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Extending Treatment Durability With Next-Generation Neovascular AMD Therapies

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Dr. Borkar:
Hello, I'm Dr. Durga Borkar, Assistant Professor of Ophthalmology, Vitreoretinal Surgery and Diseases, and Assistant Professor of Population Health Sciences Duke University Eye Center. Welcome to the Ophthalmology News Broadcast Video. In this CE activity, we'll be taking a look at the new more durable treatment options for neovascular age-related macular degeneration. The efficacy, safety and durability of these agents will be reviewed. And importantly, we will discuss how to consider the dosing intervals for these agents so that we can improve patient persistence with therapy.

I'm joined by my colleagues Dr. Diana Do, Vice Chair of Clinical Affairs and Professor of Ophthalmology, the Byers Eye Institute, Stanford University School of Medicine, and Dr. Peter Kaiser, Professor of Ophthalmology and Chaney Family Endowed Chair in Ophthalmology Research at the Cole Eye Institute Cleveland Clinic.

Before we review the clinical data for these new agents, we have a special report looking at the state of care for patients with neovascular age-related macular degeneration. We've been using anti-VEGF agents for over 20 years to address the neovascularization associated with age-related macular degeneration. Each generation of agents has improved in durability, and clinical trial results for each of these agents have been very promising. Likewise, we have developed three different treatment approaches which support a more personal approach to dosing, fixed PRN and treat-and-extend. So, how have these agents performed in the real-world?

A study by Wykoff and colleagues from the Academy IRIS registry was published just recently in January of 2024, with data from up to 6 years of treatment with anti-VEGF agents. In this study, the purpose was to evaluate anti-VEGF treatment patterns and the influence of patient demographic and clinical characteristics and up to 6 years of vision outcomes in neovascular age-related macular degeneration. This was a retrospective, multicenter, registry study with up to 6 years of follow-up and leveraged data from IRIS registry. It included over 250,000 eyes with their first anti-VEGF agent and at least 2 years of follow-up. More than half of the patients had visual acuity data. They looked at changes in visual acuity from baseline, frequency of and gaps between intravitreal anti-VEGF injections, treatment discontinuation, switching anti-VEGF agents, and the influence of baseline clinical and demographic characteristics on visual acuity.

The anti-VEGF agents included in the IRIS registry study included aflibercept, bevacizumab, ranibizumab, and brolucizumab. And you can see how the usage of these agents changed during the 6-year follow-up period. And while bevacizumab remained one of the most popular agents used, aflibercept surpassed it by year 3 of follow-up.

What was interesting about this study was after a modest mean visual acuity improvement with intravitreal anti-VEGF injections at year 1, patients actually netted a loss of visual acuity by year 6. And this was true regardless of anti-VEGF agent.

Additionally, looking at injection frequency over the 6 years, you can see that injection frequency decreased over time, and this was paired with a relatively high rate of discontinuation. Specifically, if we look at the mean number of anti-VEGF injections in year 1, it was approximately seven injections, but by year 6, it had decreased to four average injections per year. And additionally, there was an astounding 40% rate of treatment discontinuation, which is obviously much higher than what we see in clinical trials. And this follow-up was much further out than what we see in most clinical trials. Additionally, the injection interval increased over time with the majority of patients receiving one to six injections each year.

So, to summarize this study, after modest mean visual acuity improvement with intravitreal anti-VEGF injections at year 1, patients overall netted a loss of vision by year 6. Injection frequency decreased over time, and this was paired with the relatively high rate of discontinuation. Additionally, injection intervals increased over time with the majority of patients receiving only one to three injections each year.

So, these three findings from the IRIS registry study really suggest that we have room for improvement in treating neovascular AMD with the new, more durable therapies which have dosing intervals of anywhere from 16 to 24 weeks for some patients. The number of annual injections a patient might need is about two to three.

Dr. Kaiser, are you surprised by the data from this IRIS registry study? Do you see this at all in your clinical practice?

