BrightFocus® Chats

An Update on Dry Age-Related Macular Degeneration and Geographic Atrophy
March 24, 2021
1:00 PM EDT
Transcript of Teleconference with Dr. David S. Liao, Retina-Vitreous Associates Medical Group

The information provided in this transcription is a public service of BrightFocus Foundation and is not intended to constitute medical advice. Please consult your physician for personalized medical, dietary, and/or exercise advice. Any medications or supplements should be taken only under medical supervision. BrightFocus Foundation does not endorse any medical products or therapies.

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

MICHAEL BUCKLEY: Hello, I'm Michael Buckley with the BrightFocus Foundation, and welcome to today's BrightFocus Chat. Today we're going to have an opportunity to learn more about dry AMD and another form of macular degeneration called geographic atrophy. So, if this is your first time at a BrightFocus Chat, thanks so much for joining us. We're going to spend between 30 and 40 minutes hearing from one of the leading experts in age-related vision disease. We'll have a chance to ask some questions, and hopefully it's a very informative conversation for everybody. If you're new to BrightFocus, I want to tell you we fund scientific research all around the world to find better treatments and ultimately cures for macular degeneration, glaucoma, and Alzheimer's. We want to share the latest news and best practices with our audience, so that's why we created the BrightFocus Chats. So, today we are going to talk about dry AMD and geographic atrophy. We have an outstanding

guest to help us with this. His name is Dr. David Liao. He is a leading ophthalmologist in Southern California. He was with us about a year ago, and we had a great conversation, so we really wanted to bring Dr. Liao back. So, Dr. Liao, I was wondering if you could just tell us a little bit about yourself, and how did you end up doing what you're doing for a living?

DR. DAVID LIAO: Sure, thanks, Michael. So, as you mentioned, I'm a retina specialist. I've been practicing out in the Southern California–Los Angeles area for about 10 years, and I think people always ask, "Why you did you go into ophthalmology or retina, in specific?" And I think as a medical student, you always go in trying to pick a field that you could help a lot of people, and I think ophthalmology just really stood out to me as something where you can—no pun intended—see results. And there was a lot you could do to improve people's quality of life, and when I was doing training, the retina was kind of exploding in our ability to treat diseases, like wet macular degeneration, and that really got me interested in retina, and it's really just continued to expand as time has going on. There are so many new treatments out there and treatments for diseases that we weren't even treating in medical school, like wet macular degeneration and—now, hopefully, in the future—forms of dry macular degeneration and geographic atrophy, also.

MICHAEL BUCKLEY: That's exactly what we want to talk about today. We invited Dr. Liao to tell us a little bit about how these ... what these diseases are, how to manage them, and to give us an update on some really promising work that's being done in labs all around the world. BrightFocus supports a number of scientists that are working on these diseases. Again, there's not currently an approved treatment; it's just an incredibly important area. I was wondering, to get us started, Dr. Liao, could you tell us a little bit about what dry AMD and geographic atrophy are? In the family of age-related macular degeneration, what's what?

DR. DAVID LIAO: Sure. Yeah. There are two different types of broad categories of macular degeneration: There's the dry type, and there's a wet type. I think most people nowadays are familiar with the wet type, because that's the type where you get shots, and these injections have been around for a number of years—Avastin®, Lucentis®, Eylea®, and

most recently, Beovu®. And with wet macular degeneration, this was the kind of disease that we used to see a lot of vision loss with because you get swelling in the retina, bleeding in the retina, and this causes sudden loss of vision—like a spot in the vision or distortion—will lead to a lot of scarring, and these medications target the abnormal blood vessels that are causing the bleeding, causing the swelling, and they actually help that to go away. And most of the time, people improve their vision after treatment and maintain it for many, many years.

Dry macular degeneration hasn't gotten as much press, perhaps, because there hasn't been a good treatment for it, but macular degeneration always starts out as the dry type first—that's the earlier or milder type—and what we usually see is people start getting the earlier forms of it. We see drusen and pigment hair changes in the retina, and these drusen are these fatty deposits—the yellow deposits—that can be seen when your eye doctor looks at the retina. Most of the times in the early and intermediate stages of the disease, you don't get many changes. You could see some distortion, some decrease in vision. Some people with dry macular degeneration go on to develop a more advanced type of dry macular degeneration. And this is what we're talking about when we're talking about geographic atrophy.

