# BrightFocus® Chats

**New Option for Anti-VEGF Treatment for Wet AMD**
**October 25, 2023**
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**Transcript of Teleconference with W. Lloyd Clark, MD, Vitreoretinal Surgeon at Palmetto Retina Center, LLC**



Please note: This Chat has been edited for clarity and brevity.

**MS. DIANA CAMPBELL:** Hello. My name is Diana Campbell, and I'm pleased to be here with you for today's macular degeneration Chat, "New Option for Anti-VEGF Treatment for Wet AMD." This Chat is brought to you today by BrightFocus Foundation. Macular Degeneration Research is one of our programs here at BrightFocus. We fund exceptional scientific research worldwide to defeat Alzheimer's disease, macular degeneration, and glaucoma, and we provide expert information on these heartbreaking diseases. Now, I am pleased to introduce today's guest, Dr. Lloyd Clark, who will discuss a new anti-VEGF treatment option that is available for wet AMD, or macular degeneration; we will refer to macular degeneration as AMD throughout the call. Dr. Clark specializes in the treatment of vitreous and retinal diseases. He is also dedicated to the advancement of new treatments for retinal diseases through his involvement in clinical trials for the newest therapies for age-related macular degeneration, diabetic retinopathy, and retinal vein occlusion. Dr. Clark, thanks so much

for joining us today.

**DR. LLOYD CLARK:** Well, it's a pleasure. Thanks so much for having me. What a great group!

**MS. DIANA CAMPBELL:** Thanks so much. So, last month, our Chat was all about dry macular degeneration and geographic atrophy. Today, we'll be discussing another type of macular degeneration, or wet AMD. Dr. Clark, can you start us out with a description of what wet AMD is?

**DR. LLOYD CLARK:** Absolutely. Age-related macular degeneration, in general, is a very, very common condition—the most common cause of vision loss in Americans over the age of 60—with diabetes are the number 1 and number 2 causes of severe vision loss in the United States. Now, the good news is that about 80 percent of people with age-related macular degeneration only have the dry form, and it starts as the dry form. And it sounds like this group talked about dry macular degeneration during your last session, but in short, dry macular degeneration is when you develop pigmentary changes in the retina, most of the time mild to moderate vision loss unless a patient develops geographic atrophy. Now, of those patients, approximately 20 percent of patients with macular degeneration at some point in their life will develop wet macular degeneration in at least one eye—not both eyes, necessarily, but at least one eye. And wet macular degeneration is caused by an abnormal blood vessel that grows underneath the retina. If you sort of think about it like a wound healing response, it's a response to the structural damage caused by dry macular degeneration, and this abnormal blood vessel grows underneath the retina. And these abnormal blood vessels leak fluid, they bleed, they do all kinds of bad things that can damage vision much more rapidly than dry macular degeneration. Patients, once they develop abnormal blood vessels under the retina, can develop fairly rapid deterioration of vision and sometimes acute vision loss with certain complications of this abnormal blood vessel.

**MS. DIANA CAMPBELL:** Thank you. That made it very clear. We're fortunate that the first treatments—or the first treatment—for AMD was developed more than 15 years ago. Can you touch on the existing treatment landscape to date for wet AMD before we move into Eylea HD,

specifically?

**DR. LLOYD CLARK:** Sure. Prior to 2006, we really didn't have meaningful therapies for wet AMD. In 2006, we had our first drug approved by the FDA for the treatment of wet AMD; it's a drug called ranibizumab, or Lucentis. It blocks a pathologic protein called vascular endothelial growth factor, or VEGF, and this really was a revolutionary drug. For the first time, we were able to improve vision with wet macular degeneration—prior to which we had no treatments available to improve vision. Now, since that time, we've had a number of different agents that were approved by the FDA in that same class that bind and inhibit the activity of VEGF—Eylea, or aflibercept, was the next. And now, we have a number—three of four that are available—and different clinicians use different drugs in this same treatment class. This has been an incredible advancement in the management of patients with macular degeneration. More recently, we've had some novel therapies. In addition to what we're talking about today, which is Eylea HD, we've had some other fairly new therapies available. We have our first drug that targets a second molecular pathway, a drug called Vabysmo. And also, we're beginning to see novel strategies for the treatment of wet macular degeneration. There's now a surgical device that can be implanted in the eye that you can put ranibizumab in—may last up to 6 months—but the mainstay of treatment for wet macular degeneration in 2022 and before is treatment with vascular endothelial growth factor antagonists—these drugs, these biologics injected in the eye.

