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CURRENT AND FUTURE TREATMENTS IN AGE-RELATED MACULAR DEGENERATION: 2019 YEAR IN REVIEW

Provided by evolve medical education

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CONTENT SOURCE

This continuing medical education (CME) activity captures content from a roundtable 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 expanding therapeutic innovations and improved diagnostic technologies.

TARGET AUDIENCE

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

LEARNING OBJECTIVES

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

- **Identify** the current and potential future treatment options available for the management of two common retinal diseases (neovascular AMD, diabetic eye disease)
- **Summarize** the barriers preventing patients from achieving vision outcomes similar to those reported in clinical studies in clinical practice
- **Develop** individualized patient treatment plans to ensure optimal outcomes for patients with current and future treatments

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PRETEST QUESTIONS

Please complete prior to accessing the material and submit with Posttest/Activity Evaluation.

1. Please rate your confidence in your ability to apply the latest age-related macular degeneration (AMD) treatments in the clinic (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 intend to apply the latest advances in AMD treatment to "real-world" patient management (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. Which imaging modalities can be considered when evaluating a patient with treatment-naïve neovascular AMD (nAMD)?

a. Fluorescein angiography
b. Optical coherence tomography
c. Indocyanine green angiography
d. Fundus autofluorescence imaging
e. All of the above
f. None of the above; nothing beyond an Amsler grid needs to be considered

4. An elderly patient with exudative AMD and fluctuating vision has remaining subretinal fluid after more than 20 injections of aflibercept and ranibizumab. What is an acceptable treatment option?

a. Keep treating with aflibercept
b. Watch and wait
c. Switch back to ranibizumab
d. Switch to brolucizumab

5. In the LADDER trial, the median time to refill of the ranibizumab port-delivery system in the 100 mg/mL arm was _____.

a. 6 months
b. 8 months
c. 13 months
d. 15 months

6. What percentage of patients will likely remain within 3 lines of baseline vision 2 years after beginning intravitreal anti-VEGF injections for the treatment of nAMD, if managed appropriately?

a. 91%
b. 93%
c. 95%
d. 97%

7. In Protocol S, patients in the ranibizumab arm received monthly ranibizumab injections until _____.

a. The dose loading phase was complete, then went to a treat-and-extend regimen.
b. The dose loading phase was complete, then received laser.
c. The patient exited the study.
d. The proliferative diabetic retinopathy resolved or was stable for 3 months.

8. Inflammation has been observed in all cohort 1 patients with which of the following new therapeutics currently in development for nAMD?

a. RGX-314
b. APL-2
c. ADVM-022
d. Avacincaptad pegol

9. Rescue injections were given in _____ of patients in RGX-314 cohort 5.

a. 10%
b. 25%
c. 50%
d. 75%

10. _____ is a pediatric disease for which genetic testing may be considered for the entire family, including children who are asymptomatic.

a. Familial exudative vitreoretinopathy
b. Coats disease
c. Traumatic macular hole
d. Retinopathy of prematurity

Current and Future Treatments in Age-Related Macular Degeneration: 2019 Year in Review

Neovascular age-related macular degeneration (nAMD) currently has no cure, and patients need frequent, consistent anti-VEGF injections in order to optimize long-term vision. Anti-VEGF therapy is effective; 95% of patients with nAMD will stay within 3 lines of their baseline vision 2 years after beginning anti-VEGF treatment, and 40% will have an improvement of 3 lines from baseline in the same timeframe.[1] However, the injection need is a significant burden on patients and providers, leading to financial hardship, reduced productivity, and challenges with compliance.[2,3] A number of recent trial programs are exploring ways to reduce this burden through new agents, alternative therapies, increased drug durability, and novel drug delivery methods. The following roundtable brings together an expert panel of thought leaders who discuss current practice patterns across a wide range of retinal diseases and how our management approaches will evolve based on ongoing clinical trials.

— Charles C. Wykoff, MD, PhD, Moderator

Editor's Note: This roundtable took place before some of the safety concerns surrounding brolucizumab came to light.

CASE 1: TREATMENT STRATEGIES AND INTERVALS FOR AMD

GEETA A. LALWANI, MD: This gentleman with a history of nAMD presented after having been treated elsewhere with seven rounds of bevacizumab and four rounds of aflibercept. The fluorescein angiography (FA) shows an occult lesion with a vascular pigment epithelial detachment (PED; Figure 1). His vision was 20/40 at this time. We continued with aflibercept injections. After 3 monthly injections, the PED fully flattened, and his vision improved to 20/20. Two months later, another PED with subretinal fluid (SRF) developed in a different area (Figure 2). We initially continued with aflibercept injections monthly. However, when the PED and SRF did not resolve after 31 injections of aflibercept between October 2014 and August 2016 (Figure 3), we tried bevacizumab again as well as ranibizumab, and the dexamethasone 0.7-mg intravitreal implant. His visual acuity (VA) remains stable at 20/40 while undergoing monthly anti VEGF treatment.

Q | DR. WYKOFF: What's your baseline evaluation for a patient with treatment-naïve nAMD?

ANDREW MOSHFEGHI, MD, MBA: I do FA and indocyanine green angiography (ICGA) because I'm interested in seeing if polyps are present, but I wouldn't consider this required imaging. I also do optical coherence tomography (OCT). I have angiography (OCTA), but I don't use it on every patient because it slows things down. I use it on atypical cases.

DR. WYKOFF: What percent of patients in your clinic do you diagnose with polypoidal choroidal vasculopathy (PCV) at baseline? Do you treat them differently?

DR. MOSHFEGHI: About 10% of my patients have PCV, but I don't treat them differently. I'll consider integrating photodynamic therapy (PDT) if it's a difficult case, but I don't plan to do it from the beginning.

NINA BERROCAL, MD: I don't do FA on the first visit. I believe an OCT is sufficient. I follow them with OCT to see how they respond to treatment. If they don't respond as expected, then I image with FA and ICG.

ANTON ORLIN, MD: I'll get an FA and ICG at baseline for an atypical case. I'll then use OCT to guide treatment.