What happens is these areas of the retina start to thin, and the retina does work over those areas. The layers that are underneath the retina, like the RPE or the retinal pigment epithelium, start to thin, too, and these create blind spots—areas where you can't really see—that lead to difficulty reading. And, eventually, as these blind spots get bigger, these areas of atrophy get bigger; they could start to encompass the central part of your vision where your very high-definition vision is. And in those cases, the folks with that type of dry macular degeneration can get more severe loss of vision. And, unfortunately, at this point, there are no approved medications to treat that, although there are a lot of studies coming out that show that we could maybe slow this process down, and we can hopefully preserve vision for many years and avoid having this loss of the central vision—hopefully.

MICHAEL BUCKLEY: I appreciate you outlining the different forms. I think that central vision loss is going to be so hard, in terms of recognizing faces or reading or driving. So, when you look around at what's happening in research labs in the U.S. and throughout the world, are there things that make you hopeful?

DR. DAVID LIAO: Yeah, yeah, there are. I mean when I was in the medical school, I think people didn't really know the causes or the ... there are multiple causes, but they really weren't familiar with all of these causes that play a part in the progression of macular degeneration. And many years ago, people—through epidemiology or genetic studies—they found genes that were associated with more advanced forms of macular degeneration, and when people have been looking at the laboratory of what goes on in the retina of people with macular degeneration, they've started to understand a lot more about the causes, and these have led to the development of the different medications that, hopefully, will prove to be beneficial in slowing down the disease.

MICHAEL BUCKLEY: Any particular companies or products in development that you feel hopeful about?

DR. DAVID LIAO: Sure, sure. So, yeah, as we mentioned earlier, there's this progression of dry macular degeneration, where you can get ongoing thinning of the retina. Before, we didn't know why, and one of the reasons that's becoming more evident now that this role in dry macular degeneration is the role of inflammation in the side of the eye. So, when you look at those fatty deposits that are found in the retina, you could see molecules that are involved in intraocular inflammation there. There's a system in our immune system, known as a complement system, and it's there for a good reason—it helps us to fight infections and kill off bacteria that shouldn't be in our body—but the molecules that have been involved in the complement cascade have been found to be localized in these drusen, and the thinking now is that ongoing inflammation in the macular is contributing to the thinning and then eventual atrophy of the retina. And a lot of these medications now are targeting the complement cascade, not so much to prevent our body from fighting infection but rather to stop the ongoing inflammation that's going on inside the eye,

causing a slowing, if you will, of that process that's going on to stop the atrophy and to preserve, hopefully, central vision.

So, one of the companies that has had some good results in early clinical trials is Apellis—they're a company, I believe, out of Massachusetts—and they have a drug called APL-2 that blocks C3; that's one of the molecules that's necessary to activate this inflammation in the complement cascade. And they've shown in their initial trials that when this medication is injected into the eye—it's done just like the wet macular degeneration injections, it's done in the clinic on a monthly or every other monthly basis—but they've shown that they can actually slow down the progression of geographic atrophy by about 30 percent. Now, it's not going to necessarily improve vision, but if you think of the process that's going on here, you're getting these enlarging spots where the retina isn't working, you're getting more blind spots, more difficulty seeing with light, and that's impacting reading and so forth and, eventually, may actually affect the central vision—where, if you lose that, you lose the ability to drive and to recognize faces and so forth. So, if we can delay that process by 3, 5 years, we're giving folks a lot more useful vision during their lifetime. So, the trials for that are going on now—the phase 3 trials—and, hopefully, we'll expect the results sometime later this year or early next year. But results have been fairly good.

