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Decoding Variable Responses to Anti-VEGF Therapy in AMD and DME Care

Announcer:
You're listening to *Eye on Ocular Health* on ReachMD, and this episode is sponsored by Regeneron. Here's your host, Dr. Charles Turck.

Dr. Turck:
This is *Eye on Ocular Health* on ReachMD, and I'm Dr. Charles Turck. Joining me to discuss how we can create comprehensive management plans for patients who have age-related macular degeneration or diabetic macular edema who have variable responses to anti-VEGF therapy is Dr. Joseph Coney. He's an ophthalmologist at Retina Associates of Cleveland and an Executive Board Member in the Ophthalmology Section of the National Medical Association. Dr. Coney, welcome to the program.

Dr. Coney:
Dr. Turck, thank you for having me.

Dr. Turck:
Well, to start us off, Dr. Coney, how often do we see treatment response variability in patients with AMD or DME who are receiving anti-VEGF therapy?

Dr. Coney:
Anti-VEGF therapies have really revolutionized the way that we treat center-involved diabetic macular edema and exudative macular degeneration. And despite our best efforts in the clinical trials, we still have those individuals that are suboptimal responders. What do I mean by that? Those individuals that still have persistent subretinal fluid and intraretinal fluid. Now, in the real world, this is much more common because these individuals are not subjected to the rigorous protocols that we have in clinical trials.

I think the most important thing is that you want to make sure that if someone has persistent fluid or intraretinal fluid, you want to make sure that that fluid is active. You want to make sure that this is from an exudative process and not from a neurogenic process. But once you have determined that that fluid is from an exudative process, then what I typically do is look and see who has bad fluid and good fluid.

Well, what do I mean by that? We've gotten comfortable in dealing with individuals, particularly when it comes to AMD with subretinal fluid, as those individuals tend to have visual acuity gains and are able to maintain that without a significant decline of vision, even with extension. Unlike those individuals with intraretinal fluid, those eyes tend to have worse vision gains. They're also more prone to having geographic atrophy as well as subretinal fibrosis.

Now, when it comes to diabetes, we've learned a lot from an ad hoc evaluation of protocol I where individuals, after three injections, if they did not have any significant vision gains—which means less than 5 letters—those eyes tend to have similar vision at 1 and 2 years, so they had a much poorer prognosis. And so switching those individuals earlier seems to be much more important. So you really want to identify which eyes may be at risk for losing vision.

Dr. Turck:

Now, with that in mind, let's dig into some of the core factors driving that variability. Starting with the biochemical side, what do we know about key genetic or pharmacogenomic factors that influence how patients respond to anti-VEGF agents?

Dr. Coney:
I think some of the genetic factors that we deal with are some of the things that we're not currently treating. The diversity of VEGF alone I think is critically important. You have VEGF A, B, C, D, as well as placental growth factor. And I think that all these may play a role in those individuals that may be sub-responders.

There are also individuals that may have polymorphisms. We know that there are several VEGF-related polymorphisms that have been shown to contribute to nearly half of the variability in circulating VEGF levels, even in healthy individuals. And we know that the expression of VEGFR 2 is affected by the presence of VEGF-related polymorphisms. And those individuals that have certain haplotypes or genotypes have been shown to have a higher risk for developing proliferative diabetic retinopathy.

We also see variability even in the aging eye or for someone who has a retinovascular problem, and this is where we see an upregulation of hypoxia-inducible factor. This factor is present normally, and its job is to oversee cellular oxygen hemostasis. It also promotes erythrocyte production, angiogenesis, and mitochondrial metabolism.

So in the aging eye, where these individuals are going under chronic inflammatory processes, the choriocapillaris, over time, can be affected, creating small but minute hypoxic situations where the RPE and the photoreceptors cannot get enough oxygen, therefore creating a hypoxic environment. And we can see that, over time, individuals will have loss of photoreceptors, loss of choriocapillaris, and thickening of the basement membrane. And these are all factors that we see with advancing dry macular degeneration.

Now, when it comes to the retina tissue, when it comes to diabetes or retinal vascular diseases, there's these micro-occlusions, just from having high sugars over time, where that circulation can get affected. And again, you have this translational factor which is upregulated, and it has significant effects downstream, where it has upregulation of vascular endothelial growth factor.

And I think that these may be two factors that could be addressed later that may help reduce the number of suboptimal responders, and it may potentially help increase the durability of the agents that we already have.

Dr. Turck:
Now, you've been starting to touch on this, but from a clinical perspective, what comorbidities or ocular characteristics tend to predict suboptimal or inconsistent responses to anti-VEGF therapy?

Dr. Coney:
Some of the comorbidities that I typically see in my diabetic patients, which cause fluctuations in their diabetic eye disease, typically has to do with how aggressive we are initially with controlling someone's sugar or the long-term management.