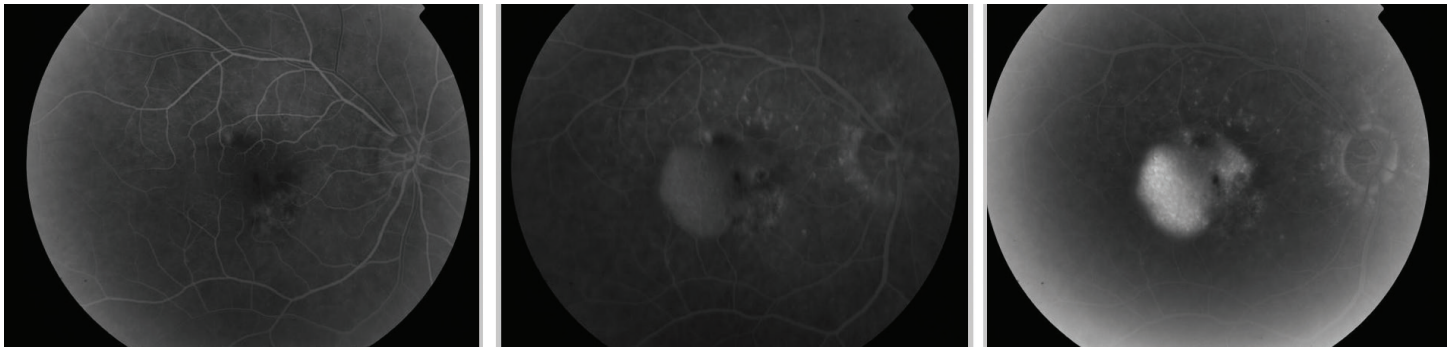

Figure 1. Case 1: Occult lesion with vascular PED on FA.

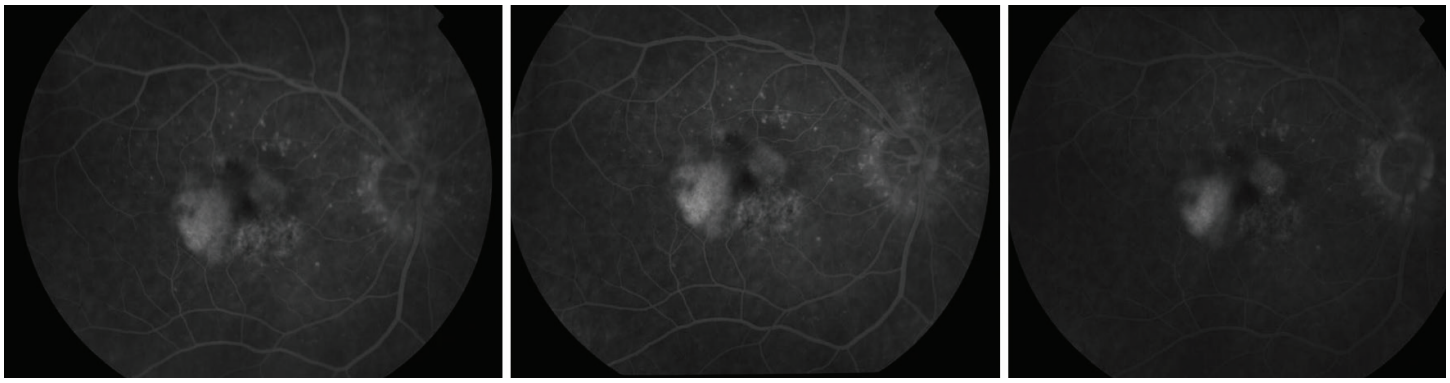

Figure 2. Case 1: Second PED 2 months after initial treatment and resolution of first PED.

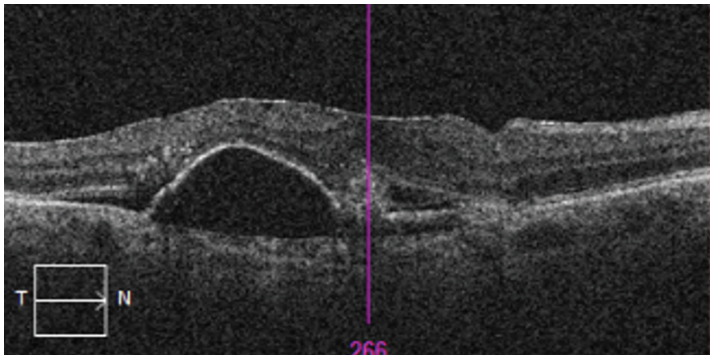

Figure 3. Case 1: Current imaging after treatment for second PED and fluid.

YOSHIHIRO YONEKAWA, MD: I start with OCT only, unless the diagnosis is equivocal.

DR. WYKOFF: What proportion of your nAMD and polypoidal patients are on monthly dosing versus quarterly dosing long-term?

DR. YONEKAWA: About 15 to 20% of my patients are on monthly injections. Half are at 6- to 8-week intervals and about a third are at 12 weeks. I avoid going beyond 12 weeks, for the time being.

DR. MOSHFEGHI: About 20% of my patients are on monthly injections.

DR. ORLIN: It's about the same for me, as well; 20% on monthly injections.

Q | DR. WYKOFF: About 25% of my patients are on monthly dosing. I have a low threshold to continue monthly dosing if there is residual central fluid that is responsive to anti-VEGF dosing. When you are dosing a patient quarterly and their retina is dry and stable for multiple intervals, do any of you ever stop injecting and transition to as needed (PRN) retreatment?

DR. LALWANI: I consider holding injections in a patient if their retina has been consistently dry at quarterly dosing. I will have them return for observation every 4 to 6 weeks for 6 months. I will gradually increase the follow-up interval to 2 months and then every 3 months if they remain dry. Recently, I had a patient who had been on quarterly dosing for a 18 months, who developed a retinal detachment following an injection. The risks of intravitreal injections are very low, but they are serious.[4] It is worthwhile to consider holding injections if a patient has been dry for a considerable amount of time.

DR. ORLIN: If a patient is doing well and remains dry on a quarterly interval, we can either continue injecting at this interval or try PRN treatment. I tend to individualize this decision based on various patient characteristics. For example, I'm more inclined to continue treatment as opposed to go with a PRN approach if the patient is monocular or on blood thinners.

DR. YONEKAWA: But another risk for stopping injections is massive re-bleeds. When this occurs, patients may experience sudden, severe vision loss.[5] This can be a big setback for visual potential. It's hard to predict who will develop these bleeds, but the severe hemorrhages may be more common in patients on blood thinners, so I try to maintain 12-week intervals for those patients in particular.

DR. MOSHFEGHI: I do treat-and-extend up to 12 weeks, and then I'll offer them to come in monthly for observational care. Only about 15% of them do it; the rest stay at quarterly dosing.

DR. BERROCAL: I like to use treat-and-extend treatment and that works well. That said, I think there are patients who need to be treated consistently to avoid bleeding, with the potential of severe visual loss. These patients, as Dr. Yonekawa stated, like patient's on blood thinners, should be treated consistently to prevent visual loss.

DR. WYKOFF: Those are great points. The LUCAS trial provided some clinically useful insight into quarterly dosing. This prospective, randomized trial compared bevacizumab and ranibizumab injections in 441 patients using a treat-and-extend protocol.[6] Once patients had resolution of exudative disease activity, the treatment interval was extended by 2 weeks at a time, up to a maximum of

12 weeks between treatments. Conversely, the treatment interval was shortened by 2 weeks if exudative activity recurred.[6] Patients who recurred at 12 weeks ultimately did relatively poorly, never gaining back all of the vision they had achieved before recurrence. The authors concluded that either dosing intervals should be restricted to less than 12 weeks, or if there is recurrence at 12 weeks, return to more frequent dosing immediately. I think the clinically relevant issue is, when you encounter recurrent exudative disease activity in a patient at quarterly dosing, don't simply decrease the interval back to 10 or 8 weeks; return to a much shorter interval to achieve ocular stability before considering extension again.