There are other companies that are looking at other medications that also inhibit complement and try to prevent this inflammatory cascade that's going on inside the eye. One is Iveric; they have a drug that's targeting a different molecule—C5—which also has been shown to have some good results in clinical trials. This also is done by an intravenous injection; the eye injections that are done in the clinic would be done in a monthly basis. There are other companies out there that are targeting different molecules in the complement cascade. There are some other companies, as well, that have earlier trials—Alexion, for example. They have plans for a trial of an inhibitor of another factor in the complement cascade. This drug, however, this is going to be oral, so this may have advantage over the injection because it's less invasive. But we don't have as much data on that one yet. For the molecular type of trials, there are a number of them going on, and hopefully, as the year progresses, there'll be more and more

results, and they'll look forward to getting approval in the next few years, if the results hold.

MICHAEL BUCKLEY: Dr. Liao, those are some very encouraging signs in terms of the complement inhibitors. Are there other approaches, whether that's in cells or vitamins or any other approaches that you're seeing promise?

DR. DAVID LIAO: Yeah, yeah. This is definitely a multifaceted approach. One of the things that is getting a lot of the attention nowadays is stem cells, like a cell-based approach. Basically, in the end stages of this disease, you've lost a lot of cells, you've lost a lot of retina there, and so people have been looking at implanting stem cells underneath the retina to try to replace the cells that have been lost. These trials are earlier, but they certainly have the potential to ... perhaps if we can replace the cells that have been lost, maybe even reverse some of the vision loss, that's the Holy Grail out there. Hopefully, we'll get some good results from the trials.

There's one company, Astellas. They have a cell line that's a human embryonic stem line to replace the RPE—the retina pigment epithelium cells—that are underneath the retina and helps support the health of the retina. Their initial trials they involved people with Stargardt disease, which is kind of a juvenile macular degeneration, if you will, and folks with geographic atrophy, as well, and what they did is they implanted some of these cells surgically underneath the retina. And the goal in the initial trials is mainly for safety—to make sure the technique is safe—but they did see in folks who had the treatment that there was an improvement in the pigmentation levels underneath the retina, showing that the cells actually went where they were suppose to go and survived and produced some pigment that may have been lacking before. The vision results, it wasn't really ... it was more geared toward safety, but some of the patients did improve vision-wise, and a modest amount, but again, that wasn't the goal of the trial—a long-term goal, of course.

There are some other companies out there that are trying to do other things. Like, they have a patch, if you will, that's grown in the laboratory, and they're also trying to introduce that surgically underneath the retina to try to replace some of the retina pigment epithelium cells that were

lost. So, a lot of companies out there are trying to do these things—in early stages, of course, but very promising. That's kind of on the replacement front.

There are also companies that are trying to kind of preserve the function, if you will. So, one of the other theories out there is that the metabolism—the byproducts of the metabolism—that the retina is very metabolically active; it uses vitamin A to basically provide vision. As the light hits these forms of vitamin A, they change their shape and allow us to perceive vision, and the byproducts of this product of the vitamin A are thought to be involved in causing toxicity to the retina over time. And so, there's a company called Alkeus that has a modified form of vitamin A out there that seeks to replace the natural form, if you will, of vitamin A, but the byproducts of this vitamin A are supposedly less toxic to the retina, so the thinking is that if that is used, then the toxicity to the retina will be less over time, and you can slow down the progression of macular degeneration or geographic atrophy over time. That medication may have some side effects. Of course, that's why they're doing the trials, but also very promising.

There other companies out there. There's one drug that's been used for glaucoma called brimonidine, and that lowers the eye pressure, but people also think that it helps preserve nerve cells in glaucoma and may help to preserve the neural-type tissue that's in the retina. So, they've actually been injecting a small, slow-release pellet of that medication into the eye, and they've also shown that it has some modest effects of slowing geographic atrophy, as well, so that's from a more neuroprotective standpoint, if you will. There are also folks out there that are looking at light or what's called photobiomodulation. Light has been used in other fields for years to try to help scar tissues, healing, and so forth—dermatology type of applications—but I believe one of the listeners submitted question about red light. So, there's a company out there called LumiThera that's using a device to expose the retina to low levels of a specific wavelength of light and infrared wavelength, and this has been shown as some of their primary ... their initial studies to improve retinal functions, so they're doing larger trials to see, does that replicate in a number of patients, or does it help patients see better or detect light

better in geographic atrophy? That's a whole other nonpharmacological approach, so very interesting ways of kind of attacking the disease, and it may turn out patients use more than one of these to get a synergistic effect on improving vision and delaying disease progression.