Dr. Kaiser:
Yeah, I certainly do. I think this is one of the sort of factors when you use treat-and-extend. So, treat-and-extend, by definition, you treat until dry and then you extend the interval. So, in the first couple of years, you may have quite a few injections because the interval is very short. And, over time, as the patient does better, the injection frequency decreases. But by saying that, you'd expect the visual acuity to stay stable, we wouldn't want to see this slow decline over time. And unfortunately, that is – there's several variables there. One is patient burnout. So, in other words, either their caregiver doesn't want to bring them as much or the patient doesn't want to come as much. And so, they are the ones reducing the interval, which certainly would translate into a worse visual acuity over time. But any of the real-world studies that we've looked at, including the IRIS registry study, as well as others worldwide have shown the same thing; that over time, we're losing vision. And again, as you mentioned, that really shows the need for more durable therapies.

Dr. Borkar:
Thanks, Dr. Kaiser. Dr. Do, what do you think of this study? And do you think that some of the newer agents we have available can fill in this very obvious treatment gap that we have?

Dr. Do:
I think these real-world database studies give us a lot of stimulating hypothesis to explore. We know that with these large numbers, that likely the results showing that vision decline over years of treatment in wet macular degeneration is the true effects that we also see in clinical practice.

Yet, it doesn't really answer completely what the cause of the vision loss is. As Peter Kaiser mentioned, there are a lot of variables including undertreatment, which is probably one of the highest factors to not having optimal visual acuity outcomes. But also, we don't have imaging available to analyze what actually happens in the macula of these eyes. Does atrophy form over time? Which unfortunately, does not have an effective treatment.

I think the new anti-VEGF agents that were just FDA approved over the past year or two, aflibercept 8 mg and faricimab, offer new and exciting hope to patients and clinicians, because they do suppress VEGF inside the eye for longer periods of time, allowing for better disease control if compliance is an issue.

Dr. Borkar:
Thank you both for your insights on this article.

To achieve optimal outcomes with anti-VEGF agents, monitoring treatment response is critical to managing dosing intervals. My colleague, Dr. Do, will share news from the field as she takes a look at the challenges in monitoring treatment response.

Dr. Do:
Now it's my pleasure to discuss challenges we face in monitoring treatment response in eyes with neovascular age-related macular degeneration.

We know that from randomized clinical trials, patients who receive intravitreal anti-VEGF therapy usually have robust and significant gains in visual acuity. However, in clinical practice, these robust visual acuity gains are not always realized in patients we see every day. Why does this occur? There are multiple factors that might affect a patient's ultimate visual acuity outcome, and many of these

factors might not be able to be controlled by the ophthalmologist or even the patient.

Some of these uncontrolled factors might include the presenting lesion size of the choroidal neovascular AMD lesion. If lesions are large, they're more difficult to control and can lead to worse visual acuity outcomes than we might see in a randomized clinical trial. In addition, in clinical practice, there's a wider range of baseline characteristics. We see a variety of patients who may have other comorbidities that may also affect their vision and their ultimate visual acuity outcome. In addition, compliance with therapy is also a challenge we see every day. In randomized clinical trials, patients are brought back at routine intervals from the clinical trial study. But in clinical practice, patients often rely on caregivers and family members to take them to the retina specialists and ophthalmologist, and those caretakers are busy and their schedule may not always be adaptable to the recommended schedule that we provide them. Therefore, compliance with a treatment regimen may be challenging in real-world clinical practice. And finally, there are constraints put on the retina specialist and ophthalmologists. There are many intravitreal anti-VEGF therapies available, but often, insurance might dictate which one we can start off with. And sometimes that might not be the most optimal choice for the patient.

There are some factors that we can try to control to improve the visual acuity outcome with patient. First, educating the patient about compliance and importance of routine visits to the retina specialists to receive intellectual anti-VEGF therapy is essential to maintain a robust visual acuity outcome. And finally, choosing a treatment paradigm that is best suited to the individual patient is also ideal. As Dr. Borkar mentioned, there are different treatment regimens that can be employed, including fixed dosing, as-needed dosing, or treat-and-extend. Whichever one the retina specialists choose has to be explained to the patient in order for them to be most compliant.