HAWK (n=1,082) and HARRIER (n=743) were parallel multicenter phase 3 trials investigating the safety and efficacy of brolucizumab to aflibercept.[7] Demographics, baseline characteristics, and primary and secondary endpoints were similar in both studies; the primary endpoint was noninferiority of mean best-corrected visual acuity (BCVA) change with brolucizumab compared with aflibercept from baseline to week 48. Secondary endpoints were central subfield retinal thickness, retinal fluid, and disease activity.

Patients in HAWK were randomized in a 1:1:1 ratio to one of three groups: brolucizumab 3 mg, brolucizumab 6 mg, or aflibercept 2 mg. In contrast, HARRIER patients were randomized in a 1:1 ratio to brolucizumab 6 mg or aflibercept 2 mg.

Brolucizumab met the primary endpoint and was also superior to aflibercept in multiple secondary endpoints indicating a signal for improved drying ability. Adverse events were similar for both agents, but rates of uveitis and iritis were higher in the brolucizumab group (2.2%, both) than aflibercept group (0.3% and 0.0%, respectively) in HAWK. These trials ultimately led to the approval of US FDA approval of brolucizumab.[8,9]

How do you plan to incorporate brolucizumab into your clinical practice?

DR. ORLIN: I'll start by using brolucizumab on patients who are suboptimal responders. Those requiring injections every 4 weeks, and still have persistent fluid.

DR. YONEKAWA: I think we'll have two populations for switching to brolucizumab: true nonresponders as Dr. Orlin mentions, but also those who do respond well but cannot be extended beyond monthly injections. Nonresponse, tachyphylaxis, and durability are all issues that new medications may be able to address.

MANAGING PERSISTENT FLUID

Q | **DR. WYKOFF:** We've seen anatomic data with abicipar, brolucizumab, faricimab, and aflibercept that all show a visible trend; when you give these medicines less than monthly, there tends to be a zig-zag or see-saw pattern of central subfield thickness (CST) change over time.[10-15] Relevant to this observation is that all of these recent trials in nAMD that have been pushing the durability limits have employed different criteria for retreatment or refill or rescue dosing. As a broad generality, maybe the field is becoming more tolerant to fluid, because we've seen that vision can be maintained, even in the presence of CST fluctuations.[16] How tolerant are you of fluid in your clinical practice?

DR. MOSHFEGHI: The messaging we receive is to be more tolerant of SRF, but that's not reflected in clinical practice. When I see SRF, I retreat. I simply don't tolerate SRF.

DR. WYKOFF: Great point to differentiate between different fluid compartments. The FLUID study specifically looked at SRF tolerance.[16] A total of 349 patients were randomized to ranibizumab 0.5 mg monthly until either both SRF and IRF resolved (intensive treatment arm) or only the intraretinal fluid (IRF) resolved with minimal central SRF (relaxed treatment arm) before extending treatment intervals; researchers continued treatment in all patients, but they extended the interval between dosing in the presence of persistent SRF in the relaxed arm. A total of 279 patients completed the 24 month endpoint, at which mean change in best-corrected VA (BCVA) from baseline was just 3 letters in the fluid-intolerant treatment group and 2.6 letters in the fluid-tolerant group. Both groups appeared to under-perform, possibly because of undertreatment in both groups. Furthermore, while patients in the fluid-tolerant group did receive fewer injections than the fluid-intolerant group, this difference was 15.8 versus 17 injections or an absolute difference of just 1.2 injections through 2 years. Do you integrate the FLUID data into everyday practice?

DR. YONEKAWA: I think there's a difference between SRF and IRF. Some studies suggest that IRF is more visually significant.[17,18] The CATT trial found that IRF had a greater negative impact on vision than SRF. IRF is also a negative prognostic factor for visual function gain and treatment response in nAMD.[19] If a patient still has a bit of SRF after aggressive treatment and their vision is good, that's my new baseline. There is some evidence that patients with subfoveal SRF actually have better visual outcomes, and suggestions that SRF may be protective against geographic atrophy.[20-23] I give patients monthly treatment and try to eliminate SRF initially. But if the fluid reminds, and their vision is good, I'll treat-and-extend as long as the fluid is stable.

Q | **DR. WYKOFF:** The long-term aspects of this disease make interpretation of visual outcomes over a short time frame challenging. In the short-term, residual fluid may not cause severe vision loss, but VA may slowly drift downward, 20/30 today, 20/40 in a year, and 20/50 in 2 years. The patient or physician may not notice a visual change over an extended interval. How do we detect VA loss at such a slow rate in our patients when we're more tolerant of fluid?

DR. LALWANI: Another challenge is the progression of dry AMD. How are you ever going to separate a decrease in VA related to the progression of dry AMD from the presence of persistent fluid? I don't know how we'll ever be able to separate those two things.

DR. WYKOFF: How does this translate to children with choroidal neovascular membranes (CNVM)? Should we be tolerant of fluid in those cases?

DR. BERROCAL: Children tend to respond very well to treatment[24] and it is effective in treating the underlying disease process. These children do not have an age-related, deteriorating disease. They have something that happened that can be treated definitively and effectively. They are treated once or twice, and many times that is all they need in their lifetime. A few patients may need supplementation with laser or steroids, but many are cured.

DR. WYKOFF: It's more of a PRN-treated disease you're describing.

DR. BERROCAL: Yes, specifically in terms of children with CNVM. I have treated children with CNVMs secondary to Best disease, trauma, pathologic myopia, angioid streaks, and chorioretinal colobomas, and the CNVMs resolved with a few treatments. There is no need for continuous, long-term, life-time treatment.

DR. YONEKAWA: Children tend to have type 2 membranes that respond well to injections like patients do with myopic CNVM.[25] Some children do have chronic disease activity, but I agree that compared to adult conditions, continuous anti-VEGF suppression tends to be less.

DR. WYKOFF: Some recent, elegant data on fluid status was presented in 2019 by Usha Chakravarthy, MD, PhD, CBE, and colleagues looking at the IVAN and CATT data, independent of drug.[26, 27] She considered patients in quartiles based the variability of CST longitudinally, meaning she looked at patients in quartiles from the least variability to the most variability. Doing this, she found a strong correlation with increasing variability and worse visual outcomes. This difference persisted despite correcting for baseline differences between the populations. The patients with none to minimal fluctuation did far better than patients with a great deal of fluctuation. The differences were large in the numbers of letters gained, challenging the clinical practice of being more tolerant of recurrent fluid, a trend we are seeing in clinical practice and clinical trials.