Systemic blood pressure also has a significant role in how diabetic eye disease progresses. Those individuals, even with normal controlled hemoglobin A1c levels and if they still have uncontrolled blood pressure, can still have worsening of their disease.

We know that in individuals that have, let's say, congestive heart failure or renal disease, when patients are fluid overloaded, these also can make diabetic macular edema much more difficult to treat. Individuals that are pregnant or have anemia can also worsen the level of diabetes.

I do think we have to be very aware when patients have been stable in between their dosing intervals and have wide fluctuations in their change in anatomy. So many times, I've had patients develop an acute infection or an inflammatory problem where, even on therapy, they've had wide changes in their diabetic status.

As an ophthalmologist, you should be aware of different systemic problems as well as changes in people's lives that may impact their overall quality of life and their diabetic eye disease.

Dr. Turck:
For those just tuning in, you're listening to *Eye on Ocular Health* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Dr. Joseph

Coney about managing treatment response variability in anti-VEGF therapy for patients with age-related macular degeneration or diabetic macular edema.

So, Dr. Coney, once you've identified a patient who does not respond optimally to therapy, how do you reassess and re-strategize their treatment?

Dr. Coney:
Typically, once I identify someone that is not hitting the anatomical marks I'm looking for or the visual gains that I expected them to have, I am typically switching those individuals to a second-generation anti-VEGF agent, such as faricimab or a high-dose aflibercept. In some degrees, these medications have shown to have greater durability than the first generation of agents for exudative macular degeneration.

So for example, if I have a patient that is doing well, let's say on a 2-mg aflibercept, and they're stable at 8 and 10 weeks but can't extend beyond that, it's easier for me to switch them over to a high-dose aflibercept as I can typically extend that patient out to 14 to 16 weeks.

For those individuals that may need more aggressive therapy, faricimab is a great choice, but you have much more flexibility than you have with aflibercept HD, which after three injections, you need to extend past 7 to 8 weeks.

Dr. Turck:
And as a follow-up to that, would you share how you approach treatment sequencing and modification?

Dr. Coney:
So, Dr. Turck, when I think about suboptimal responders and patients that may need to be reassessed, I think sometimes it comes down to what type of lesions we're treating. Not all lesions are the same.

The lesions that really come to mind are RAP lesions—retinal angiomatous proliferation—which is a type 3 lesion, and polypoidal vasculopathy, which is more of a type 1 lesion, typically occur between the RPE and on the basement membrane. These individuals are known to be suboptimal responders. They have a high risk of recurrence, and they typically require high frequency of injections to make sure that they remain stable.

Morphologically, typically they have a high peak PED, they have more subretinal fluid, and they also often present with multiple PEDs and even a hemorrhagic component. These individuals have shown that even with aggressive therapy, it's really hard to close down these aneurysmal branching dilatations, which can be deleterious. And every time you try to extend patients out, the subretinal fluid can reoccur.

The EVEREST II trial showed us that individuals with PCV typically respond better with combination of anti-VEGF injections as well as photodynamic therapy compared to those individuals that received anti-VEGF injections alone. They also showed at 2 years a much better visual response with half of the amount of injections.

And so oftentimes, you find yourself in dilemmas on what's driving a person's disease, or is it something you're missing. And I think sometimes reevaluating a particular lesion type with different ancillary tests that we have—whether it's using OCT or OCTA—all these things may be important in identifying different types of lesions, which either do better on more durable medications, augmenting their therapy, or supplementing their therapy with photodynamic therapy.

Dr. Turck:
Before we close, Dr. Coney, let's look ahead for a moment. What innovations or strategies show the most promise in reducing variability and improving durability response?

Dr. Coney:
When we look at the possibility of decreasing intervals or just addressing suboptimal responders, the tyrosine kinase inhibitors, particularly gene therapy, I think are really exciting. RGX-314 is a medication that is given in the subretinal space. This gene is incorporated into the retinal tissue to continuously make anti-VEGF therapy, so you don't need multiple injections. This may be a one-and-done type of medication. Other routes of administration that have been considered are intravitreal gene therapy along with

suprachoroidal injections.

All these therapies are really, really exciting. When it comes to gene therapies, what's going to limit that may be rates of inflammation or even RPE changes, which we have seen with subretinal gene therapy.

Dr. Turck:
As those forward-looking comments bring us to the end of today's program, I want to thank my guest, Dr. Joseph Coney, for sharing his perspectives on how we can manage treatment response variability in patients with age-related macular degeneration or diabetic macular edema who are receiving anti-VEGF therapy. Dr. Coney, it was great having you on the program.

Dr. Coney:
Thank you very much.

Announcer:
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