and ranibizumab.

Dr. Lim: These are encouraging data. What percentage of eyes can improve 15 or more letters with KSI-301? You may not have data on this, but do you think we can expect more, less, or the same as with other anti-VEGF drugs?

Dr. Do: We do not yet have data on 15 or more letter gainers, but they presented the mean gain in VA from baseline to week 44. Those gains are on par with what we've seen with other anti-VEGF agents.⁴⁸ Of course, this is a phase 1b trial with a small number of treatment-naïve eyes. But the data are still promising. We'll need to wait for the pivotal trial data to know more.

Q | Dr. Lim: We've all seen the reports and are very much aware of the intraocular inflammation with brolocizumab and, most importantly, the retinal vasculitis with the severe decreases in vision.²³⁻²⁷ That being said, are any of you using brolocizumab currently?

Dr. Singh: I'm still using it on occasion but not as a primary or secondary therapy. It's now a tertiary therapy for patients who have failed almost every other drug and have no other choices. When I do use it, I closely monitor the patient with slit lamp examination. I look at the posterior pole and the peripheral retina and make sure that there's no vasculitis.

Dr. Lim: Did you see the improved drying ability of brolocizumab shown in HAWK and HARRIER as compared to aflibercept or ranibizumab?¹⁶

Dr. Singh: Yes, no question. Brolocizumab is far superior in drying than the other drugs. With aflibercept and ranibizumab, it would take two to three injections to get the patient to a stable state where we could extend. But with brolocizumab, that stable state would take one injection. Thankfully, I haven't experienced intraocular inflammation in patients on brolocizumab, but other practices have not been so lucky.

Dr. Csaky: I have not used it myself, but I have been referred patients who have received it. There's a lot that we don't know about its effect on the various components of the eye. I'm still leery and will not be using it for a while.

Dr. Lim: Jeffrey S. Heier, MD, presented data during the 2020 Retina Subspecialty Day at Virtual American Academy of Ophthalmology (AAO) Annual Meeting that suggested neutralizing antibodies (NAb) may be associated with the cases of retinal vasculitis and retinal vascular occlusion seen with brolocizumab. Based on IRIS Registry data of 12,000 patients treated with brolocizumab, researchers determined that patients who experienced intraocular inflammation or retinal occlusion within a year of their

first brolocizumab injection were at higher risk for retinal vasculitis and occlusion. Interestingly, they also found that 60% of patients in HAWK/HARRIER who had retinal vasculitis or occlusion developed antitherapeutic antibodies before the complication. An overwhelming majority of patients (86%) who had retinal vasculitis or occlusion had NAb at baseline or shortly thereafter.⁵⁴

Dr. Csaky: Even before the brolocizumab injections, a significant number of patients in HAWK and HARRIER had antitherapeutic and antidrug antibodies. It's unclear why, especially because there were no significant cases of retinal vasculitis associated with ranibizumab or aflibercept. There appears to be something unique about the inflammatory potential of brolocizumab, specifically.

Q | Dr. Lim: It appears that drugs with longer durability cause more inflammation. In terms of their molecular design, is the inflammation expected? Or is the inflammation unique to abicipar and brolocizumab?

Dr. Csaky: Abicipar and brolocizumab are foreign antigens.^{55,56} Aflibercept is an immunoadhesin, which is essentially a synthetic antibody but it's still the construct of an antibody.⁵⁷ Ranibizumab is a monoclonal antibody fragment. But abicipar and brolocizumab have unique structures. It may be that their molecules are so foreign in terms of their origins that the body reacts to it, causing this inflammatory component.

Dr. Holekamp: I'd like to offer a very different perspective. I don't think the inflammation is related to the drug or the molecule; I think it has to do with the manufacturing process. For abicipar, patients in the phase 3 CEDAR and SEQUIOA trials had a 15% inflammatory rate.²¹ They were able to reduce that to 9% in MAPLE by improving the manufacturing process.¹⁹ The eye is an immune-privileged place in the body, and we're really quite fortunate that we can inject foreign substances into it that are not detected by the immune system. The CEDAR, SEQUIOA, and MAPLE trials tell us that it is still very difficult to manufacture a completely clean drug that doesn't have host/cell impurities because many of these drugs are manufactured in a recombinant fashion within *Escherichia coli*. We don't know for sure, but I don't think the problem is with the molecule itself.

