

INTEGRATING NEW AMD THERAPIES INTO THE CLINIC

Experts weigh in on how the growing armamentarium will affect patient care.

A DISCUSSION WITH ROBYN GUYMER AM, MBBS, PHD, FRANZCO, FAHMS; CHARLES C. WYKOFF, MD, PHD;
AND DIANA V. DO, MD; MODERATED BY ALLEN C. HO, MD



Anti-VEGF therapy, a staple in our clinics for 16 years now, has been transformational for patients with conditions such as wet AMD, diabetic retinopathy (DR), diabetic macular edema (DME), retinal vein occlusion, and myopic choroidal neovascularization. We are now on version 2.0 as we move into more durable therapies, more mechanisms of action, and combination therapies. But how are we going to use these new therapies in our practices? To answer that question, I sat down with some of the best and brightest medical and surgical retina specialists to share their perspectives and pearls.

- Allen C. Ho, MD

DR. HO: HOW DO YOU THINK THE NEW THERAPIES WILL FIT INTO YOUR ARMAMENTARIUM FOR WET AMD?

Robyn Guymer AM, MBBS, PhD, FRANZCO, FAHMS: Faricimab (Vabysmo, Genentech/Roche) adds an extra choice to our standard options, and it will fit in nicely. We will likely use it in a treat-and-extend protocol and start with cases that are currently being treated but for whom we haven't been able to extend past 8 weeks.

Recent experience with other new treatments is likely to make us a little bit more hesitant now, so I don't think we will change everyone over immediately. In Australia, we will be fortunate to have real-world experience from the United States before we are able to start with these new treatments, which will hopefully be later this year or early next year.

The port delivery system (PDS) with ranibizumab (Susvimo, Genentech/Roche) is very different because it requires surgical intervention. In Australia, many AMD patients are treated by a medical retina specialist like myself,

so we will have to figure out how to manage patients back and forth with our vitreoretinal colleagues and who will do the refills moving forward. Medical retina specialists don't want to hand over the care of these patients, so it will be interesting to see how we manage this change. The PDS won't be for every patient with wet AMD; as with faricimab, it's likely we will start with those who aren't able to extend.

AT A GLANCE

- The panelists speculate that most clinicians will recommend the new longer-duration therapies first to AMD patients who have been unable to extend treatment beyond 8 weeks on their current anti-VEGF therapy.
- Even though the port delivery system refill-exchange usually occurs at 6-month intervals, routinely following patients is still necessary to watch for disease activity and because there is a higher risk of endophthalmitis with the device.
- The success of any geographic atrophy therapy will hinge on patient selection and education because many patients may cease treatment if they do not perceive any benefit.

DR. HO: DIANA, YOU ARE A VITREORETINAL SURGEON AND A MEDICAL RETINA SPECIALIST; HOW WILL THESE THERAPIES FIT INTO YOUR TOOLBOX?

Diana V. Do, MD: Office-based therapies will remain my first choice because they are convenient for the patient and offer immediate treatment. As for the PDS, it's the first wet AMD treatment in more than 15 years to provide an alternative to our current standard of care office-based intravitreal injections. The PDS with ranibizumab continuously delivers medicine into the eye through a refillable implant, and it may help people with wet AMD maintain their vision with as few as two treatments per year, which is unheard of with our standard of care. The phase 3 Archway clinical trial showed that refill-exchanges of the PDS every 6 months sustained vision compared with eyes that received monthly ranibizumab (Lucentis, Genentech/Roche).¹

Even though the refill usually occurs at 6-month intervals, routinely following patients is still necessary and important because there is a higher risk of endophthalmitis with the PDS. In the clinical trials, there was almost a threefold higher rate of endophthalmitis in eyes that received the PDS compared with those that received intravitreal ranibizumab injections.² The PDS is a foreign device placed in the pars plana and covered by the Tenon's and conjunctiva. The surgery must be done very precisely to prevent the risk of conjunctival retraction or erosion, which would expose the implant to potential harmful bacteria.