DR. MOSHFEGHI: The problem is that these studies looked only at the quantity of fluid, not the quality of the fluid. If they correct for SRF versus IRF, it may be more compelling.

DR. ORLIN: Did they account for the size of the lesion and amount of fluid of the lesion at baseline?

DR. WYKOFF: Some baseline factors were considered and controlled for. But, you make a good point. This is a post-hoc analysis; it's hypothesis generating and needs to be studied further.

DR. LALWANI: Does that mean there is some predictability for future treatment intervals based on the response after the loading dose? In HAWK and HARRIER, 80% of those retinas that were dry at week 16 went on to need quarterly treatment. Only 20% of the patients with dry retinas after the loading doses moved down to 8-week treatment.

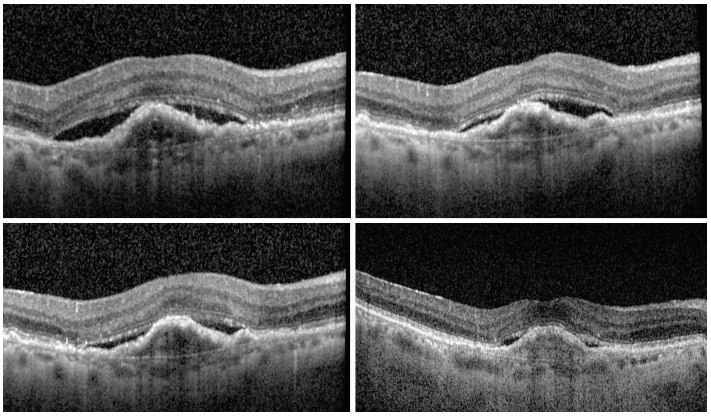

Figure 4. Case 2: Persistent fluid in a female patient with nAMD.

DR. WYKOFF: Yes, I agree there does seem to be some predictability after the loading doses.

DR. LALWANI: Should we be using the presence of fluid after three injections of brolucizumab as a prediction that those retinas may need more frequent treatment; maybe more frequently than every 8 weeks.

DR. ORLIN: Is anyone bringing a patient in more frequently if there is still significant fluid at a monthly interval?

DR. LALWANI: I bring them back at 2-week intervals to check if the retina is dry at any point. But I do not typically inject more frequently than monthly.

CASE 2: MANAGING PERSISTENT FLUID AFTER SWITCHING

DR. ORLIN: Our next case is a 77-year-old woman with 20/50 VA who was diagnosed with wAMD in her right eye. We treated her with monthly ranibizumab, and her VA remained 20/50. She initially improved, but then plateaued with persistent fluid after the next 4 to 6 monthly injections. We switched her to monthly aflibercept. Her VA remains 20/50 but has persistent fluid on OCT despite monthly treatment. The amount of fluid increased whenever treatment was extended beyond 4 weeks. Figure 4 shows her most recent follow-up.

The patient is receiving monthly injections, and as discussed, the fluid worsens whenever she travels or is lost to follow-up, delaying treatment for a couple of weeks. Now that brolucizumab is available, I am going to consider switching her to that.

Q | **DR. WYKOFF:** Let's take the hypothetical situation in which you achieve a dry macula with monthly loading doses of brolucizumab and extend the patient's interval to

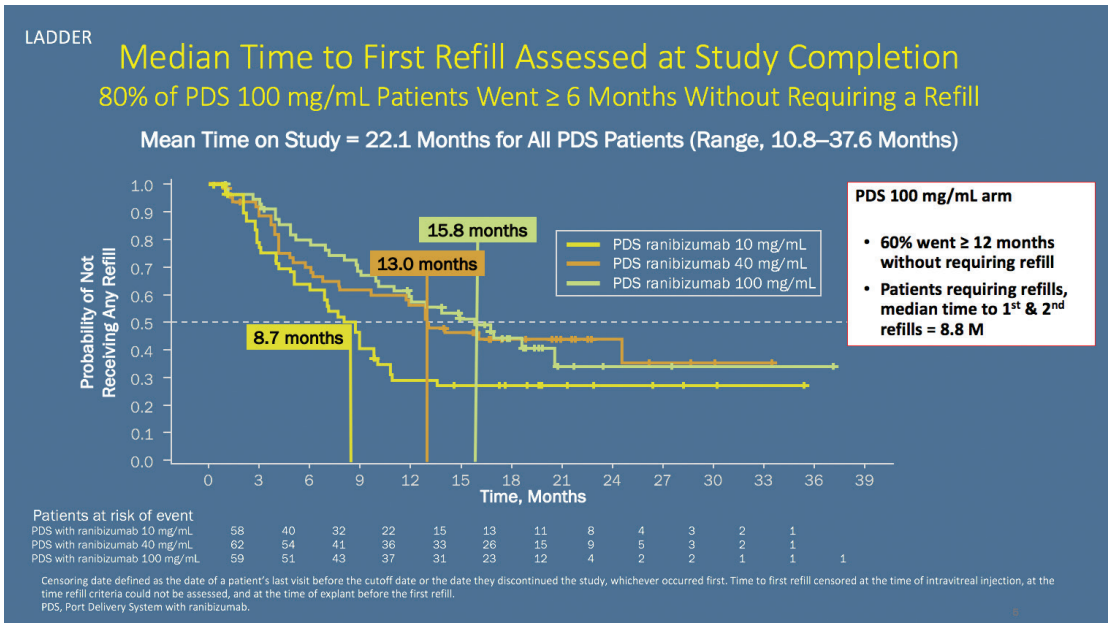

Figure 5. LADDER trial: Median time to first refill assessed at study completion.

trial compared three doses of ranibizumab (10 mg/mL, 40 mg/mL, and 100 mg/mL) within the port-delivery system with monthly ranibizumab injections. The primary endpoint was time to first refill of the port-delivery system. The data were impressive; median time to first refill in the 10 mg/mL group was 8.7 months; 13 months in the in the 40 mg/mL group; and 15 months in the 100 mg/mL group. That's a long time between refills compared to monthly dosing. About 80% of patients in the 100 mg/mL group were able to go at least 6 months and 60% went more than a year before needing a refill. Of the patients who did require refill, their average time to refill was 8 to 9 months (Figure 5). VA outcomes appeared equivalent to monthly dosing, if not better with the highest dose port-delivery approach.

Is this data meaningful? Would you incorporate this treatment into your practice, and, if so, in which patients?

DR. YONEKAWA: These are very impressive data. In terms of efficacy and durability, this is game-changing.

DR. LALWANI: I agree with Dr. Yonekawa—the efficacy and durability data is very strong. It would be worthwhile to consider for patients requiring frequent dosing.