I was also underwhelmed by the AAO presentations on anti-drug antibodies and NAb. Those studies only showed us who has a good immune system and who doesn't. Women with a history of intraocular inflammation had the highest inflammatory rate.⁵⁴ In these analyses, perhaps people with an adverse reaction to brolocizumab merely showed a proclivity to a good immune system. Unfortunately, I don't think anyone has the answer, which is likely very complex. To me, the bottom line is it's very difficult to make a completely clean drug that you can inject into the eye. Our success with ranibizumab, bevacizumab, and aflibercept have shown that it's possible, but it's not easily mimicked or reproduced.

Dr. Lim: That's a good point, Dr. Holekamp. You may remember that there was some early inflammation seen with the lyophilized form of ranibizumab. This was overcome with the liquid formulation. We do see some inflammation with aflibercept as well.⁵⁸

Dr. Csaky: I agree with Dr. Holekamp, yet when you see contaminant-related inflammation, it occurs within a relatively short period after the injection. But there were some cases of inflammation with brolocizumab that occurred long after the injection. If the inflammation was caused by a contaminant, should these not have occurred rather quickly? I've had an aflibercept-related eye inflammation that occurred within a week. Ranibizumab inflammation also occurred relatively quickly. What's worrying about brolocizumab is some of these cases of inflammation occur quite late after the injection. The underlying risk remains to be seen.

Dr. Lim: Dr. Holekamp's point about abicipar is well-taken, but Dr. Csaky's point about brolocizumab in terms of the timeframe is also valid; it may be the eye reacting to the novel molecular construct and it takes time to build up that reaction.

INCORPORATING NEW THERAPIES INTO CURRENT PRACTICE

Q | Dr. Lim: Assuming the FDA approves the new drugs in the pipeline like faricimab and the PDS, how will you use them in practice?

Dr. Do: I typically reserve novel agents for patients who have undergone anti-VEGF treatment but have had a suboptimal response to medicines that are currently available. After I gain experience with the new agents, assuming it's positive, then I start using it in my treatment-naïve patients. These new agents are extremely exciting, but most retinal specialists, including myself, will favor therapy that can be delivered in the office.

For example, although the PDS data looks promising, it requires a surgical procedure. There were some serious adverse events that occurred in ARCHWAY because of this indwelling implant, which is a concern for our elderly population.^{59,60} I think the PDS will be used in a select patient population, but I don't see myself using it as a first-line treatment. If the faricimab data are positive, then I would be open to using intravitreal faricimab because it's an office-based procedure and does not require going to the operating room.

Dr. Singh: I think the first thing we'll see is bevacizumab biosimilars, and we'll likely favor injectable therapies as a first step. But the second step needs to be a consideration of the barriers to treatment. Those barriers aren't with the patient or the understanding of the drug, it's with the providers being able to deliver these treatments and the payors approving the treatments for use. Although these novel injectable therapeutics are advantageous, we may be unable to use them for the first 3 to 6 months if we can't show a clinical benefit.



"I typically reserve novel agents for patients who have undergone anti-VEGF treatment but have had a suboptimal response to medicines that are currently available."

—Diana Do, MD

Dr. Lim: We'll have to prove that the patient failed X to move onto Y.

Dr. Singh: Exactly. Combination therapy is ultimately the way to go, but I don't know how it will translate to insurance companies who need to understand how treatment is progressing or doing in patients.

Dr. Holekamp: I think it's important to look at the time horizon of these therapies and how we will adopt them into our practice. I think biosimilars are on the horizon. There are some insurance companies that have bevacizumab biosimilars as preferred agents although they have never been injected into the eye. Clinicians are used to 2-year long studies, but clinical trials for biosimilars in ophthalmology are only 8 weeks. Retinal specialists will soon be dealing with "preferred agents" that are very foreign to us.

The next novel therapy on the horizon is likely the PDS, assuming it receives FDA approval. There's a unique set of potential complications associated with a surgical procedure that we don't have with anti-VEGF injections. We'll have to calculate the risk of undertreating patients against the risk of the PDS surgery, but it could be the next treatment incorporated into practice. Interestingly, patients enrolled into the PDS trials had an average of five anti-VEGF injections before getting the implant.¹⁷ This suggests that we could transition patients who started on anti-VEGF therapy to the PDS implant. ARCHWAY showed that 93% of patients preferred the PDS to their injection regimen.⁵⁹ It remains to be seen how and when we'll incorporate this into our practice, but we should take a patient's preference for long-term disease management into account.