MICHAEL BUCKLEY: I really appreciate such a comprehensive look at, really, what seems like a really helpful scientific pipeline, and I appreciate your point that maybe, in the end, it could be one than more treatment for a person. When you mentioned different promising drugs, you frequently mentioned clinical trials, and I think in the last 6 months or so, the nation has paid so much attention to clinical trials for COVID, and I think we've all learned a lot. I was wondering how does ... tell us a little about clinical trials in vision. Is it similar to how the clinical trials were that got us the COVID vaccines?

DR. DAVID LIAO: Sure. Yeah, I mean, all of these trials, we have to do them, and we do a lot of trials for macular degeneration here at the clinic, but they're running conjunction with the FDA and the sponsor. And really, they're trying to get new drugs, obviously, out to the market, but FDA really wants the drug to be safe; their job is to protect patients, as all our jobs are, and they want the drug to be tested in a very specific way. So, basically, these new medications already had some preclinical data and small trials or tests, perhaps in animal models, that show they are fairly safe, but we don't really know until they're tested in people.

Basically, if you have a certain disease, like geographic atrophy, and you're interested in a trial because there is no approved treatment, then you go to your retina doctor, for example, and discuss trials with him or her, and they'll see whether your eyes are appropriate for the trial first because they want to do statically analysis and really prove that the medication is doing what it's doing, so they have sometimes fairly strict entry criteria. For example, you have to have severe geographic atrophy or maybe moderate geographic atrophy—and each trial is a little bit different—they'll do what's called a screening exam and do complete eye exams and see whether you meet all these criteria. After that, they'll go ahead and enter you into the trial if all the criteria are met. And usually, they're comparing an established treatment, if there is an established treatment,

or a placebo—a sugar pill, if you will—if there's no treatment. And you'll get assigned to one of these two groups. You might not necessarily know during the trial, but they'll certainly reveal that to you after the treatment, During the trial, you'll receive the treatment, and you'll get very close follow-up, they monitor you very closely for any side effects, and they'll take pictures and so forth to assess the role of the drug and see how the geographic atrophy is progressing. After that, then they take a look at all the data, and they see over a large number of people: Does this drug really work? And if it's safe, and after that, they will apply to the FDA, and that will be approved for general use out of the populations.

I also remind my patients that this is not an obligatory thing. Folks that, for whatever reason, decide they don't want to participate in the trial, they can just exit the trial. Those types of things patients often have concerns about, and it's really a working relationship between you and your doctors. So, the doctors are really trying to do whatever is best for you, and the advantage sometimes is it takes 3, 4, 5 years for these medications to get approved, and a lot of times we saw with the wet macular degeneration studies that folks got medicines before they were on the market, so that's sometimes a huge advantage. But sometimes the drugs turn out not to be as effective, and they don't get approved, but that's why we do the studies, and they're very helpful to society as a whole to get new medications out there and to get conditions treated that we never really could treat before.

MICHAEL BUCKLEY: I think you're exactly right. I do feel like there is a pay-it-forward type of citizenship there. When you and your patients talk about possibly going into a clinical trial, are there common questions or concerns that you address from your patients?

DR. DAVID LIAO: Sure, sure. Yeah, so folks who are certainly concerned, a lot of folks ... it's an experimental medication, and they're certainly concerned if it's safe or not. And the FDA and the trial monitor folks very closely to make sure that they don't have any side effects, and if there are significant side effects that, they'll stop the trial. The patients often ask, "If I get tired of the trial, am I obligated to stay in it?" And the answer is "no." It's totally voluntary, and folks can exit the trial whenever they need to. It's

just a voluntary participation, and if you feel like you're getting a benefit out of it, then certainly continue, and, hopefully, these medications prove to be better than what's available on the market—which, unfortunately, for geographic atrophy at this time, there's really not much.

MICHAEL BUCKLEY: Thank you. Dr. Liao, we just got a question about clinical trials. Are there any that would have people who have the geographic atrophy in one eye but also wet in another? Is there research on clinical trial opportunities for these folks?