And finally, let's look at selection of disease activity criteria. How do you look at disease activity criteria when you encounter a patient with wet age-related macular degeneration? Randomized clinical trials have used various different disease activity criteria to allow for treatment in these clinical trials. Some of these factors include changes in visual acuity, changes in optical coherence tomography macular thickness measurements, a change in visual acuity and its association with macular thickness, or qualitative features such as the presence of subretinal fluid or intraretinal fluid, and also the presence of macular hemorrhage seen on examination or imaging. And finally, many studies also look at fluorescein angiography and how the lesion changes over time, and that might also trigger retreatment.

Let's take a closer look at some of the measures of disease activity and the challenges we face in clinical practice. When we evaluate visual acuity in clinical practice, it's less precise than what is measured in a randomized clinical trial. We are not using best corrected visual acuity, and a patient's visual acuity measured in the clinic could be affected by ocular surface disease, cataract, other factors that aren't necessarily indicative of the patient's active wet macular degeneration. In addition, visual acuity might not correlate with optical coherence tomography finding. And finally, there's a ceiling effect in visual acuity change. For example, eyes that start off with worst baseline visual acuity have a better chance of improvement because they have more letters to gain.

Now, let's discuss macular thickness change which is often detected on OCT imaging. In clinical trials, many of the retreatment criteria are based on a change in macular thickness. But in clinical practice, it's also cumbersome to also look and measure macular thickness at every visit. Often, we use more qualitative imaging, such as the presence of fluid in different compartments of the retina in order to make a retreatment decision.

Let's look at structural OCT imaging. As I mentioned, in wet age-related macular degeneration, active with CMV can present with fluid underneath the retina, subretinal fluid, or even intraretinal fluid. And many studies have suggested that the presence of fluid can lead to worse visual acuity outcomes, especially if the fluid is intraretinal. And certainly, when we see this in clinical practice, we aim to give another treatment in order to control the disease.

Finally, let's look at macular hemorrhage. Hemorrhage in the retina is a sign of disease activity, and often can be an indicator of active wet age-related macular degeneration. If I encounter a hemorrhage seen on a patient's examination, that will prompt me to give another anti-VEGF treatment. We also discuss that macular lesion size can also be assessed in both clinic and in clinical trials. Many people use fluorescein angiography to look at the size of the choroidal neovascular lesion. More recently, patients can also be imaged with OCT angiography, which is a non-invasive imaging tool to also look at CMV lesions. It is challenging sometimes to obtain fluorescein angiography in patients, because it's an invasive procedure and it takes more time. But if a patient is not responding well to a certain therapy, it is important to reevaluate the patient's lesion and to obtain that extra imaging test to understand what's happening in the disease activity.

Now, I'd like to ask Dr. Borkar, when you practice and evaluate patients with neovascular AMD, how do you assess disease activity in your clinic?

Dr. Borkar:
That's a great question. I think all of the factors that you mentioned are clearly relevant to looking at disease activity, and all of them are used well in the clinical trial setting. In routine clinical care, I primarily look at qualitative OCT features, specifically the presence of

subretinal, and in particular, intraretinal fluid. And I also look at whether that's associated with the visual acuity change, but I think there are a couple issues with only focusing on vision. One, you mentioned that the visual acuity change can often lag behind these structural OCT changes. And the other is that there are often other comorbidities such as advanced glaucoma or cataract that may also be contributing to visual acuity change.

I also do not routinely check the visual acuity at every injection visit; I usually check it every three visits or so, so that they are getting routine visual acuity assessments, but it may not be at every visit. So, that does also hamper the ability to use that at every checkpoint. I think that's important, though, because it does help streamline the visits for patients. And as we've discussed, you want to make the decisions based on information we need, but also streamline their visits and treatment burden.

Dr. Do:
Thank you for that insight. I'd like to ask Dr. Peter Kaiser, when you're looking at these activity and analyzing OCT, do you feel it's important to eliminate all types of fluid in the retina, both intraretinal and subretinal fluid?