DR. YONEKAWA: It's important to remember the inclusion criteria for the study, where they chose patients who were confirmed to respond well to anti-VEGFs. Patients included in the study had a diagnosis of nAMD within the previous 9 months with vision between 20/20 and 20/200. They received previous treatment, with at least two or more anti-VEGF injections prior to screening and demonstrated response.[28] In order to see similar outcomes, we would probably need to focus on anti-VEGF responders with a relatively new diagnosis. Patients with nonresponsive chronic disease probably would not be the best candidates.

Q | **DR. WYKOFF:** For safety, out of 179 patients, there were a small number of cases of endophthalmitis (n=2) and retinal detachment (n=3) more than a month after surgery. The surgical technique was modified early on in the phase 2 trial and this modification successfully reduced the vitreous hemorrhage rate.[29] The initial surgical technique required a stab incision using a 3.2-mm blade and no cautery of the choroid. The revised technique involved a scleral incision to visualize the choroid with laser-applied coagulation

8 weeks. If she has recurrence of fluid, will you keep her on 8-week brolucizumab? Or do you go back to monthly injections with one of the other anti-VEGF agents?

DR. ORLIN: If it's a similar amount of fluid as before, then I'm going to keep her at 8-week brolucizumab injections, which at least decreases her treatment burden.

DR. WYKOFF: Well done. The patient has the best prognostic indicators—a type 1 lesion with an intact retinal pigment epithelium. There's no IRF. Who would keep dosing this patient monthly versus considering a new baseline?

DR. YONEKAWA: I'm actually pretty happy with her follow-up OCT. If the patient is happy with his or her vision and the small amount of SRF is draping outside of the fovea, I'm fine with this as a new baseline. If something is working for a patient, I usually stick with it, but I know this patient doesn't want to come in monthly for years to come, so we would have the discussion about more durable options also.

DR. ORLIN: What impact will the fluid have on her vision in the future?

DR. MOSHFEGHI: For the sake of lessening the treatment burden, I might tolerate a small amount of fluid as long as the patient's vision doesn't change.

SURGICAL TREATMENT FOR nAMD

DR. WYKOFF: The LADDER trial was a phase 2 multicenter trial evaluating the safety and durability of a port-delivery system containing ranibizumab in 220 patients with neovascular AMD.[28] The

of the visible choroid before entry into the vitreous cavity using the same size blade as before. What do you make of the safety profile? Are you worried that a foreign body is going to cause a problem?

DR. YONEKAWA: The endophthalmitis rate was 1.6%, which is a lot higher than you would get with intravitreal injections. However, this is a very different type of procedure that's more similar to a glaucoma surgery. These numbers are comparable with tubes and trabeculectomy.

DR. MOSHFEGHI: The endophthalmitis rate is too high. I'm curious to see if they can modify the technique further and reduce the adverse events.

DR. YONEKAWA: We're getting better in selecting patients. I think it's important to make sure patients have good Tenon's tissue and conjunctiva. I would avoid patients with any history of buckles or thin conjunctiva.

CASE 3: MANAGING PROLIFERATIVE DIABETIC RETINOPATHY

DR. MOSHFEGHI: Our next case is a 51-year-old Asian male with type 2 diabetes. He's insulin-dependent, on dialysis, has gout, and had a traumatic brain injury at the age of 20. His VA is 20/40 in both eyes with new floaters in his left eye. He has an early proliferative diabetic retinopathy (PDR), but his diabetic macular edema (DME) isn't bad. His intraocular pressure is 14 mm Hg in his right eye and 15 mm Hg in his left. He did not fully cooperate with the exam.

DR. WYKOFF: Let's pause here. How do you manage PDR today without center-involved DME?

DR. ORLIN: I think it depends on the patient. I tend to start treating most patients with anti-VEGF therapy and then combine that with laser at a later date. If a patient has a history of noncompliance, or is unable to return at frequent intervals, I would recommend just starting with panretinal photocoagulation.

DR. BERROCAL: The laser is ideal for patients who are not compliant with treatment and for those who miss appointments.[30] A good number of patients do not to come back consistently for injections. These are the patients who get lost to follow-up when they are on an injection-only treatment and later present with aggressive tractional retinal detachments. Before I begin treatment, I have a very serious discussion of treatment options and complications of noncompliant behavior. If the patient chooses injection-only management, then I need a strong, realistic commitment from the patient. I do tell them we can always reassess treatment options if it becomes a burden to their life and the life of their caretakers. Many patients are honest, and they will tell me they prefer laser treatment.

DR. MOSHFEGHI: I agree with Dr. Orlin. I like to start patients with anti-VEGF injections knowing that I'll likely move to laser at a later date.

Q | **DR. WYKOFF:** Let's take the patients who are compliant with their anti-VEGF injections but don't want laser treatment. Is PDR a PRN disease, or is this a chronic disease? Do you use a treat-and-extend approach or fixed intervals? What do you do for your PDR management with anti-VEGF?

DR. LALWANI: There are two previous studies that have looked at anti-VEGF injections as a way to control PDR: Protocol S with ranibizumab and the PANORAMA study with aflibercept. Both studies used some degree of monthly loading doses, between three to six doses. In Protocol S, after 6 monthly doses, patients received additional treatment on a prespecified PRN basis. In PANORAMA, patients received either five or three loading doses, and then moved to an every 8- or 16 week treatment, respectively. The difficulty for me lies in the long term. How long should we treat these patients after 2 years? There's no treatment endpoint, in other words.

DR. YONEKAWA: We're always going to try to undertreat patients if possible. That's what occurs in the real world. I do three monthly loading doses and then quarterly injections unless it's still very active. I carefully select my patients, and have a similar conversation that Dr. Berrocal just mentioned about commitment. I usually start with PRP, but will do anti-VEGF injections for very fresh neovascularization. If they have any fibrosis, I go with laser because those patients were excluded from Protocol S.[31,32]

DR. WYKOFF: To clarify, none of you treat PDR as a PRN disease?

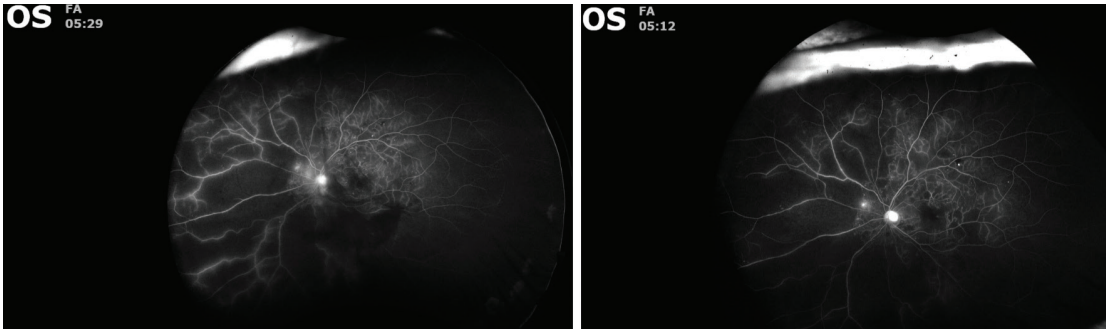

Figure 6. Case 3: Male patient with PDR.