The third set of things in the pipeline are designer anti-VEGF agents like KSI-301 and faricimab. Top-line results from the faricimab phase 3 studies in DME were recently announced. The clinical trials met the primary endpoint of noninferiority with more than 50% of patients reaching extended an extended dosing

interval of 16 weeks. The results from the faricimab phase 3 studies in AMD are pending, but faricimab is likely to be available before KSI-301.

Dr. Csaky: We will likely follow the same model that we did when aflibercept was approved; we'll take poor anti-VEGF responders and switch them to the new therapy. We all knew pretty quickly that there was something unique about aflibercept because a plethora of literature was published showing that patients switched to aflibercept improved anatomically.⁶¹ The clinical trial data was validated in the clinic, therefore we all started using aflibercept. We'll start with the poor responders and see if they improve. If they do, then we'll use the novel therapy on treatment-naïve patients. That's how I see it evolving.



"We will likely follow the same model [with faricimab] that we did when aflibercept was approved; we'll take poor anti-VEGF responders and switch them to the new therapy."

—Karl Csaky, MD, PhD

Dr. Lim: I agree with most of what everyone has said in terms of how they would do the implementation. Once safety of a new drug has been established, we'll evaluate its efficacy against what we already have. If the efficacy is about the same, I'll then consider durability. What will push me to use a new therapy is similar safety and efficacy, but longer durability. I also agree that I'm more likely to use a new therapy in poor responders.

In terms of the implants, I agree that I would not reach for the PDS as a first-line treatment. I'd reserve it for patients who require monthly anti-VEGF injections but who still have a good response, or for patients whom you can't extend beyond 8 weeks. I may also consider it in patients who need frequent injections but who have trouble getting to the clinic.

Q | Dr. Lim: Thank you all for the lively discussion. In closing, what are your final thoughts on the future of AMD treatments?

Dr. Csaky: My hope is that we'll have agents with better durability a year from now to help relieve that treatment burden for our patients.

Dr. Do: As we wait for new agents to be approved, we must prevent the undertreatment of patients with wet AMD. We must continue to engage our patients and treat them at the appropriate dosing intervals, especially during the COVID-19 pandemic, when it's so challenging for them to leave their home.

Dr. Holekamp: The last 15 years have been an era of what I call anti-VEGF 1.0. We've prevented blindness and we've helped our patients. But I'm looking forward to anti-VEGF 2.0. I think the designer anti-VEGF injections will be incremental improvements in durability. I'm hoping for a paradigm shift. The PDS implant and gene therapy could be what shifts that paradigm forward.

Dr. Singh: Retinal specialists are the driving force behind reducing blindness worldwide. We're yearning to improve the quality of life for our patients even further. I hope some of these more durable treatments will allow us to accomplish that.

Dr. Lim: We are entering into an era where we'll be using different mechanisms of action in our armamentarium against neovascular AMD. The future is bright for our patients. Many thanks to our panel for participating in this robust conversation and providing thoughtful commentary. ■