**MS. DIANA CAMPBELL:** Great. Thank you. Over the summer, FDA approved a new higher dose of Eylea called Eylea HD (8 mg). Could you please talk a little bit about the data from the clinical trials leading up to this approval and how this new version of Eylea differs from the standard 2 mg formulation that so many are already familiar with?

**DR. LLOYD CLARK:** One of the great things about Eylea HD is it's just a different formulation of a drug that has been a tried-and-true therapeutic option for us for close to 15 years—2 milligrams of Eylea has really become the gold standard in clinical practice. It's also the gold standard in clinical research trials, so any clinical trial that's done to evaluate

a new therapy for macular degeneration today is compared against 2 mg Eylea. And so, thinking about the current landscape, 2 mg Eylea is the gold standard for treatment of retinal diseases, including macular degeneration. Building on that, Eylea HD is really nothing other than the same molecule—the aflibercept molecule—supplied in an 8 mg dose. The dose is more concentrated, but there's also a slightly higher volume delivered in the eye. What did we see in clinical trials with the 8 mg dose? Well, we saw three important clinical signs that this is an excellent new option. The first is that visual outcomes with reduced treatment burdens demonstrated similar visual acuity outcomes. Patients saw the same or better with Eylea HD compared to 2 mg of aflibercept, so we're not giving up any improvements in visual acuity by utilizing the new therapy. The new therapy, though, is designed to be used much less frequently. In the clinical trials, evaluating aflibercept 8 mg, or Eylea HD, there was no monthly group—many of you that are getting injections for macular degeneration start out with monthly injections, and many patients continue on monthly injections for an extended period of time. This drug was not studied past three initial injections for monthly therapy. Patients immediately went out to 8-week therapy and could be extended as infrequently as every 16 weeks, so keep in mind, 16—that's three injections per year. And many, many patients were managed very, very well after that initial loading phase with increasing treatment intervals 4 or 8 weeks. So, the second important finding is that we were able to extend treatment intervals substantially longer than what's been previously shown with single-agent anti-VEGF drugs. And then finally, the other encouraging piece is that looking at patients during the early course of therapy, this drug appears to have a better capability of drying the retina, of inactivating the disease. And so, it appears to have a higher potency than the 2 mg dose, particularly early in the course of treatment, and we as clinicians feel like one of the more important things to do for our patients is to get this under control quickly. So, in summary, the drug works just as well as our gold standard, using it much less frequently and has a much higher potency. So, it has a number of potential advantages for what we currently have.

**MS. DIANA CAMPBELL:** That's a huge benefit, to be able to extend out that far. When people are starting with the 8 mg formulation, do they

start with ... I guess what I'm trying to get at is the frequency when they start: Do they start at 8 weeks, or how does that rollout look? That might eventually lead then to 16 weeks.

**DR. LLOYD CLARK:** Well, we're still learning in terms of ... you know, it's interesting. All these drugs have labeled dosing strategies that are in the FDA-approved label. We, as doctors, sometimes monkey with that schedule. I think that schedule would be modified a little less than the previous-generation drugs because it's a fairly prescriptive label. The way that the drug is currently labeled for wet macular degeneration treatment is the patient is treated monthly for 3 months and then extended at least out to 8 weeks after the initial three doses. So, what I would anticipate, most patients that are started on Eylea HD will get three monthly injections by their doctor and then extend out to 8 weeks from there, evaluate the patient in terms of clinical response, and then based on experience or review of the clinical trial data, many patients will be able to be extended out as far as every 16 weeks in the chronic treatment phase.

**MS. DIANA CAMPBELL:** Great. That's really exciting news for folks who are set to going to the office sometimes every month. So, for people who have recently been diagnosed with wet AMD, do they need to have an existing treatment history with an anti-VEGF treatment in order to switch over, or can they be started on this as a first line of treatment?