DR. DAVID LIAO: Sure, yes. As I mentioned, certain trials have different entry criteria, and there are trials out there for geographic atrophy that do have requirements for both eyes to be dry, but there certainly are trials out there that it's okay if one eye is wet. And I believe … I'd have to check the inclusion criteria, but there also are studies out there that are looking at treating geographic atrophy with gene therapy; I didn't mention in the earlier discussion, but I believe that trial also does include folks who have wet in one eye, but I'll have to check. Any questions like that can certainly … folks can question their local retina doctor, or they can be referred to a clinical trial center; they'll have all that information available to them, and they can go through it step by step.

MICHAEL BUCKLEY: Thank you. We have a number of people submitting questions today about vitamin supplements—specifically, the AREDS product that's available over the counter. I was wondering if you could tell us a little bit about AREDS—both who is it right for and who is it not right for? It seems to be the core of the questions today, people wondering, will it help them or not?

DR. DAVID LIAO: Of course, yeah. Because you see advertisements on TV and in magazines and everything, but the, basically, how the AREDS came about was there were these large landmark clinical trials, actually, for vitamin supplementations conducted by the NIH. So, we know that people that have diets that are lower in antioxidants tend to have more severe macular degeneration. The AREDS supplements are basically antioxidants, and so the AREDS1 study, a certain formula of medication … of vitamins, and they showed that they could decrease your risk of getting wet macular degeneration by taking this supplement

formulation. Now, that initially had beta-carotene in it, and they found out that beta-carotene sometimes gives smokers a higher risk of developing lung cancer, actually, at the doses that were in the trial. In the AREDS2, among other things, they took that out, and they found that that vitamin supplement without beta-carotene actually did just as well as preventing the wet macular degeneration. Now it doesn't really prevent geographic atrophy, unfortunately. It's more for wet macular degeneration. But that is a significant side effect of macular degeneration, so still a very useful tool.

For folks who don't necessarily have macular degeneration, it's not really necessary to take those vitamins. It's more ... when you're at that stage, it's more advisable to simply take a multivitamin, eat a healthy diet with a lot of antioxidants and omega-3s—spinach, kale, broccoli, salmon once or twice a week—and that's sufficient. Even if you have a family history but you don't have any symptoms of macular degeneration, that's probably all you need. Now, when you start to develop early or certainly moderate macular degeneration, that's when your doctor will start advising you to considering taking the AREDS supplement, because that's when you're more at risk for developing wet macular degeneration.

MICHAEL BUCKLEY: Thank you. It's very helpful, because you see these ads on TV, and it gets your mind wondering a little bit. Several people have left us questions today about AREDS wondering about zinc, that they have heard that there could be a problem with too much zinc in their nutritional supplements. Is that something you can comment on?

DR. DAVID LIAO: Sure. Yeah, so they did see in the AREDS study that zinc did cause some side effects, such as actually stomach upset and those things, and there is a theory out there ... there's all these ...there was a boom a few year back in genetic testing for macular degeneration because there are certain genes that predispose you to getting more advanced macular degeneration, and there was a theory that they found a trend in the data that certain types or combinations of genes predispose you, perhaps, to getting more macular degeneration if there are high doses of zinc in the vitamins. The authors of the study noted that, and they themselves actually don't advise routine genetic testing for genotypes of macular degeneration, because it's more of research type

of tool, but the newer formulations have less zinc, and they're equally as effective. I think if you're taking the AREDS2 formula, I mean, that's proven to be fairly safe. There are some theories out there that they're actively looking at, but at this point, we don't necessarily know. And the AREDS2 study was done over a large number of patients. For the patients as a whole, that was a safe dose to take.

MICHAEL BUCKLEY: Thanks. You may have touched on this a couple of minutes ago, but we had a caller wondering about, if they're not a smoker, is AREDS1 still available, and is a nonsmoker better off with AREDS1 or AREDS2?

DR. DAVID LIAO: Right, right. So, the primary reason, as we mentioned, was that for smokers, AREDS1 did cause an uptick in lung cancers. Now, when they compared the formulas in AREDS and AREDS2, there was really no difference in the protective effect, so either one would be fine. I believe the AREDS1 is still available, but most of the formulas out there are now the AREDS2. I would just advise them to consider taking the AREDS2, since it's just as effective, and that's probably easier to get now, actually.