1. Obeid A, Gao X, Ali FS, et al. Loss to Follow-up among patients with neovascular age-related macular degeneration who received intravitreal anti-vascular endothelial growth factor injections. *JAMA Ophthalmol.* 2018;136(11):1251-1259.
2. Czeisler ME, Marynak K, Clarke KEN, et al. Delay or avoidance of medical care because of COVID-19-related concerns - United States, June 2020. *MMWR Morb Mortal Wkly Rep.* 2020;69(36):1250-1257.
3. Elam AR, Ehrlich JR, Lee P. Insights into eye care practice during COVID-19. *JAMA Ophthalmol.* 2020;138(9):988-989.
4. Varano M, Eter N, Winyard S, et al. Current barriers to treatment for wet age-related macular degeneration (wAMD): findings from the wAMD patient and caregiver survey. *Clin Ophthalmol.* 2015;9:2243-2250.
5. Wecker T, Grundel B, Reichl S, et al. Anti-VEGF injection frequency correlates with visual acuity outcomes in pro re nata neovascular AMD treatment. *Sci Rep.* 2019;9(1):3301.
6. Holekamp NM, Liu Y, Yeh WS, et al. Clinical utilization of anti-VEGF agents and disease monitoring in neovascular age-related macular degeneration. *Am J Ophthalmol.* 2014;157(4):825-833 e1.
7. Holz FG, Tadayoni R, Beatty S, et al. Key drivers of visual acuity gains in neovascular age-related macular degeneration in real life: findings from the AURA study. *Br J Ophthalmol.* 2016;100(12):1623-1628.
8. Ciulla TA, Hussain RM, Pollack JS, et al. Visual acuity outcomes and anti-vascular endothelial growth factor therapy intensity in neovascular age-related macular degeneration patients: a real-world analysis of 49 485 eyes. *Ophthalmol Retina.* 2020;4(1):19-30.
9. Hussain RM, Hariprasad SM, Ciulla TA. Treatment burden in neovascular AMD: Visual acuity outcomes are associated with anti-VEGF injection frequency. *Ophthalmic Surg Lasers Imaging Retina.* 2017;48(10):780-784.
10. Kandula S, Lamkin JC, Albanese T, Edward DP. Patients' knowledge and perspectives on wet age-related macular degeneration and its treatment. *Clin Ophthalmol.* 2010;4:375-381.
11. Greenlee TE, Wang YV, Kang H, et al. Consequences of lapses in treatment with vascular endothelial growth factor inhibitors in neovascular age-related macular degeneration in routine clinical practice. *Retina.* 2020 Jul 8. Epub ahead of print.
12. Yalamanchili SP, Maatouk CM, Enwere DU, et al. The short-term effect of a single lapse in anti-vascular endothelial growth factor treatment for diabetic macular edema within routine clinical practice. *Am J Ophthalmol.* 2020;219:215-221.
13. Goldberg R, et al. Impact of delayed time to treatment on visual outcomes in the HARBOR trial. Presented at: American Society of Retina Specialists; August 11-15, 2017; Boston, MA.
14. Chang TS, Tokame G, Casey R, et al. Short-term effectiveness of intravitreal bevacizumab versus ranibizumab injections for patients with neovascular age-related macular degeneration. *Retina.* 2009;29(9):1235-1241.
15. Comparison of Age-related Macular Degeneration Treatments Trials Research G, Martin DF, Maguire MG, et al. Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: two-year results. *Ophthalmology.* 2012;119(7):1388-1398.
16. Dugel PU, Singh RP, Koh A, et al. HAWK and HARRIER: Ninety-six-week outcomes from the phase 3 trials of brodalumab for neovascular age-related macular degeneration. *Ophthalmology.* 2021;128(1):89-99.
17. Campochiaro PA, Marcus DM, Awh CC, et al. The port delivery system with ranibizumab for neovascular age-related macular degeneration: results from the randomized phase 2 LADDER clinical trial. *Ophthalmology.* 2019;126(8):1141-1154.
18. Sahni J, Patel SS, Dugel PU, et al. Simultaneous inhibition of angiotensin-2 and vascular endothelial growth factor-a with faricimab in diabetic macular edema: BOULEVARD Phase 2 randomized trial. *Ophthalmology.* 2019;126(8):1155-1170.
19. Eyewire News. Allergan and Molecular Partners announce topline safety results from MAPLE study of abicipar pegol 2020. <https://eyewire.news/articles/allergan-and-molecular-partners-announce-topline-safety-results-from-maple-study-of-abicipar-pegol/>. April 2, 2019.
20. Adverum Biotechnologies. Adverum Biotechnologies announces positive interim data from cohorts 1-4 from OPTIC phase 1 trial of ADVM-022 intravitreal gene therapy for wet AMD, reports recent business progress and second quarter 2020 financial results. 2020.
21. Khurana RN, Kunimoto D, Yoon YH, et al. Two-year results of the phase 3 randomized controlled study of abicipar in neovascular age-related macular degeneration. *Ophthalmology.* 2020;128:1e12.
22. The FDA Does Not Approve Allergan's Wet AMD Drug Candidate Abicipar Pegol. Eyewire News. <https://eyewire.news/articles/allergan-and-molecular-partners-receive-complete-response-letter-from-fda-on-biologics-license-application-for-abicipar-pegol/2020/>.
23. Haug SJ, Hien DL, Uludag G, et al. Retinal arterial occlusive vasculitis following intravitreal brodalumab administration. *Am J*