**DR. LLOYD CLARK:** Well, you can do either, and that's one of the really exciting things about Eylea HD. Obviously, the clinical trial data was all done with what we call treatment-naïve patients—patients with a new diagnosis of wet AMD, had not been treated with any previous drugs for wet AMD—so the trial data that we discuss here and in other settings is all based on patients with a new diagnosis of wet AMD. But another very exciting group of patients are patients that are on chronic therapy today. Many, many patients ... this disease, in general, is not ... you can't cure wet macular degeneration. Most patients stay on injections for a chronic period of time, perhaps for life. And many, many of these patients stay on or end up on Eylea, and end up on Eylea at some dosing regimen between 4 and 12 weeks. When you understand how 8 mg works in the eye, it gives you a mathematical advantage of about 4 or 5 weeks. Another real

exciting opportunity here with Eylea HD is to take, let's say, for example, a patient that's currently on chronic Eylea injections every 8 weeks and their disease is under good control. Well, mathematically, you should be able to take that 8-week patient and get them to, at least, 12 weeks with Eylea HD, if not possibly longer. So, clearly, this is a great treatment option for treatment-naïve patients. It's also a very, very good option for stable patients that want to reduce their treatment burden.

**MS. DIANA CAMPBELL:** Great. Are there any significant side effects or anything that folks should know as they are making decision related to side effects? I imagine they're similar to the 2 mg formulation.

**DR. LLOYD CLARK:** Right, so we have now 15 years—close to 20 years—of experience in clinical trials, giving anti-VEGF agents for a variety of retinal diseases. The good news is that this class of agent appears to be safe given as an intravitreal injection. We were worried about these VEGF inhibitors when we started using them in clinical trials because the first anti-VEGF inhibitors were used to treat cancer, and the doses used to treat cancer were 500 times the dose of what's given in the eye. And in these patients with end-stage solid tumors, there was an increased risk of heart attack and stroke in the clinical trials, so we were concerned—very concerned—earlier on if we might introduce an increased risk of cardiovascular events in this otherwise fairly healthy patient population. As it turns out, these small doses in the eye do not increase the risk of heart attack and stroke, even the 8 mg dose, so the agent is a safe agent. The main risk associated with giving these treatments is the way it's delivered as an intravitreal injection, so people can get ... there is a risk of retinal detachment if the needle hits the wrong thing. There's the risk of an infection if the drug or the needle is contaminated. Certainly, patients that have gotten injections are familiar with developing pain after the injection, either due to irritation from the betadine or a corneal abrasion. So, there's a number of things that can occur, but they are typically all related to the procedure itself, and so the drug choice is somewhat independent of the risk profile.

**MS. DIANA CAMPBELL:** Great. You've essentially already answered this, but I just want to ask it again this way to kind of call it out and verify it. So, if an individual is currently taking a different anti-VEGF treatment, and we

did have somebody specifically mention Avastin, they can switch to Eylea HD, and it sounds like what you're saying is there's not a different safety profile. There aren't necessarily safety concerns that they would need to be aware of if they are switching from one anti-VEGF over to Eylea HD. Is that correct?

**DR. LLOYD CLARK:** Well, in the case of Avastin, I think there's a couple of specific issues. My comments were generally directed toward the FDA-approved agents. In terms of Avastin, there's a couple of other things to at least consider. The first is to understand that when we give patients Avastin, Avastin is compounded at an outside facility, so when we get Eylea HD or Lucentis or Vabysmo or any of these FDA-approved agents, the drug comes sealed in a sterile vial from the manufacturer. When we get Avastin for wet macular degeneration treatment, we receive it in repackaged tuberculin syringes that we get from a compounding pharmacy, and so the term I use is a "break in a chain of custody." There's an extra step in processing with Avastin, and there's some theoretical concern that you may introduce contamination. So, to me, there's a little bit of an increased risk of using Avastin in terms of contamination relative to the FDA-approved drugs. The second issue specifically related to Avastin, though, is efficacy. Certainly, Avastin has been a tremendous benefit to the treatment of retinal diseases, but in specifically age-related macular degeneration, the only clinical trials that we got to support the use of Avastin is a trial called the CATT study, which was paid for by your tax money, that compared one of the approved drugs and Avastin. And Avastin performed very well in the CATT study, and it was demonstrated equivalent to Lucentis as long as it was used monthly, right? The trouble with Avastin, when you look at clinical trial data, is that Avastin is an inferior drug if it's used less than every 4 weeks. When you compare a drug like Eylea HD where the majority of patients can be extended to 12 weeks—really 75 percent of people can go out past 12 weeks, and you compare that to Avastin where it's an inferior drug if it's not used 12 times a year, there's a significant benefit in terms of the idea of treatment burden and also the incremental risk of treatment. You know, each injection has an incremental risk. When we talked about the main issues related to the complications, the complications occur every time you get an injection, so if you get three injections a year with Eylea HD and

you get 12 injections a year of Avastin, you have four times the risk of a complication because you're getting that many more procedures. Avastin is a wonderful option for many people, but it does have some limitations.