DR. HO: PERHAPS THAT THREEFOLD RISK WILL BE MITIGATED AS WE EVOLVE THE SURGICAL TECHNIQUE. CHARLIE, CAN YOU GIVE US SOME PEARLS?

Charles C. Wykoff, MD, PhD: It's valuable to have additional tools in our toolbox, and it's fantastic from a patient perspective to have more choices and a highly differentiated approach to wet AMD management. For clinicians, I recommend being aware of the options and educating patients on your perception of the benefits and risks of each. Even if you are reluctant to use the PDS because of the safety profile and associated boxed warning included on the package insert, it's important that your patients at least hear of it and hear your perspective; it's better that they learn about it from you than from someone else.

Meticulous attention to the surgical technique—in the OR when implanting the device and during the in-office refill-exchange—is crucial to optimize the local anatomy and minimize risks of side effects associated with the device. The specific details of the procedure are extremely well-defined by the manufacturer. We have evolved the surgical technique substantially over time and may continue to do so by incorporating past learnings. The two most important points to appreciate during the implantation are to deeply respect conjunctiva and Tenon's capsule manipulation and make the scleral incision length exactly 3.5 mm and not any larger.

Dr. Ho: Those are great pearls from someone who has done a lot of PDS implantations, and many clinicians have probably had their patients ask about this procedure. I tell patients that the current safety profile is evolving and that it requires a trip to the OR. We do our patients a service by discussing the option—it's just good practice.

DR. HO: HOW ARE YOU GOING TO FOLLOW PATIENTS, AND TO WHOM ARE YOU GOING TO OFFER THE DEVICE?

Dr. Wykoff: We are still learning which patients are the best candidates. I have been fortunate to be able to implant a lot of these devices and have been actively managing dozens of patients with the PDS for years at this point. In my experience, most patients who do not have any adverse events are extremely happy with it, and it is highly effective. Before the phase 2 and 3 data were available, I was skeptical that a protein placed at body temperature would maintain biological activity for months to years; but the trials have clearly demonstrated that ranibizumab maintains activity for many months after implantation and refill-exchanges. For most, the efficacy demonstrated through the phase 2 Ladder trial, the phase 3 Archway trial, and the long-term extension study of wet AMD patients has been remarkably strong.

While the protocol in the phase 3 program is to perform refill-exchanges every 6 months, based on the phase 2 data it appears that many patients may be able to achieve the same clinical outcomes while receiving refill-exchange far less frequently. Among the PDS patients I am managing outside of clinical trials, I am using a treat-and-extend approach.

DR. HO: AS FOR VABYSMO, I WAS A LITTLE DISAPPOINTED THAT THIS DUAL MECHANISM DIDN'T IMPROVE EFFICACY. MAYBE THERE IS SOME SIGNAL OF DURABILITY, BUT WERE YOU A LITTLE SURPRISED BY THE EFFICACY?

Dr. Wykoff: That's an understandable perspective. The phase 3 trials used very strong control arms with fixed 8-week dosing of Eylea (aflibercept, Regeneron) after the monthly loading doses. From an efficacy perspective, non-inferiority with aflibercept was achieved with faricimab in both DME and wet AMD with an indication of differentiated durability with faricimab, with about 78% of patients at every 12- or 16-week dosing in the DME program at the end of 2 years in the personalized treatment interval arms. More directly relevant to clinical practice, though, is that in the DME trials, many of the OCT-based anatomic outcomes assessing fluid status favored faricimab, including change in central subfoveal thickness, the proportion of patients

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A LOOK AT SHORT-PULSE LASER TO SLOW PROGRESSION OF INTERMEDIATE AMD

Commentary by Robyn Guymer AM, MBBS, PhD, FRANZCO, FAHMS

We conducted the Laser in Early Stages of AMD (LEAD) study, which used a nanosecond laser to target intermediate AMD.¹ In a post hoc analysis, we found that most patients with intermediate AMD, those without reticular pseudodrusen, who had this laser treatment every 6 months for 3 years experienced a significant slowing of their progression compared with those who had reticular pseudodrusen, which was a quarter of the intermediate AMD patients at baseline. Overall, there was no difference, but when we subdivided patients into those two groups, there was a significant difference. There is something important we still need to know about reticular pseudodrusen, which we currently don't understand.