Dr. Kaiser:
Yeah, I think it's important for our viewers to understand that in clinical studies, they're largely just using the central subfield thickness and visual acuity. And in clinical practice, we can delve deeper, different levels of fluid have different levels of response. So, for instance, I'm more concerned about intraretinal fluid than I am about subretinal or sub-RPE fluid. In fact, of the three, sub-RPE fluid or a pigment epithelial detachment will be the one that I've been least worried about, especially if it's not growing in size. If there was a small layer of subretinal fluid, studies have shown that that's not necessarily detrimental to vision. However, intraretinal fluid is something that we really chase and make sure we want to treat that aggressively, because every study has shown that intraretinal fluid can lead to poor visual outcomes, especially if we see those in the central fovea.

Dr. Borkar:
Thank you, Dr. Kaiser. And Dr. Do, what is your approach when looking at these various factors

Dr. Do:
I think my approach is very similar to the both of yours. I look at OCT in a qualitative manner, and treat when there is fluid. I do try to eliminate both intraretinal and subretinal fluid if possible. But I also take into account on examination if I see any other signs of activity, such as hemorrhage, that also will prompt a treatment as well. But the objective is to not undertreat the patient. Because I know through multiple studies that the more frequent the treatment, and the more better the disease is under control, the better likelihood of a good visual acuity outcome for the patient.

Dr. Borkar:
Well, thank you both for this valuable insight.

Now, for our feature story with Dr. Kaiser, who will share the latest clinical data on the efficacy, safety, and durability of the new anti-VEGF therapies.

Dr. Kaiser:
So, thank you. That's a very good question because we have some new anti-VEGF therapies that appear to be more durable. Before we go there, though, I wanted to kind of go through some of the ways we can improve durability for a drug. One way to do this is to increase the binding affinity, so the tighter that a drug binds to something, the longer it will last. Half-life is another. So, obviously the longer the half-life, the longer the drug will last. And in general, half-life is based on size of a molecule. So, a larger molecule will have a longer half-life. And the final area that's big will be molar dose. So, in other words, if you put a bigger dose of a drug into an eye, it should also last longer. Less on the list, we'll be changing targets. So, if you target more than one cytokine, for instance, that may allow the drug to last longer. And potency is also lower on the list, versus the three I just mentioned.

So, let's look at some of these newer anti-VEGF that we have. The first is a drug called brolucizumab. And the reason this drug was thought to last longer is it's a very small molecule, so the half-life would be short. But because it's so small, they could use a dose up to 6 mg. So, this is a much larger dose than many of our other anti-VEGF agents. And because of that, it was thought to last longer. And this was tested in the phase 3 clinical studies called HAWK and HARRIER. In these studies, they use two different dosages of brolucizumab, compared to aflibercept 2 mg, which was dosed every 8 weeks. In contrast, the brolucizumab was dosed at a 12-week interval. But if the patient wasn't doing well, so in other words had evidence of disease activity, the interval was dropped downward to 8 weeks. The results of this study showed that both dosages, as well as both intervals of brolucizumab, were non-inferior to aflibercept dosed every 8 weeks, and this was both for visual acuity outcomes, as well as OCT outcomes. But more importantly, what it showed is that the durability of the drug was excellent in that roughly 40 to 45% of the patients were able to maintain a 12-week dosing interval, so showing an increased durability.

When we look at the safety of brolucizumab, in the clinical studies, the safety was pretty good. However, after the drug was approved in post-marketing surveillance, we saw episodes of intraocular inflammation, including episodes of retinal vasculitis and occlusive retinal vasculitis. Again, these weren't really noticed so much in the clinical studies, this was only later. And so, this inflammation is certainly a safety issue that anybody using this drug needs to be aware of.

The second new drug is called faricimab, and it is based on several of the items that I talked about previously. First of all, it uses a 6-mg dose, so having a higher molar dose allows it to last longer. Second, it also has a good binding affinity for both VEGF-A, but it also uses another idea which is it blocks angiopoietin-2 or Ang2. So, the idea then in the clinical study was very similar to HAWK and HARRIER, that we wanted to test the drug at an extended interval versus aflibercept 2 mg dosed every 8 weeks on label. The 6-mg dose after a loading dose, you could increase the interval up to a 16-week interval, and the patients had their interval reduced if they met certain disease activity criteria. In the second year of this study, you could increase the interval using a form of a personalized treatment interval that allowed patients to be either extended at up to 4- to 8-week increments or reduced depending on disease activity. And by disease activity, I'm talking about OCT and visual acuity outcomes. The primary outcome of the study showed that 2 mg aflibercept was non-inferior to the 6-mg faricimab, but at a greatly increased dosing interval for faricimab.