**MS. DIANA CAMPBELL:** That was an excellent description of the comparing and contrasting of Avastin and the slightly different safety profile. That's outstanding. Thank you. I realize you may not have the answer to this right now; I'll still ask. The first part of the question is: Is this already available in doctors' offices? And then the follow-up to that is regarding coverage. And I know with approval, sometimes Medicare, specifically, tends to lag 6 months or so behind that decision, but is it readily available, and is there any other comment you'd like to make regarding coverage?

**DR. LLOYD CLARK:** Sure. Well, the simple answer is, "Yes, it is available." It is available from distributors. We do have Eylea HD in our office. I have used it commercially on a number of patients already. Now, that being said, there are a number of headwinds during the first 6 months or so. You described it well. There are a number of headwinds in terms of adoption of early treatments, particularly in the first 6 months after a drug is approved by the FDA. The first is payors. It takes a little bit of time for payors to get comfortable with a new agent. Medicare oftentimes—straight Medicare actually, oftentimes does better than many of the commercial payors; the commercial payors tend to go a little bit slower. But the other issue that affects availability is the availability of a billing code. This is really getting in the weeds in terms of practice management, but we utilized what's called a J-code. A J-code is a billing code that we use to bill Medicare and commercial insurance companies for drugs. And whenever a drug is approved by the FDA, there is a temporary J-code and a permanent J-code. The temporary J-code is issued at the time of FDA approval, but the temporary J-code is very difficult for many payors to manage. And so, our experience is that it is much easier for drugs to be reimbursed once the permanent J-code is in place, and that typically takes about 6 months. So, that's really the main structural issue which affects immediate access to drugs, is really a procedural issue, but I would say large, large numbers of retina practices around the country are already ordering Eylea HD and are already using it, and it's certainly an exciting

option.

**MS. DIANA CAMPBELL:** That's great, and I think certainly folks can talk with their own doctors to see if it's available or when it will be available. And again, if you don't have the answer to this next question, which is a follow-up, perfectly fine, but overall with the treatment, is there significant cost difference with the 8 mg formulation over, let's say, the 2 mg formulation?

**DR. LLOYD CLARK:** Yeah, the 8 mg dose is a little more expensive than the 2 mg—makes sense; it's four times the amount of drug in the eye. It also gives the opportunity to reduce treatment burden. If you go do an apples to apples comparison, and what I mean by that is 8 mg gives you what's called three half-lives more the drug, and half-life's about 12 days, theoretically you should get 36 more days out of an 8 mg dose compared to a 2 mg dose. Well, if you apply that over a year's period of time, the actual cost of drug with the 8 mg is less than the 2 mg, but the individual dose is more expensive. How that plays out in terms of the medical economics is a challenging one. The issues related to what it costs the insurance company and the out-of-pocket costs. I would say that in terms of the patient, all the patient-support programs that are currently in place for Eylea 2 mg are available for Eylea 8 mg, as well, so I think that patients are more likely or just as likely to get help in situations where they need it. And due to the reduced number of injections likely needed, they're more likely not to run out of things like foundation assistance for patients that need assistance.

**MS. DIANA CAMPBELL:** That's a really important thing to mention. Thank you for bringing that in. Are there questions that you receive from your patients who are interested in this treatment? What are the types of things you're hearing kind of on the ground, or are there questions that you would suggest that folks ask their own doctors after this call if they're considering potentially asking to switch to this treatment?