DR. MOSHFEGHI: Not for PDR by itself.

DR. WYKOFF: I strongly agree. It's interesting because the majority of patients in Protocol S from the Diabetic Retinopathy Clinical Research Network still needed anti-VEGF dosing, but there was a minority of the population who did not receive

retreatment in years 4 and 5 in the anti-VEGF monotherapy arm.[31, 32] The problem is that this is a chronic disease and the concern is the high likelihood of eventual recurrent activity. Tell us more about the case.

DR. MOSHFEGHI: Going back to the case, I treated this patient monthly in the beginning, but then extended him out to quarterly dosing. I started him on bevacizumab and then switched to aflibercept. His vision remained stable but the capillary nonperfusion didn't really improve. It's less leaky, but we still see a little bit of leakage nasal to the disc and on the disc itself (Figure 6). I wasn't treating him to be completely dry. I was trying to pick a pragmatic, reasonable interval, and 3 months seemed to work. It's probably a little too long, to be honest, to get him completely dry. The interval should likely be 1 or 2 months.

DR. WYKOFF: Do you obtain a baseline widefield FA before treatment in most of your patients? For those of you who do get widefield imaging, when do you repeat it?

DR. BERROCAL: I like widefield FA for adults (and especially for children). I'll repeat it if a patient has break-through bleed or they don't respond as I expect. Understanding the entire retinal vasculature angiographically is essential.

DR. LALWANI: Yes. I'm always surprised with the severity of the disease on widefield FA my exam. It is often worse.

DR. ORLIN: Most of my patients with significant retinopathy get a widefield FA. Sometimes I'll see significant neovascularization and ischemia where I don't expect to. It can help guide the type of treatment and how often to follow a patient.

DR. MOSHFEGHI: I don't do it on everybody. For somebody who has incomplete laser, I'll do follow-up FAs.

DR. YONEKAWA: I think widefield FA is amazing. I love it and wish I had it at every single office. There's no data that indicates it's a must-have, but it's very nice to have.

EARLY-STAGE DIABETIC RETINOPATHY

DR. WYKOFF: Aflibercept was approved by the FDA for the treatment of diabetic retinopathy (DR) based on 6-month and 1-year PANORAMA data, illustrated in Figure 7. PANORAMA included three randomized arms: sham, aflibercept every 8 weeks, and aflibercept every 16 weeks, after 5 and 4 loading doses respectively.[33] The primary endpoint was the proportion of patients who improved on the DR severity scale from baseline by 2 steps or more at weeks 24 and 52. A total of 65% of patients who received aflibercept every 16 weeks experienced a 2-step or more improvement, while 80% of patients in the 8-week group saw improvement; compared to 15% of patients in the sham arm. Two-year data will be available in February of 2020.

Has this trial moved the needle? Are any of you regularly talking to your patients about treatment of nonproliferative DR (NPDR) without DME?

DR. YONEKAWA: I'm definitely talking to them about it, but not many patients are interested. I always bring it up, especially if they have moderate to severe DR, but most patients prefer to hold on treatment.

DR. ORLIN: With injection therapy, you're committing patients to multiple follow up visits when they already have frequent appointments with various other physicians to contend with. In clinical practice, patients are not eager to commit to this, particularly if their vision is good and they do not have advanced findings. With that said, we know patients will have better vision in the long run if we treat them actively rather than watching and observing until a problem arises.

DR. WYKOFF: PANORAMA structured the loading doses. I'm not convinced that we need loading doses in a real-world setting. I often will initiate with quarterly or every 16-week dosing with these patients. I explain to the patient that I'm going to see them every 3 to 4 months regardless, and I can proactively treat them or wait for progression of the disease before treatment initiation. I have found quite a few patients are interested in initiation of treatment earlier in the disease process.

DR. LALWANI: I also offer treatment to patients with severe NPDR because the conversion to PDR within 1 year is 50%.[34] That number is striking.

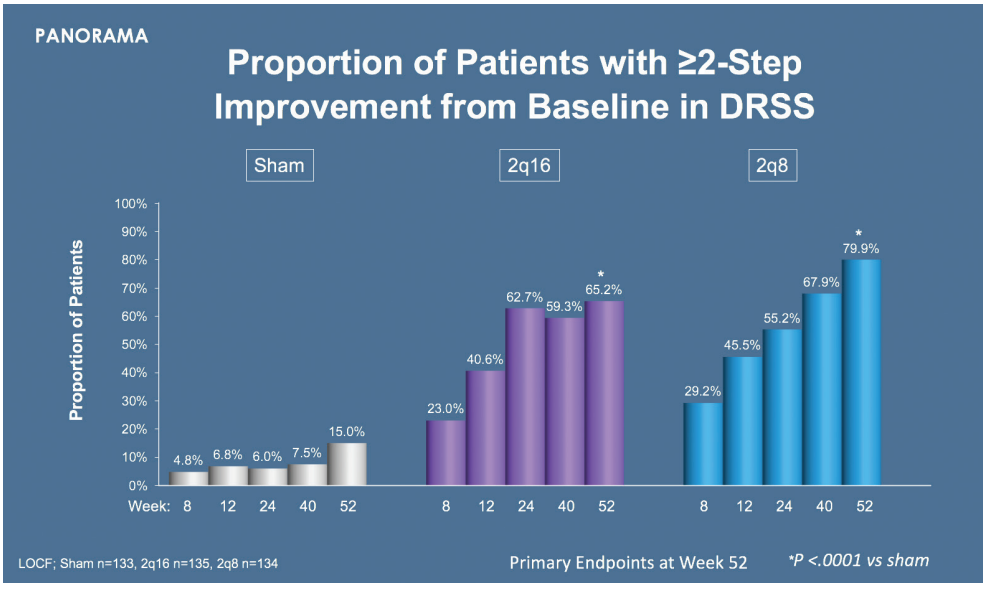

Figure 7. PANORAMA data: Proportion of patients with at least a 2-step improvement from baseline in DRSS.

DR. MOSHFEGHI: I don't like the concept of treating this type of NPDR patient with intravitreal anti-VEGF monotherapy that frequently. I'd much prefer to initiate treatment when more clearly vision threatening diabetic complications are encountered (eg, DME, PDR). The potential complications associated with intravitreal injections are non-trivial, not to mention the long-term treatment burden for the patient and their caregivers.

CASE 4: RETINAL SURGERY IN PATIENTS WITH A HISTORY OF PEDIATRIC DISEASE

DR. WYKOFF: Our next case will explore surgery in adults who have a history of pediatric disease.