Now, many of the criteria that are used both in HAWK and HARRIER, as well as in TENAYA and LUCERNE, were based on very well-defined disease activity criteria. Some of these criteria included visual acuity, it looked at differences in central subfield thickness on OCT, as well as the presence or absence of hemorrhage. And if there was evidence of activity, the patients would drop their interval in that first year. As I mentioned, they could increase the interval, but that was only later in the study, that wasn't in the first year of the study.

So, when we looked at the outcome of the clinical study, roughly 45% of patients were able to maintain an every-16-week interval. So again, increasing the durability of our treatment for macular degeneration.

The safety was good. There were some episodes of intraocular inflammation, but they were similar between the faricimab and aflibercept group. So, unlike brolucizumab, where the rates were considerably higher than aflibercept, in this case, the rates were very low. So, the safety of the two drugs in comparison, were similar.

The final drug I want to talk about is aflibercept HD. And the HD stands for high dose in that they tested an 8-mg dose versus the normal dose in the past of 2 mg. And using the idea that increasing the molar dose we can increase durability, in the PULSAR study, which was the phase 3 clinical study for macular degeneration, they tested the drug against 8-week aflibercept. Whereas the 18-week doses – 8-mg doses were tested at a 16-week interval. If there were any evidence of disease activity, just like the other studies, they were dropped in terms of the interval. And in a second year of this study, you could adjust increasing the interval up to 20 or even 24 weeks. The study met its primary outcome in that the drug, the two different dosages of aflibercept, were non-inferior in terms of visual acuity outcomes. But more importantly was the durability of the 8-mg dose, where up to 30% of patients that week 96 were scheduled to be at a 24-week interval, and almost half the patients were at a 20-week interval.

So, we're seeing with each one of these studies progressively increased durability, without any sacrifice in efficacy, and with similar safety. So, this is an exciting time for our patients as well as ourselves in terms of the treatment of age-related macular degeneration.

Are you starting new patients who are diagnosed with neovascular age-related macular degeneration with one of these more durable therapies?

Dr. Borkar:
Welcome to our panel discussion. In this Ophthalmology News Broadcast Video, we've talked about the existing gaps in treatment, the challenges to assessing disease activity, and the new, more durable treatment options. Now we want to turn our attention to the approaches we use to establish dosing intervals.

Before we start, what challenges do you face when using new therapies? We know that there are several different options for treatment patterns, there's a fixed dosing regimen, PRN or as needed, and treat-and-extent. Dr. Kaiser, how do you decide which treatment pattern to use, particularly for these newer agents?

Dr. Kaiser:
When we talk about using these newer agents, I use them the same way that I use all the previous agents, which is a treat-and-extend formula. It's kind of how the clinical studies were based on, sort of. But what I use in clinical practice doesn't really rely so much on what they used in the clinical studies. I find that treat-and-extend offers the best combination of safety in that we don't let the patients go too long without treatment, as well as efficacy, in that we continue the treatments just extending intervals as they do well. And I extend the intervals based on the clinical trial results. So, brolucizumab up to 12 weeks, faricimab up to 16 weeks, and aflibercept 8 mg up to 24

weeks.

Dr. Borkar:
And Dr. Do, how do you decide which treatment pattern to use for these newer agents, particularly in treatment-experienced patients, since most of the clinical trials look particularly at treatment, naive patients?

Dr. Do:
That is really good question, because in real world, we often see patients with different baseline characteristics than those that were enrolled in randomized clinical trials. I try to personalize the approach to each individual patient. But in the vast majority, I do start off with initial monthly injections, usually about three with a particular intravitreal anti-VEGF agent. And then if the lesion is stable and I'm having a good response, I'll try to extend the intervals of treatment if the disease activity is under control. I usually prefer are a treat-and-extend type regimen for the vast majority of my patients, and I'll usually extend by 2-week intervals. With these new individual anti-VEGF agents such as aflibercept 8 mg or faricimab, we have seen that these patients can go longer intervals between treatments while maintaining disease control.