**DR. LLOYD CLARK:** Yeah. I think the first issue is that this is a pretty easy conversation with patients that are already on an Eylea. You know, if you talk to a patient about some other agent, we've had other agents come along that appeared to be either the same or slightly better, but they have

a different mechanism of action, and so there's some uncertainty as to whether or not you're actually going to improve treatment burden in that case. In the case of Eylea HD, again, it's the same molecule. You would believe and it would make sense that a patient's response to 8 mg in terms of disease activity would be similar to the 2 mg, and the only difference is that the drug would last longer. It's a pretty easy conversation with patients that are already on Eylea—the idea of switching and reducing treatment burden, increasing intervals. In terms of treatment-naïve patients, Eylea 2 mg has been the standard of care now and is by far the most widely used VEGF agent and has been that way for a number of years, and so when we take a drug that's been compared head-to-head in clinical trials and is shown to have a better drying effect with reduced treatment intervals, again, it's a very easy conversation. If you're considering putting a patient on 2 mg Eylea, then it makes a lot of sense that 8 mg Eylea is a very, very interesting choice, as well.

**MS. DIANA CAMPBELL:** Great. That's wonderful news. I am going to pivot at this point to some of the questions that we've received over the course of the call and a couple that we received prior to when we started the call today. It's all about wet AMD, although the first one is a good segue, and I don't actually know the answers to this yet. Is Eylea HD also good for retinal vein occlusion, or RVO? I know frequently other indications are eventually submitted and approved for approval by the FDA? Is this something that's in place already, or is this something that might happen in the future?

**DR. LLOYD CLARK:** Eylea HD is already approved for age-related macular degeneration, diabetic macular edema, and diabetic retinopathy—so, any type of diabetic eye disease. It is not approved for retinal vein occlusion currently. Typically the companies that develop these drugs for us in the retina space address age-related macular degeneration and diabetic macular edema first because these diseases are so much more common than any other disease state in our practices. Now, that being said, retinal vein occlusion is an incredibly attractive target for VEGF inhibition. The target protein, vascular endothelial growth factor, has very, very high levels in these diseased eyes with retinal vein occlusion. And so, what we've seen with the first-generation VEGF inhibitors is a dramatic and

profound improvement with even a single injection of Eylea 2 mg, so it makes sense that 8 mg is going to be an incredibly effective choice for patients with retinal vein occlusion. The clinical trials are currently being enrolled. These trials are relatively short. The primary endpoint with retinal vein occlusion trials is 24 weeks or 6 months, so we anticipate that Eylea HD will be approved by the FDA probably in the 12- to 18month window for retinal vein occlusion.

**MS. DIANA CAMPBELL:** That's wonderful news. This is one is actually still kind of related to one of the previous questions I asked you. Given that Vabysmo addresses the two pathways, are there additional questions that should be asked or considerations that one should make when considering perhaps exploring use of Eylea 8 mg, or do you have thoughts on that that those particular patients that are now on a slightly different treatment might consider?

**DR. LLOYD CLARK:** Well, let me answer that this way. The patient that you may be a little bit concerned about switching to Eylea HD is a patient that's on monthly Eylea 2 mg and still has active disease. And that is uncommon, but it does occur, where a patient, despite the most aggressive therapy currently available with 2 mg Eylea, they still have active disease. That is a patient that it makes sense to try an agent that has dual action, so that to me is a patient that's a very, very attractive patient to do a treatment trial with Vabysmo. It may be that Ang2 inhibition, the other pathway, may offer that patient an additional benefit. That's one group of patients I would consider utilizing a dual-action drug prior to switching to Eylea HD. In terms of a patient that's on Vabysmo going to Eylea HD, it's certainly possible that they'll have a very, very similar clinical response. One of the characteristics that's not discussed much about Vabysmo is that, yes, it does have the second pathway (the Ang2 inhibition), which basically helps stabilize blood vessel complexes, but Vabysmo also has an increased concentration of the VEGF inhibition, as well—somewhere roughly between Eylea 2 mg and Eylea 8 mg—so Vabysmo is covering both areas. It does offer a second pathway, but it also gives you a little more VEGF inhibition. One of the problems switching from Eylea to Vabysmo is you didn't really know what you're going to get because the drugs are different enough that I think sometimes the clinical

response was a little bit unpredictable, and I would say the same might be true going from Vabysmo to 8 mg. Many patients may do well, but it's difficult to predict because the mechanisms are different. What I will say is a patient that's stable on Eylea 2 mg should be very comfortable going to 8 mg, and clinical trial data, looking at the efficacy and treatment of naïve patients, makes 8 mg a great choice.

**MS. DIANA CAMPBELL:** Great, and just to repeat what we said at the top, treatment naïve means that they're starting treatment for the very first time, so they're not making a switch.