- Ophthalmol Case Rep.* 2020;18:100680.
24. Jain A, Chea S, Matsumiya W, et al. Severe vision loss secondary to retinal arteriolar occlusions after multiple intravitreal brolicizumab administrations. *Am J Ophthalmol Case Rep.* 2020;18:100687.
 25. Bauml CR, Spaide RF, Vajzovic L, et al. Retinal vasculitis and intraocular inflammation after intravitreal injection of brolicizumab. *Ophthalmology.* 2020;127(10):1345-59.
 26. Witkin AJ, Hahn P, Murray TG, et al. Occlusive retinal vasculitis following intravitreal brolicizumab. *J Vitreoretin Dis.* 2020;4(4):269-279.
 27. Kondapalli SSA. Retinal vasculitis after administration of brolicizumab resulting in severe loss of visual acuity. *JAMA Ophthalmol.* 2020;138(10):1103-1104.
 28. Rosenfeld PJ, Browning DJ. Is this a 737 max moment for brolicizumab? *Am J Ophthalmol.* 2020;216:A7-A8.
 29. Campa C. New anti-VEGF drugs in ophthalmology. *Curr Drug Targets.* 2020;21(12):1194-2000.
 30. Sharma A, Kumar N, Kuppermann BD, et al. Faricimab: expanding horizon beyond VEGF. *Eye (Lond)* 2020;34(5):802-804.
 31. Danzing C. Clinical effects of blocking Ang-2 and VEGF with faricimab in the phase 2 STAIRWAY trial. ASCRS 2020 Virtual Annual Meeting.
 32. Roche. Roche's faricimab meets primary endpoint and shows strong durability across two global phase III studies for diabetic macular edema, a leading cause of blindness. <https://www.globenewswire.com/news-release/2020/12/21/2148299/0/en/Roche-s-faricimab-meets-primary-endpoint-and-shows-strong-durability-across-two-global-phase-III-studies-for-diabetic-macular-edema-a-leading-cause-of-blindness.html>2020.
 33. Liu K, Song Y, Xu G, et al. Conbercept for treatment of neovascular age-related macular degeneration: results of the randomized phase 3 PHOENIX Study. *Am J Ophthalmol.* 2019;197:156-167.
 34. Usui T, Sugisaki K, Iriyama A, et al. Inhibition of corneal neovascularization by blocking the angiotensin II type 1 receptor. *Invest Ophthalmol Vis Sci.* 2008;49(10):4370-4376.
 35. Khanani AM. Simultaneous inhibition of VEGF and Ang2 with faricimab in neovascular AMD: STAIRWAY phase 2 results. Presented at: Retina Subspecialty Day; American Academy of Ophthalmology Meeting; Oct. 27-30, 2028; Chicago, Ill.
 36. Lobov IB, Cheung E, Cao J, et al. Effects of combined inhibition of VEGF and Ang2 using aflibercept (VEGF Trap) and anti-Ang2 antibody on the developing retinal angiogenesis in mice. *Invest Ophthalmol Vis Sci.* 2015;56(7):2308.
 37. Dunn EN, Hariprasad SM, Sheth VS. An overview of the fovista and rinucumab trials and the fate of anti-VEGF medications. *Ophthalmic Surg Lasers Imaging Retina.* 2017;48(2):100-104.
 38. Stawski L, Han R, Bujor AM, Trojanowska M. Angiotensin II induces skin fibrosis: a novel mouse model of dermal fibrosis. *Arthritis Res Ther.* 2012;14(4):R194.
 39. Yang S, Zhao J, Sun X. Resistance to anti-VEGF therapy in neovascular age-related macular degeneration: a comprehensive review. *Drug Des Devel Ther.* 2016;10:1857-1867.
 40. Christakis PG, Agron E, Klein ML, et al. Incidence of macular atrophy after untreated neovascular age-related macular degeneration: age-related eye disease study report 40. *Ophthalmology.* 2020;127(6):784-792.
 41. Domalpally A, Danis RP, Trane R, et al. Atrophy in neovascular age-related macular degeneration: age-related eye disease study 2 report number 15. *Ophthalmol Retina.* 2018;2(10):1021-1027.
 42. Bailey C, Scott LJ, Rogers CA, et al. Intralesional macular atrophy in anti-vascular endothelial growth factor therapy for age-related macular degeneration in the IVAN Trial. *Ophthalmology.* 2019;126(1):75-86.
 43. Saddy SR, Tuomi LL, Ding B, et al. Macular atrophy in the HARBDR study for neovascular age-related macular degeneration. *Ophthalmology.* 2018;125(6):878-886.
 44. Jaffe G. Macular Atrophy (MA) in the phase 2 LADDER trial. Presented at: The Retina Society 2020 Annual Meeting 2020.