Remember that nanosecond laser is different from traditional thermal laser; it does not damage the neural retina. The concept is that the short-pulse laser rejuvenates the retinal pigment epithelium either through cell division, which certainly happens in animal models, or through cell rejuvenation. It also appears that you can detect changes in the peripheral blood, indicating an immune response, after laser, which may

bring about a bilateral effect of a unilateral treatment. We don't know all the mechanisms of laser therapy, but it seems the nanosecond laser triggers a local effect as well as a systemic immune response.

We are working with the regulatory authorities to conduct another study in the United States and internationally. The problem is the trial design around an endpoint. Ideally an intermediate AMD trial would follow cases longitudinally to an earlier endpoint of the beginning of atrophy, but currently this endpoint is not accepted. In LEAD, we enrolled patients with intermediate AMD and tried to stop the development of nascent GA (nGA), the OCT sign of early cell death. We know that nGA has a 78-fold increased risk of GA;² thus, if we can stop nGA, we can stop GA, but for registration we have to prove that we can stop GA. That means a very long and large study.

1. Guymer RH, Chen FK, Hodgson LAB, et al: LEAD Study Group. Subthreshold nanosecond laser in age-related macular degeneration: observational extension study of the LEAD clinical trial. *Ophthalmol Retina*. 2021;5(12):1196-1203.

2. Guymer RH, Wu Z, Hodgson LAB, et al: Subthreshold nanosecond laser intervention in age-related macular degeneration: the LEAD randomized controlled clinical trial. *Ophthalmology*. 2019;126(6):829-838.

achieving central subfoveal thickness < 325 µm, and the proportion of patients achieving absence of intraretinal fluid.

In clinical practice, this improved drying capacity may translate to better outcomes. My hope is that once we get into the real world where patients, on average, do not receive every-other-month dosing, a more durable agent may translate into a more sustained visual benefit.

Dr. Guymer: Also, the faricimab trial was somewhat artificial in that after a certain number of weeks, patients were split into 16-, 12-, or 8-week treatment arms, and once they were in these categories, they had to stay there. In the real world, we change the regimen based on how the patient is doing. Thus, in terms of efficacy, we may see better results in the real world when we can change the interval depending on response. In addition, the true benefit may well come in the medium term, as we know that many patients continue to lose vision in the real world, and results don't match the clinical trials. Part of the loss of vision is because of the development of atrophy and fibrosis. The hope is that, with an anti-VEGF and an anti-angiopoietin-2, there may be an opportunity to have persistent good vision, which we don't currently see in our real-world outcomes.

DR. HO: SPEAKING OF ATROPHY, WHAT ARE YOU TELLING YOUR PATIENTS ABOUT THE APELLIS PROGRAM FOR GEOGRAPHIC ATROPHY (GA)?

Dr. Do: It is exciting that we have new therapeutic options potentially coming to the clinic for GA. Many of these

clinical trials are investigating complement inhibitors, and pegcetacoplan is being evaluated in the phase 3 DERBY and OAKS clinical trials. These pivotal trials are looking at whether this intravitreal C3 inhibitor, given every month or every 8 weeks, could slow the progression of atrophy. One of the clinical trials met the primary endpoint, but the second trial did not.

The sponsor is continuing to follow these study patients through 18 months and beyond to determine if the benefits seen in the phase 2 clinical trial bear out with longer follow-up in this pivotal trial study population. The challenge with these complement inhibitors is that they cannot reverse the atrophy that has already happened. Thus, the goal is not to improve vision, but to slow down the expansion of the atrophy area, and that will make adherence to a frequent administration protocol a challenge for our patients. It will be hard to motivate our patients to come back for monthly or bimonthly treatment because they will not be experiencing an improvement in vision.