**DR. LLOYD CLARK:** That's right.

**MS. DIANA CAMPBELL:** They're at onset of disease.

**DR. LLOYD CLARK:** New diagnosis. Yeah.

**MS. DIANA CAMPBELL:** Okay. Perfect. This is a question that came in specifically about Eylea HD, but we actually already had somebody else ask a similar question I think can be extrapolated to anti-VEGF, although you're the expert, and you can tell me. Does Eylea HD—or to broaden it, other anti-VEGF treatments—help improve vision in addition to stopping the bleeding?

**DR. LLOYD CLARK:** Oh, without a doubt. Absolutely. Let's go back to 2006 with Lucentis and 2009 with Eylea. The reason why these drugs were so revolutionary is that, on average, patients gained between 8 and 10 letters with monthly therapy with these drugs. And that's why the difference between that and the current standard of care was dramatic. On average, with even the first-generation drugs, we expect somewhere around a two-line improvement of visual acuity on the eye chart (8 to 10 letters), so that's a completely different expectation than we had prior to 2006. In terms of the newer—the next-generation—drug, like Eylea HD, the visual acuity improvements are the same. So far, we really had not identified any new agent that does a better job at improving vision than Eylea 2 mg, but the difference is that these next-generation drugs we can give much less frequently, on average.

**MS. DIANA CAMPBELL:** Which is so important for patient satisfaction and lifestyle and ability to have the freedom to do the things they love to do.

**DR. LLOYD CLARK:** Right. And one more comment about that. We've got long-term data on patients treated with Avastin for 5 years that were treated less frequently than monthly, treated on a treatment schedule similar to what we're talking about here. And after 5 years, all their visual acuity gains were lost, right? Avastin has its role, but as a drug that can offer long-term, consistent improvement of vision, Avastin is not very good at doing that.

**MS. DIANA CAMPBELL:** Thank you for mentioning that. I think that the longer-term benefit certainly, people are looking to have an injection and be able to see that marked improvement, certainly that longer-term efficacy or ability to keep things at bay is equally important, especially once people have gotten adjusted to the fact that they're using injections and are more familiar with the whole landscape and the whole treatment process. Similar to that question, with longer-term anti-VEGF treatment, for people that have been on treatment for a while, we've had people ask or we've had people report back from their doctors that their eyes are dry or they don't use an injection on that particular visit, at least. Can wet AMD be totally changed back to dry AMD, or can it dry out to the point where folks may not need ongoing treatment?

**DR. LLOYD CLARK:** I mean this is kind of an issue with semantics a little bit. I would say, from my perspective, once you develop wet macular degeneration, you always have wet macular degeneration. Now, you may have inactive wet macular degeneration, and I think that's the difference. Some people may say it's turned dry, but to me, when I think about it, if it develops wet macular degeneration then you've got it for life. The question is whether you can come off of treatment. I think that's an area of still somewhat controversy in the field of management of retinal disease. The best data suggest that only about 30 percent of eyes can safely come off of treatment for life, so that means what you would expect is if you stopped therapy, you've got a 30 percent chance that you'll never need another injection again, but you have a 70 percent chance that you will. It's very, very difficult, if not impossible, to predict what a recurrence

can look like. Sometimes they can be very mild. Sometimes they can be quite severe, so there's really two schools of thought, I'd say largely, among thoughtful retina doctors. Many retina doctors give patients a chance to come off treatment because patients want to stop injections, and I totally get that. For me, particularly in patients to have a good outcome, I'm very reluctant to stop therapy. What I am more likely to do is to leave patients on a maintenance dose, which is, like, for instance, with 2 mg Eylea, you know I've got dozens and dozens of patients in my practice. They get four injections a year, what would amount to an insurance policy. With 8 mg, that number should go to three times a year. You know, and you're going to be seeing them two or three times a year, even if you're not giving them injections. And the idea of giving them a shot as an insurance policy against any recurrence, I'm not trying to minimize the discomfort and anxiety and the non-fun factor of an injection, but my job is to think about the long term (5, 10, 15 years from now), and these drugs are incredibly effective, and I've seen too many recurrences to not take them seriously.

