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Comparing Anti-VEGF Therapies: Real-World Insights on Efficacy, Safety, and Dosing

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. Today, we're diving into anti-VEGF therapies and their real-world efficacy, safety, and durability outcomes in patients with wet age-related macular degeneration, or AMD, and diabetic macular edema, or DME. Joining me in this discussion is Dr. Michael Javaheri, who's the Managing Partner and Director of Research at Retina Specialists of Beverly Hills, as well as an Adjunct Clinical Professor of Ophthalmology at the Keck School of Medicine at the University of Southern California. Dr. Javaheri, thanks for being here today.

Dr. Javaheri:
Well, it's a pleasure to be with you and discuss these great things going on in our field.

Dr. Turck:
Well, to start us off, Dr. Javaheri, would you walk us through the anti-VEGF therapies currently available for wet AMD and DME and how they compare in terms of real-world efficacy?

Dr. Javaheri:
We can't start talking about injectables without starting with bevacizumab. It was and still is an oncology drug, and it was used off label and changed the way we treat patients forever. It's still widely used in wet AMD and DME due to its cost effectiveness, but it is an off-label treatment.

Ranibizumab was the first on-label treatment that was FDA approved for wet AMD and DME. It was used very widely and is still used in its form and in its biosimilar form, which is available in a newer, lower cost alternative.

Aflibercept became the gold standard for many years for wet AMD and DME, with a very low level of immunogenicity and with fantastic treatment outcomes in many patients. Those I tend to classify as older-generation agents.

Newer-generations include faricimab, a dual VEGF-A and Ang-2 inhibitor, which is approved for wet age-related macular degeneration and DME, in addition to aflibercept 8 mg, which is a newer version of aflibercept 2 mg, and—as you can guess—is four times the dose and a slightly larger volume that is administered to patients.

We do have a port delivery system with ranibizumab, which is FDA approved, but this is a surgical implementation of this device, and it's different than the injectables that we're talking about.

Dr. Turck:
Now, in terms of these agents' safety profiles, where do we see meaningful distinctions between these therapies?

Dr. Javaheri:
Well, we see common and some not common side effects in these agents. Common ocular side effects include subconjunctival hemorrhage, transient IOP changes, and cataract progression. Sometimes we can see retinal detachment, which is very rare, or sterile inflammation, which is very rare but more frequent in brolucizumab.

The risk of endophthalmitis is about 0.05 percent per injection, which is limited due to the sterile technique that we use. And systemically, it was once believed that there is a concern for stroke or myocardial infarction from VEGF suppression, but large meta-analyses have showed minimal or no clear risk. But we still do caution high-risk patients that are getting these injections.

Some of our agents have specific side effects, like brolucizumab, which has a much higher risk of retinal vasculitis or occlusive vasculitis when compared to other drugs. Bevacizumab has a risk due to the compounding.

We've seen excellent long-term data with ranibizumab and aflibercept due to their low levels of immunogenicity with regard to any serious ocular side effects.

Dr. Turck:
Now, if we zero in on durability for a moment, what have real-world data taught us about how long these agents maintain their therapeutic effect?

Dr. Javaheri:
Well, when we compare real-world to clinical trials, obviously in clinical trials, we see people getting injections on a monthly or every-other-month basis throughout. Those patients seem to do very, very well but with a very high injection burden.

In the real world, most people, in all of the questionnaires that you see, use a treat-and-extend methodology. And in our real-world findings, we're looking for patients that we can extend to longer intervals and maintain excellent vision.

And with the newer-generation drugs, we see longer intervals of extension, meaning that the drug has a longer duration of action. And we're seeing with the new-generation drugs faricimab and aflibercept 8 mg the ability to extend our patients to intervals of 3 or 4 months in treatment-naïve patients.

Now, how does that correspond to what goes on in the real world? Well, when switching patients, we can see extensions from older-generation drugs with these new-generation drugs of about 2 to 3 weeks. So that, again, is buying our patients time between injections and also keeping their vision doing very well. Anytime we can decrease the injection burden in our patients and keep their vision excellent, I think the drugs are doing a great job doing that.

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. Michael Javaheri about real-world impacts of anti-VEGF therapies on patients with age-related macular degeneration, or AMD, and diabetic macular edema, or DME.

So, Dr. Javaheri, now that we know how these anti-VEGF agents perform, let's explore the science behind them. Would you break down for us the differences in molecular structure or binding mechanisms across this therapeutic class, and why those differences matter in terms of clinical outcomes?

Dr. Javaheri:
Well, we'll start with bevacizumab. It's a full antibody that attacks VEGF-A. Ranibizumab is an antibody fragment that attacks VEGF-A; it has a high tissue penetration and rapid systemic clearance.

Aflibercept, on the other hand, is a VEGF trap fusion protein. It binds VEGF-A, VEGF-B, and PlGF with a very high affinity and has very low immunogenicity.

Faricimab is a bispecific antibody binding to VEGF-A and Ang-2 and stabilizes vessels beyond just the VEGF blockade.

Brolucizumab has a very small fragment that has the highest molecular concentration but has a high level of immunogenicity.

How does this impact what we're doing clinically? Smaller molecules can better penetrate the eye, and a higher molar dose can sometimes act quickly to help disease go away. But sometimes you can see in some of these patients higher immunogenicity, which can cause inflammation. We want drugs with high binding affinities and high durability, and sometimes that comes along with a higher molecular dose.

Dr. Turck:
And in clinical practice, dosing intervals often vary between different patients and medications. So how do you determine the optimal dosing interval? And what impact could that decision have on both patient outcomes and clinic workflow?

Dr. Javaheri:
Well, getting our patients on aggressive treatment is always a cornerstone of care. And once we're able to do that, we look to use the treat-and-extend methodology to extend them by 2-week increments and make sure that they are doing well, both with regard to their

vision and their OCT outcomes.

By doing this, we're able to A, make sure that they keep adhering to their appointments because they don't feel overburdened and they know that they're doing well, and B, we lower the clinic burden on given days, and I think this makes everyone happy.

We sometimes have patients that need fixed dosing based on the amount of disease that they have, but hopefully, as the disease improves, we're able to extend them by 2- or 3-week intervals and get them to a place where they're more comfortable.

Dr. Turck:
Well, given everything we discussed today, Dr. Javaheri, I just have one final question for you. In sum, how do these differences in efficacy, safety, durability, and dosing influence your treatment selection?

Dr. Javaheri:
As a clinician, I tend to move towards treatments that are efficacious and have a longer duration of action. I feel like I'm making a deal with my patients that I'm going to do the best I can for them. And in doing so, I like to treat them aggressively, and then I'll look to extend them to longer intervals once they're stable.

I tend to use agents with a longer duration of action because I feel it makes my patients understand that I am doing the best I can for them to have the best possible vision and to not have any potential side effects from continued visitations or injections.

Dr. Turck:
Well, with those key insights in mind, I want to thank my guest, Dr. Michael Javaheri, for joining me to compare anti-VEGF therapies for patients with wet age-related macular degeneration and diabetic macular edema. Dr. Javaheri, it was great having you on the program.

Dr. Javaheri:
Thank you very much for having me. It was a pleasure.

Announcer:
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