DR. BERROCAL: Common pediatric disorders relevant to adult retinal management include myopia/Stickler's syndrome, retinopathy of prematurity, X-linked retinoschisis, Coats disease, familial exudative vitreoretinopathy (FEVR), and incontinentia pigmenti.[35-40] For example, patients with Coats disease were diagnosed and treated at a young age. These patients stop going to the ophthalmologist and present as adults with new exudation and telangiectasia. This is a common occurrence in childhood ophthalmic diseases. Any of these patients may present with complications of their underlying disease as a result of the "aging" vitreous. For example, as the vitreous changes, patients may present with vitreous hemorrhages from posterior vitreous detachments or traction from organized tight vitreous (trampoline vitreous).

Another common disease in my clinic is FEVR. If patients with FEVR, make it to adulthood without a problem, then they have a mild peripheral smoldering disease.[40] Classically, we have thought of FEVR parents as carriers of the disease, but I believe if genetically confirmed they have the disease and need to be followed angiographically.

This case is of a 39-year-old asymptomatic mother of a child with LRP5 mutation. The mother also has the mutation. In Figure 8, the leakage and avascularity of the retina in the far periphery is visible.

DR. WYKOFF: What's your evaluation plan?

DR. BERROCAL: The more familiar I become with the different mutations in FEVR, the more interesting I find this disease. I have come to realize there are many patients who go undiagnosed into adulthood. The findings in adults with FEVR might be confused with other common diseases of adulthood. I believe genetic testing will solve many of these issues. My present evaluation is widefield angiography with genetic testing, realizing that approximately only 50% of the FEVR mutations are known.

DR. MOSHFEGHI: What's your treatment threshold?

DR. BERROCAL: In this particular case, I treated her with laser photocoagulation to the avascular area because of the leakage present on angiography. Her son, who was my original patient, presented at age 3 with very aggressive bilateral tractional retinal detachments. This led to the genetic pursuit of a diagnosis. In this case, LRP5 FEVR mutation. Her two daughters, who were born later, were genetically tested and in the positive child, followed by widefield angiography. Testing the children genetically has reduced unnecessary examinations under anesthesia for widefield angiography in the genetically negative LRP5 daughter.

DR. WYKOFF: What are the clinical differences between FEVR and Coats disease?

DR. BERROCAL: FEVR is typically bilateral and can be seen in both men and women. Coats disease tends to be unilateral and it is seen mostly in boys.[40,37] The oldest Coats patient I have is age 65 and I have followed him for 20 years. He developed areas of telangiectasia throughout his life, which we treated with laser. He also had a vitreous hemorrhage at the time of a posterior vitreous detachment that resolved with observation (all in one eye), despite having hypertension. That said, one has to realize that FEVR can be present with a exudation (Coats-like response). In my mind, bilateral exudation with what seems to be telangiectatic vasculature is FEVR, not Coats.

DR. WYKOFF: Tell us about genetic testing. How and where do you recommend clinicians perform genetic testing?

Figure 8. Case 4: A 39-year-old asymptomatic patient with LRP5 mutation.

DR. BERROCAL: Many families can't afford genetic testing, although this is quickly changing since gene therapy has arrived. Now there are companies that offer free genetic testing, such as Invitae. Invitae performs free genetic testing for up to 200 genes related to eye disorders, including most of the known FEVR genes. The testing is conducted using saliva or blood. If the testing comes back negative but I'm still suspicious,

I'll do a bigger panel with the Molecular Vision Lab, the MVL panel, which tests for up to 500 genes.

DR. WYKOFF: With the diagnosis of an LRP-5 mutation, confirming a diagnosis of FEVR, does that change your management? Are you more or less likely to treat because of the genetic diagnosis? How does it help you?

DR. BERROCAL: It helps because this patient, for example, has three children. I will monitor the children in a different way, knowing they likely have FEVR. Before genetic confirmation of the disease, we would do serial FA in the operating room in order to diagnose and treat the disease as early as possible. Now with genetic confirmation, we hone our efforts in the genetically positive family members, decreasing unnecessary testing. Also, I believe that in the future we will have a good idea of how these different mutations behave and how to monitor them and treat individually.

DR. YONEKAWA: We don't have good genotype phenotype studies yet for FEVR, but we will in the future. It's a hard disease to study because the penetrance is variable. In terms of how genetic testing influences management, it changes who I refer the patient to. Some FEVR genes will have systemic manifestations, like osteoporosis in LRP5 mutations. KIF mutations are associated with microcephaly. If the FEVR panel comes back negative and I'm still suspicious because of concurrent systemic issues, whole-exome sequencing is a possibility for these patients; it's cheaper now. There is a lot of noise that can come back with genetic testing, so I always refer patients to our genetic counselor also.

FUTURE THERAPEUTICS IN AMD TREATMENT

GENE THERAPY

DR. WYKOFF: Gene therapy for the treatment of neovascular AMD is in development. We currently have two options using different approaches: ADVM-022 (Adverum Biotechnologies) is an intravitreal delivery of a vector that expresses aflibercept following a one-time injection. RGX-314 (Regenxbio) uses a vector expressing ranibizumab delivered to the subretinal space with vitrectomy.[41-43]

Both approaches have reported positive trial data and both trial programs enrolled neovascular AMD patients requiring ongoing anti-VEGF dosing. In the OPTIC study using ADVM-022, 6-month data for cohort 1 involving six patients has been reported and no patients have received a rescue anti-VEGF injection, with anatomic improvements as well as manageable inflammatory reactions observed in all patients.

A larger dataset has been reported with RGX-314. Data from 42 patients has been reported from the phase 1/2a program, including patients in five dosing cohorts, ranging from 3x109 to 2.5x1011 GC/eye.

Data through 6 months has been reported for the majority of patients in cohorts 4 and 5; patients in both cohorts had a meaningful reduction in their anti-VEGF treatment burden. A total of 42% and 75% of patients in cohort 4 and 5, respectively, had no rescue injections during the 6-month follow-up period. Furthermore, patients in cohort 5 demonstrated improved VA (mean BCVA increase of 4 letters) and decreased retinal fluid.[42] The retreatment criteria in this trial were remarkably conservative, meaning investigators could retreat for basically any level of disease activity that they believed warranted a bolus anti-VEGF injection. What do you think about the change in dosing frequency?

DR. LALWANI: With the highest dose, the dosing frequency was significantly lower, 4.5 versus 1.3 injections, respectively. One patient, accounted for most of those injections.

DR. WYKOFF: Right. If you had access to RGX-314, and the safety profile was excellent, would you use gene therapy in every patient? Who is gene therapy for?

DR. MOSHFEGHI: This is a lot of patients to take to surgery. I'd probably do it on the recalcitrant, monthly patients who respond well.