 45. Siedlecki J, Fischer C, Schworm B, et al. Impact of sub-retinal fluid on the long-term incidence of macular atrophy in neovascular age-related macular degeneration under treat & extend anti-vascular endothelial growth factor inhibitors. *Sci Rep.* 2020;10(1):8036.
 46. Jang L, Gianniou C, Ambresin A, et al. Refractory subretinal fluid in patients with neovascular age-related macular degeneration treated with intravitreal ranibizumab: visual acuity outcome. *Graefes Arch Clin Exp Ophthalmol.* 2015;253(8):1211-1216.
 47. Khanani AM, Kiss S, Turpcu A, et al. Phase 1 study of intravitreal gene therapy ADVM-Q22 for neovascular AMD (OPTIC Trial). *Invest Ophthalmol Vis Sci.* 2020;61(7):1154.
 48. Kodiak Sciences. Kodiak Sciences Announces New Longer-Term Safety, Efficacy and Durability Data from Ongoing Phase 1b Study of KSI-301 in Patients with Wet Age-Related Macular Degeneration, Diabetic Macular Edema and Retinal Vein Occlusion at the American Society of Retina Specialists (ASRS) 2020 Virtual Annual Meeting 2020.
 49. Al-Kharsan H, Hussain RM, Ciulla TA, et al. Innovative therapies for neovascular age-related macular degeneration. *Expert Opin Pharmacother.* 2019;20(15):1879-1891.
 50. Patel SS, Naor J, Qudrat A, et al. Phase 1 first-in-human study of KSI-301: a novel anti-VEGF antibody biopolymer conjugate with extended durability. *Invest Ophthalmol Vis Sci.* 2019;60(9):3670.
 51. ClinicalTrials.gov. A trial to evaluate the efficacy, durability, and safety of ksi-301 compared to aflibercept in participants with diabetic macular edema (DME) (GLEAM). ClinicalTrials.gov identifier: NCT04611152. <https://clinicaltrials.gov/ct2/show/NCT046111522020>; v. 2020.
 52. ClinicalTrials.gov. A Study to evaluate the efficacy and safety of KSI-301, an anti-VEGF antibody biopolymer conjugate, versus aflibercept in patients with neovascular (wet) age-related macular degeneration. (DAZZLE) ClinicalTrials.gov identifier: NCT04049266. <https://clinicaltrials.gov/ct2/show/NCT040492662020>; v. 2020.
 53. ClinicalTrials.gov. A study to evaluate the efficacy, durability, and safety of KSI-301 compared to aflibercept in patients with macular edema due to retinal vein occlusion (RVO) (BEACON). ClinicalTrials.gov identifier: NCT04592419. <https://clinicaltrials.gov/ct2/show/NCT045924192020>; v. 2021.
 54. Heier J. Assessing characteristics of patients with or without intraocular inflammation (IOI) in the brolicizumab treatment arms from the HAWK and HARRIER phase 3 studies. Retina Subspecialty Day at the Virtual American Academy of Ophthalmology Annual Meeting Paper presented on November 13, 2020.
 55. Nguyen QD, Das A, Do DV, et al. Brolicizumab: Evolution through preclinical and clinical studies and the implications for the management of neovascular age-related macular degeneration. *Ophthalmology.* 2020;127(7):963-976.
 56. Rodrigues GA, Mason M, Christie LA, et al. Functional characterization of abicipar-pegol, an anti-VEGF DARPIn Therapeutic that potently inhibits angiogenesis and vascular permeability. *Invest Ophthalmol Vis Sci.* 2018;59(15):5836-5846.
 57. Chamow SM, Ashkenazi A. Immunoadhesins: principles and applications. *Trends Biotechnol.* 1996;14(2):52-60.
 58. Souied EH, Dugel PU, Ferreira A, et al. Severe ocular inflammation following ranibizumab or aflibercept injections for age-related macular degeneration: a retrospective claims database analysis. *Ophthalmic Epidemiol.* 2016;23(2):71-79.
 59. Campochiaro P. Primary analysis results of the phase 3 archway trial of the port delivery system with ranibizumab (PDS) for patients with neovascular AMD. 2020 American Society of Retina Specialists Virtual Annual Meeting 2020.
 60. Roche. Phase III data show Roche's port delivery system with ranibizumab enabled over 98% of patients to go six months between treatments for neovascular age-related macular degeneration. www.roche.com/media/releases/med-cor-2020-07-22b.htm2020.
 61. Spooner K, Hong T, Wijeyakumar W, et al. Switching to aflibercept among patients with treatment-resistant neovascular age-related macular degeneration: a systematic review with meta-analysis. *Clin Ophthalmol.* 2017;11:161-177.