**MS. DIANA CAMPBELL:** Yeah, that makes absolute sense, and you essentially said this, but if folks are taking a pause on treatment for whatever reason, maintaining that appointment schedule and still seeing their retina specialist is, I think, of utmost importance so that if any changes are occurring that they're not noting at home, that can be addressed immediately so that vision loss does not occur. This is a newer question. We haven't had to ask this question very many times, but given that over the course of the past 6 months or so there is now approved injection therapy, as well, for geographic atrophy. Many folks that might have both wet AMD and geographic atrophy who are trying to figure out what they are going to do and if they're going to be getting injections for dry AMD, what does that look like? Is it recommended to alternate months? Do you have any comment—and if you don't, that's fine—but do you have any comment on incorporating an additional injection therapy for a different form of AMD for people that have already been on or may have onset of wet AMD?

**DR. LLOYD CLARK:** Boy, that's a lot of injections. I have a handful of people that are getting treatment concurrently for dry AMD and wet

AMD. Most people that I've talked to about it or not are not particularly excited about it. First thing I would say is that treatment for wet macular degeneration is mandatory. Treatment for dry macular degeneration is largely optional at this point. We're really excited about the dry AMD treatments, but the reality is they are not particularly effective when you compare them to groundbreaking therapies, like anti-VEGF agents for wet AMD. We're talking about a 20 percent reduction in the growth of geographic atrophy lesions. It's very difficult to measure treatment response, and it's a treatment that has to be continued forever, so I think where we are is we're at the very, very beginning of dry AMD therapy. I think it gives patients hope, and I think that it's certainly worth doing in highly motivated patients. Now, when you add on wet macular degeneration treatment, it is a daunting prospect to get two injections every 6 to 8 weeks forever because you can't ... you really do have to spend a little more time and be a little more thoughtful because the volume of Syfovre, in particular, is enough that you can't just give these injections back to back. You've got to take some time in the office. So, these are very long, drawn-out visits, and it is difficult. I applaud people for being motivated to do both, but the conversation that I've had more than once is, the patient goes, "Well, I just can't do both of these. Which one should I do?" The answer is, again, anti-VEGF therapy is mandatory, and at this point, if that's the question, then the GA question is optional.

**MS. DIANA CAMPBELL:** I think I know the answer to this question, and I'm fairly certain that somebody will ask it if they haven't already. I'm assuming that you cannot get both injections on the same day, especially if it's in the same eye.

**DR. LLOYD CLARK:** Oh, sure you can. Yeah, you can. There's a couple of ways to manage that. The easiest way to manage that actually is to use a third needle, and some people do this where you actually take a little fluid out of the eyes to start with and then give an injection and get another injection, so that's actually three procedures in one eye on one day. That doesn't sound like a lot of fun, does it? But that's a way to do it. The other way I do it when I do it on the same day is I'll typically give the anti-VEGF agent first because it is a smaller volume, and then I'll let the pressure re-equilibrate. The issue of getting both injections on the same day is

pressure. The eye can't really tolerate the amount of volume from a dry and wet AMD injection at the same time. You'd run the risk of causing an artery occlusion because the pressure in the eye would be so high, so you have to wait. You can do it, but you have to wait between two.

**MS. DIANA CAMPBELL:** Okay. And then there's no ... with this thing so new, there's nothing yet where you can do them all with one needle, so it is a longer day at the office and time waited in between. I'm glad I asked that, though, because I guessed in my unexpert mind that that might not be possible, so thank you for clarifying that. Okay, two more that are more broad to the wet AMD experience. Is there a forecast, or how long on average, if we know this ... what's the lifetime value of injection? Is there a time when they won't work anymore? And then this person, in particular, had some shadows and spots moving in their eye and were wondering if it was related to that. So, is that a common experience, and is there an anticipated timeframe where they may not work as well anymore in the life cycle of the disease?

**DR. LLOYD CLARK:** To get to your second question first, if you've got new visual symptoms and you're being treated for wet macular degeneration, you really need to go in and get them evaluated. It's very difficult to interpret changes—any type of vision symptoms—in that setting over the phone, so I think if you're seeing new spots or new areas of distortion, that's a reason to call your doctor, and that's a reason to come in and be evaluated. There are technologies that work hopefully in the future that may help manage that at home, in particular. One thing I'm really excited about is there's a company that's developing a home version of the OCT. For those of you getting injections, you get that scan of your eye every time. Well, there's a company building one that you could have at your house, which I think is very exciting and because we would be able to see the results at home, and you might not have to come in but, short of that, today, you need to come in if you've got vision symptoms.