Dr. Borkar, how do you treat patients in your clinical practice?

Dr. Borkar:
That's a great question. Similar to you, I also use a treat-and-extend approach. I typically do load patients with an initial three to four q4-week injections. I will say though, many of the patients that I'm switching to the newer agents are anxious to have a more extended treatment interval. And that's often why they are so invested in switching to a different agent. For some of those patients, I may only do one or two loading doses before trying to extend. And similar to you, I do extend by 2 weeks at each visit if their disease activity is stable.

Dr. Do:
When using new therapies in clinical practice, do you adhere to the approach used in the clinical trials?

In clinical trials, different dosing regimens were used to test in these patients. For example, in the aflibercept 8-mg clinical trials, patients were initially given monthly injections, and after three monthly injections, they were extended immediately to every-12-week or every-16-week dosing of aflibercept 8 mg.

I wanted to ask Dr. Borkar, in clinical practice, do you think using these type of regimens can be useful, because they were shown in clinical trials to produce significant and robust visual acuity outcomes?

Dr. Borkar:
That's an interesting question. You know, in clinical trials, especially in the recent clinical trials, they've used a combination of best corrected visual acuity, CST, and presence of macular hemorrhage, either requiring all of them or one of them to decide if treatment interval can be extended or not. And I don't know that in the real world we are doing that to that same extent, I think there are a few issues that make it difficult. One, and we saw this in the IRIS study, is that there are frequent inadvertent treatment lapses. So, we often don't have the opportunity to evaluate patients at these very structured time points. Additionally, we may not check visual acuity, particularly in a clinical trial standardized manner at every visit in order to incorporate that criteria. So, I think many of us are using qualitative OCT measures to really decide, as well as potentially the presence of macular hemorrhage, to make a decision about treatment interval extension.

Additionally, a lot of these trials give us information for 1 to 2 years at most. And we don't really see what happens when we use these retreatment criteria 4, 5, or 6 years out, and really only time will tell with that. So, it will be interesting to see how we can extend patients out with these more durable agents, the longer we have them in our hands.

Dr. Do:
Thank you for that insight. I also wanted to ask Dr. Peter Kaiser, retina specialists typically like to use treat-and-extend, but right now that these new agents such as faricimab and aflibercept 8 mg, we don't yet have a lot of data on treat-and-extend. What is your regimen when you're using these agents?

Dr. Kaiser:
So, you're right, Diana, we don't really have all that much information about treat-and-extend, as we do for aflibercept, say, 2 mg or ranibizumab. However, the thought behind treat-and-extend holds no matter what drug you're using, in that you treat the patient until they're dry and then you extend the interval. And as they develop more fluid, then you reduce the interval. So, I don't think it really matters what drug you're using, the treat-and-extend paradigm is useful no matter what.

The thing that I really need from the clinical studies is how far can I actually go in terms of safely getting there? And I think we're reliably

at the, say, 16-week interval with faricimab, 12 weeks with brolucizumab, and up to 24 weeks with aflibercept 8 mg. Now, bear in mind that in the HAWK and HARRIER, and TENAYA and LUCERNE studies they didn't go past 12 and 16 weeks, so it is possible that patients on a treat-and-extend paradigm with these agents may be able to go further, we just need to be careful not to go too far since it was never studied.

Dr. Borkar:
Well, what a great discussion we've had today. We've seen that there are multiple treatment options that are currently available to treat neovascular AMD: bevacizumab, ranibizumab, aflibercept, brolucizumab, faricimab, and aflibercept high dose. And in clinical trials, the data has been very promising. We've seen though in the real world that for some of the agents, the real-world data does not match what we've seen in clinical trials. More durable anti-VEGF agents may be able to be used with dosing intervals up to every 24 weeks, and a selection of disease activity criteria and treatment approach is important for outcomes.

Thank you to our panelists, Dr. Do and Dr. Kaiser, for their insights on the treatment of neovascular age-related macular degeneration in this program. There are exciting new developments using anti-VEGF agent treatment regimens that reduce injection burden while maintaining treatment efficacy. The durability of these agents looks promising for patients with neovascular AMD who need treatment. Thank you all for participating in this activity.

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