DR. HO: CHARLIE, HOW DO YOU THINK THIS GA THERAPY WILL BE USED IN PRACTICE IF IT IS APPROVED?

Dr. Wykoff: Patients who present with vision loss from an exudative retinal disease like DME and wet AMD typically notice an improvement in visual function following treatment. GA is a completely different situation. Even though we understand that vision is not going to improve with treatment, it is going to be very hard to communicate this

to patients regardless of what we say because patients are hopeful by nature. We can tell them their vision is not going to get better, but they will still be disappointed when it does not improve after a few shots. It's going to be a challenge to maintain consistent dosing, and our current data suggests that long-term, repeated therapy is going to be necessary to maximize the benefit. Patient education will be critical to long-term success.

These treatments are a start, an important step forward, and I hope these products receive regulatory approval. There are many patients who are motivated to initiate treatment. We must start somewhere, and I'm hopeful that next-generation therapies will be even better.

Dr. Guymer: I agree that it's going to be an individual patient discussion because it's not clear who will take to this therapy. What is useful is the concept of fovea-threatening GA, and we must find a way to define it because I can't imagine the authorities are going to pay for everybody to get treatment for GA. The question is, who would we suggest to start treatment? I would, for example, recommend treatment for a patient who has atrophy that is threatening the fovea within, say, the next 2 years, if we could predict that. Thus, we should be following patients now as we anticipate treatment, so that we can show patients their own change over time, which will likely help predict when their central vision is going to be threatened.

For example, if you have a few years of prior imaging to show change over time, it's going to be easier to educate and discuss with patients as to whether they are good candidates for treatment. I encourage our colleagues to start taking fundus autofluorescence images if possible, or OCT, so that we can have that conversation with the individual patients. As a profession, we would like to start before there is cell loss, and once these agents get approved, there will be patients who will want to start earlier and earlier.

But the trial design makes it hard to start trials earlier in the disease process. We have been very active in trying to identify and define OCT signs of the first evidence of cell loss. Even though these signs may not be regulatory-approved endpoints, at least companies can start doing early-phase studies to see which drugs and techniques to take forward.

DR. HO: ANY LAST THOUGHTS FROM THE PANEL?

Dr. Do: I'm thrilled to be in the field of ophthalmology and retina, because there is so much innovation here; just in the past year we have two new FDA-approved therapies for wet AMD. I'm excited to educate patients about them and start using them for certain patients. In the future, I'm hopeful that we will address some of our unmet needs with the novel molecules in early-stage clinical trials.

Dr. Guymer: Fancy being in a field where we have been able to reduce the rate of legal blindness in more than half of our population with wet AMD. Any treatment for atrophic

AMD will be a huge step forward. We will get better at the delivery of the treatment, but we have to start somewhere.

Dr. Wykoff: It's great to have new opportunities and tools in the toolbox. Looking down the pipeline, I believe that we will continue to see innovation and improved options for patients. There are many promising agents currently in phase 2 trials exploring new molecular pathways.

It's important that we communicate with patients the value of maintaining optimal outcomes with current treatments today so that they can reap the benefits of the next-generation treatments that are going to be even better tomorrow.

Dr. Ho: We are in a very rich ecosystem of pharmacologic, biologic, and device options all focused on doing better for patients. We are lucky that patients value vision because many of these treatments are not inexpensive. Vision is one of the most important aspects of a patient's health, particularly for aging patients and working-age diabetics. ■

1. Holekamp NM, Campochiaro PA, Chang M, et al. Archway randomized phase 3 trial of the port delivery system with ranibizumab for neovascular age-related macular degeneration. *Ophthalmology*. 2022;129(3):295-307.

2. Wykoff CC. 2-Year outcomes from the phase 3 Archway trial: management of neovascular age-related macular degeneration using the ranibizumab port delivery system. Presented at Angiogenesis, Exudation, and Degeneration 2022. February 12-13, 2022. Virtual.

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