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DEMOGRAPHIC INFORMATION

Profession	Years in Practice	Patients Seen Per Week (with the disease targeted in this activity)	Region	Setting	Models of Care
___ MD/DO	___ >20	___ 0	___ Northeast	___ Solo Practice	___ Fee for Service
___ OD	___ 11-20	___ 1-15	___ Northwest	___ Community Hospital	___ ACO
___ NP	___ 6-10	___ 16-30	___ Midwest	___ Government or VA	___ Patient-Centered Medical Home
___ Nurse/APN	___ 1-5	___ 31-50	___ Southeast	___ Group Practice	___ Capitation
___ PA	___ <1	___ >50	___ Southwest	___ Other	___ Bundled Payments
___ Other				___ I do not actively practice	___ Other

LEARNING OBJECTIVES

Did the program meet the following educational objectives?	Agree	Neutral	Disagree
Compare the challenges faced in management and treatment of patients in clinical practice and describe their impact on treatment outcomes.	_____	_____	_____
Evaluate potential advantages of long-acting delivery options for wet age-related macular degeneration.	_____	_____	_____
Interpret how novel pipeline candidates are being developed to address longer treatment intervals.	_____	_____	_____

POSTTEST QUESTIONS

Please complete at the conclusion of the program.

1. Based on this activity, please rate your confidence in your ability to discuss potential advantages of long-acting delivery options for wet 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. Treatment compliance among patients with wet AMD can be improved by _____. Select ALL that apply.
 - a. Insisting on a monthly dosing strategy to ensure trips to the clinic
 - b. Establishing a strong physician-patient relationship
 - c. Properly educating the patient on their disease and the purpose of treatment
 - d. Referring patients to retinal specialist within 10 miles of their residence
3. A 70-year-old female with cardiovascular disease was referred to your practice. She has 20/25 visual acuity and a blind spot in her central visual field. She is on Medicare. You diagnose her with wet AMD. What does the panel suggest should be your next step for treating this patient?
 - a. Treat immediately with aflibercept, bevacizumab or ranibizumab
 - b. Provide the diagnosis, but delay treatment until insurance authorization is received
 - c. Observe her to see if her vision worsens
 - d. Treat immediately with brolocizumab
4. In the MAPLE study, _____ patients experienced inflammation with abicipar.
 - a. 15%
 - b. 10%
 - c. 9%
 - d. 7%
5. If and/or when should brolocizumab be considered in patients with wet AMD?
 - a. Brolocizumab should not be considered for any patient with wet AMD due to retinal vasculitis
 - b. Brolocizumab should be used in a the first-line setting in treatment-naive patients due to its superior drying power as compared with other anti-VEGF agents
 - c. Brolocizumab should be used in the second-line setting after starting patients on bevacizumab and switching after insurance approval
 - d. Brolocizumab can be considered in patients who have not responded to other anti-VEGF agents and who have significant intraretinal and/or subretinal fluid
6. If the port delivery system is approved, what will need to be considered when implementing it into practice?
 - a. The rate of inflammation
 - b. The surgical procedure and its potential risks
 - c. The increased rate of geographic atrophy
 - d. Its limited durability
7. _____ is a novel antibody biopolymer conjugate that allows for increased durability of action inside the eye.
 - a. ADVM-022
 - b. KSI-301
 - c. Faricimab
 - d. Port delivery system
8. What percentage of patients with wet AMD do not adhere to treatment?
 - a. 20%
 - b. 31%
 - c. 40%
 - d. 80%
9. What is known about the link between anti-VEGF therapy and development of macular atrophy?
 - a. Macular atrophy is definitely caused by anti-VEGF treatments in wet AMD
 - b. Macular atrophy may part of the natural history of choroidal neovascularization or may be present concurrently at the time of choroidal neovascularization diagnosis
 - c. Eyes with choroidal neovascularization rarely have macular atrophy present
 - d. Patients with wet AMD have preexisting macular atrophy, and no direct link can be made to anti-VEGF treatment