MICHAEL BUCKLEY: One last question on the AREDS; we got a number of questions on that today. A caller has some concerns that ... could AREDS ever accelerate the progression for AMD? Does it ever work in the opposite direction?

DR. DAVID LIAO: In the opposite direction? Yes. So we had alluded to that earlier; there was this possible trend that for certain combinations of genes, it might do so. But that's not really definitive at this point, so at this point, we have good data that for the general population that AREDS is protective. The other issue that's out there is somewhat controversial at this point, so the answer is that I don't think we have a good idea, but we do have good data that the AREDS is protective. So, we'll wait and see if there's any other information that comes out, and I think if they found that to be the case, they would certainly publicize that.

MICHAEL BUCKLEY: One more question before we move into our concluding remarks today. About the mental health toll of an AMD diagnosis and about quality of life, when you talk with your patients

and you see some—and I think there will be very, obviously, stress and worry, what do you say to them and just, in effect, how do you do it operationally, how do you guide people toward different apps or devices, or how do you help people live as best they can?

DR. DAVID LIAO: Sure, yeah. I mean, the first thing I tell people is because in earlier times in macular degeneration, the diagnosis would be a diagnosis of blindness. At this point, that's not the case. We have good treatment, especially for wet macular degeneration—and we're getting good treatments, I think, for dry macular degeneration—but there's no question, there's going to be some vision loss associated with that and that affects your quality of life. Things we all like to do—read; watch TV; driving, even. But the goal, I think, is to keep a positive outlook and to maximize the vision that you do have, which still can be pretty good. I have lots of patients with macular degeneration that really just live full lives; they go about their everyday lives without too many problems. There are some inconveniences, like we all have, but as the vision loss starts getting more, there are simple things you can do: use more light, use magnifiers, and so forth.

But there are cases where it certainly is more severe, and those cases I like to work with a low vision therapist. In most cities, there are centers—in Los Angeles, there's the Braille Institute that's does a great job. There are superb groups out there, like the Foundation Fighting Blindness, that can get folks in touch with low vision specialists, and there are individual doctors in each city that will do these specialized devices and will help folks order those types of things that can people with apps and things like that. Even sometimes just your nephew or something can help you go to the app store and download these magnifiers that you can get on the iPad or simply blowing up the font and so forth. The goal is maximizing what you have, and there are certainly professionals out there—low vision therapists—that do a great job of making devices available that can really help in the day-to-day life.

MICHAEL BUCKLEY: Thank you. Dr. Liao, before we conclude, I just want to thank you very much for just giving us a lot of ... a lot of reasons for hope, a lot of specific examples of the field of vision research making

some really exciting progress. I was wondering if you could leave us with something "big picture," sort of one big thing you feel like you've learned in your career, or is there one piece of advice that you'd wish all your patients ... you want to make sure all your patients know about, or is there something you want to end with today?

DR. DAVID LIAO: Sure. Yeah, yeah. I think the big picture is things are always improving, things are always getting better, and staying in touch with your doctor and learning about these clinical trials, learning about other options, like low-vision therapy that are out there, can really keep you abreast of all the things that are going to on. And there are certainly things out there today that weren't around 5 years ago, so the field is consistently changing. There's certainly hope out there to provide longer quality vision and, perhaps, even better quality vision in the future; we're living in exciting times. Hopefully, the COVID will go away, but for macular degeneration, I think that the future is bright. I mean there are lots of treatments out there or coming available that will likely change and shape the way we treat this and change the prognosis in the very near future.

MICHAEL BUCKLEY: That's good to hear. Dr. Liao, on behalf of BrightFocus Foundation, I'd just want to thank you so much for coming back a second time. I think you've really given us a lot of hope for the future.

DR. DAVID LIAO: Thank you for having me. It was a pleasure.

MICHAEL BUCKLEY: On behalf of BrightFocus Foundation, this concludes this month's BrightFocus Chat. Thanks so much for joining us, and we will be back April 28. Thanks.

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—

- 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
- 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—

- AREDS1 and AREDS2
- Avastin, Lucentis, Eylea, and Beovu