DR. WYKOFF: One piece of data that has been controversial for the ADVM-022 program is the inflammation reported. Most of the inflammation seems to be relatively mild and readily controlled with topical steroids. However, no inflammation has been seen in the RGX-314 program.

DR. LALWANI: Weren't ADVM-022 patients placed on oral steroids in cohorts 1 and 2?

DR. WYKOFF: Yes, in the ADVM-022 program, there's a 10-day baseline prophylactic course of oral steroids given in cohort 1. In cohort 3 and beyond, the oral steroid baseline prophylaxis is being replaced by topical steroids because the inflammation in cohort 1 appeared to be well-managed with topical steroids. Is the inflammation a concern to you?

DR. MOSHFEGHI: It depends on how clinically relevant it is, if it causes vision loss, and how long they need to be treated.

DR. BERROCAL: Yes. If we know that it goes away without any long-term, negative visual outcomes, then I'd say it's manageable.

DR. YONEKAWA: There's also a big difference between one intravitreal injection and an incisional surgery. Mild inflammation may be tolerable compared to taking a patient to the OR. It will be a thorough discussion with the patient and family about these pros and cons. We also have to remember that it's still a phase 1 study.

GEOGRAPHIC ATROPHY

DR. WYKOFF: Apellis Pharmaceuticals reported 18-month results of their phase 2 FILLY study of APL-2 in patients with geographic atrophy (GA) associated with AMD. The primary endpoint at 12 months was met, with a 29% reduction in GA growth with monthly APL-2 dosing and a 20% reduction in GA growth with every other month APL-2 dosing compared with sham. Supporting an effect of APL-2 on slowing GA progression, during months 12 to 18 patients were followed without treatment and during this off-treatment period, GA lesions grew

at a similar rate to sham. As for safety, there were 26 cases of exudative AMD development across all cohorts, a conversion rate that appeared to be dose dependent: 20.9% in the monthly APL-2 group, 8.9% in the every-other-month APL-2 group, and 1.2% in the sham group.[44,45]

In October 2019, another positive phase 2 study was also reported targeting GA growth. Top-line results from the aptamer complement C5 inhibitor avacincaptad pegol (Iveric Bio) showed that active treatment significantly slowed GA growth. Reduction in mean GA growth rate was reported to be approximately 27% in both avacincaptad pegol groups compared with sham controls at 12 months.[46] Of interest, similar to observations in the FILLY study with APL-2, there were numerically more conversions to exudative AMD in the active treated arms, 9% and 9.6%, compared to sham at 2.7%.

Are these phase 2 datasets an indication that we are onto something with complement inhibition in slowing GA growth? Or, do you think we need to be cautious and wait for more robust data from larger phase 3 trials?

DR. BERROCAL: Let's wait and see.

DR. ORLIN: Agree, we need to see.

DR. LALWANI: I think it's compelling. We still have the challenge of intravitreal delivery, which means monthly injections.

DR. WYKOFF: So, we're cautiously optimistic.

DR. YONEKAWA: There's so much more hope now during discussions with our patients. I think we need to be optimistic. I'm hoping that it works.

DR. WYKOFF: How many of you discuss these trials and potential future therapies with your patients?

DR. BERROCAL: You have to discuss future prospects with them because they need hope. Patients constantly ask what else can be done for them. I tell them there have been advances in medicine during the past few years that we never imagined possible. Hope is the best medicine.

DR. WYKOFF: Does the observed increased development of exudative AMD in both of these phase 2 programs with active treatment worry anyone?

DR. LALWANI: It doesn't worry me; it's treatable.

DR. MOSHFEGHI: It's worth it if it actually turns out to stop GA.

DR. YONEKAWA: It's definitely a signal, and we need to be aware of it.

DR. WYKOFF: Many thanks to our expert panel for providing comments on current and future treatments for AMD and a host of both common and rare retinal diseases. ■

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CURRENT AND FUTURE TREATMENTS IN AGE-RELATED MACULAR DEGENERATION: 2019 YEAR IN REVIEW

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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
Identify the current and potential future treatment options available for the management of two common retinal diseases (nAMD, diabetic eye disease)	_____	_____	_____
Summarize the barriers preventing patients from achieving vision outcomes similar to those reported in clinical studies in clinical practice	_____	_____	_____
Develop individualized patient treatment plans to ensure optimal outcomes for patients with current and future treatments	_____	_____	_____

POSTTEST QUESTIONS

Please complete prior to accessing the material and submit with Posttest/Activity Evaluation

1. Based on this activity, please rate your confidence in your ability to apply the latest age-related macular degeneration (AMD) treatments in the clinic (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 intend to apply the latest advances in AMD treatment to "real-world" patient management (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. Which imaging modalities can be considered when evaluating a patient with treatment-naïve neovascular AMD (nAMD)?

a. Fluorescein angiography
b. Optical coherence tomography
c. Indocyanine green angiography
d. Fundus autofluorescence imaging
e. All of the above
f. None of the above; nothing beyond an Amsler grid needs to be considered

4. An elderly patient with exudative AMD and fluctuating vision has remaining subretinal fluid after more than 20 injections of aflibercept and ranibizumab. What is an acceptable treatment option?

a. Keep treating with aflibercept
b. Watch and wait
c. Switch back to ranibizumab
d. Switch to brolucizumab

5. In the LADDER trial, the median time to refill of the ranibizumab port-delivery system in the 100 mg/ml arm was _____.

a. 6 months
b. 8 months
c. 13 months
d. 15 months

6. What percentage of patients will likely remain within 3 lines of baseline vision 2 years after beginning intravitreal anti-VEGF injections for the treatment of nAMD, if managed appropriately?

a. 91%
b. 93%
c. 95%
d. 97%

7. In Protocol S, patients in the ranibizumab arm received monthly ranibizumab injections until _____.

a. The dose loading phase was complete, then went to a treat-and-extend regimen.
b. The dose loading phase was complete, then received laser.
c. The patient exited the study.
d. The proliferative diabetic retinopathy resolved or was stable for 3 months.

8. Inflammation has been observed in all cohort 1 patients with which of the following new therapeutics currently in development for nAMD?

a. RGX-314
b. APL-2
c. ADVM-022
d. Avacincaptad pegol

9. Rescue injections were given in _____ of patients in RGX-314 cohort 5.

a. 10%
b. 25%
c. 50%
d. 75%

10. _____ is a pediatric disease for which genetic testing may be considered for the entire family, including children who are asymptomatic.

a. FEVR
b. Coats disease
c. Traumatic macular hole
d. Retinopathy of prematurity

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

I plan to make changes to my practice based on this activity. _____ 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

_____ Medical Knowledge

_____ Practice-Based Learning and Improvement

_____ Interpersonal and Communication Skills

_____ Professionalism

_____ 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 below.

_____