Now, in terms of long-term treatment, I'll give you two answers. The short answer is: Thoughtful, aggressive treatment can maintain vision for a long, long periods of time, and I'll give you two examples of that as we wrap up. The first is a clinical trial—a trial called the FIDO study. A good

friend of mine in Tampa, Florida, has followed a group of patients. He does something different than many of us. We all thought that we were smart by limiting the number of injections, and he said, "This clinical trial data is pretty exciting, so I'm going to treat patients every 4 to 6 weeks forever because that seems to be the best thing to do." And he now has 15-year data on a group of patients that have been treated long term aggressively with injections for macular degeneration. And on average, they're all seeing better than they were at time of diagnosis after 15 years, and so that is a great endorsement for the idea that aggressive therapy works, and aggressive therapy works for the long time. A second example that I'll give you is an anecdotal patient of mine. One of the first patients that I ever enrolled in a clinical trial, and I enrolled her in a Lucentis clinical trial in 2003, and she had already lost vision in her first eye from macular degeneration, and she died in 2021, 18 years after enrolling in a Lucentis clinical trial, and when she left the Lucentis clinical trial, in her better eye, she was 20/40 in 2006, and when she died 18 years after diagnosis, she was 20/60, so she maintained vision to the level of 20/60 after almost 20 years of injections in her second eye with macular degeneration. So, yes, patients can do well long term. There's no reason to stop. These are very effective therapies. I know it gets old. I know it gets challenging for the patients and their families, but it works, and you really need to stick to it.

**MS. DIANA CAMPBELL:** That's a wonderful case study there. That's great. I'm going to ask one last question, and this can be relatively quick, if we can make it quick. We have a lot of people who have sensitivity to betadine, and they're just asking the names of the other products and the other ways the doctor can sanitize and clean the eye before the injection if that's a quick answer. I do realize we are running out of time, too.

**DR. LLOYD CLARK:** Yeah, it's a quick answer: pHisoHex is a skin cleaner that you use in surgery, as well. It doesn't work quite as well as betadine, but it certainly is not a bad option. And the final option is, if you can't tolerate betadine at all and that's not available, there is some rationale to just use topical antibiotic drops prior to an injection. By far the most effective way to get this injection is with betadine, but we all recognize that betadine can be pretty irritating.

**MS. DIANA CAMPBELL:** Okay, great. That's wonderful. And we'll have that in the transcript for those who are asking that. And I think this is a simple yes or no; I'll ask one more. Can you get injections in both eyes on the same day using Eylea or whatever the anti-VEGF injection that they're getting is?

**DR. LLOYD CLARK:** Absolutely.

**MS. DIANA CAMPBELL:** Okay. This has been wonderful. So, I am going to wrap up here. I sincerely hope that everybody found today's Chat helpful. I certainly learned some. And thank you so much for your time today. This has just been outstanding, Dr. Clark. I am so grateful that you joined us today. Do you have any final remarks or tips you'd like to share with the audience before we conclude for the day?

**DR. LLOYD CLARK:** None other than thanks so much for having me. It was a pleasure.

**MS. DIANA CAMPBELL:** Thank you, everybody, for joining us today, and this concludes the BrightFocus Macular Chat. Have a wonderful day.

## Useful Resources and Key Terms

To access the resources below, please contact BrightFocus Foundation: (800) 437-2423 or visit us at www.BrightFocus.org. Available resources include—

- Amsler grid
- Apps for People with Low Vision
- BrightFocus Foundation Live Chats and Chat Archive
- *Clinical Trials: Your Questions Answered*
- *Healthy Living and Macular Degeneration: Tips to Protect Your Sight*
- *How Low Vision Services Can Help You*
- *Macular Degeneration: Essential Facts*
- Research funded by BrightFocus Foundation
- *Safety and the Older Driver*
- *The Top Five Questions to Ask Your Eye Doctor*
- *Treatments for Age-Related Macular Degeneration*
- Understanding Your Disease: Quick Facts About Age-Related Macular Degeneration (AMD)

## Other resources mentioned during the Chat include—

- Eylea (2 mg) and Eylea HD (8 mg)
- Lucentis
- Vabysmo
- Avastin
- pHisoHex
- CHATT study
- FIDO study