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VOLUME 2 — ISSUE 1: TRANSCRIPT

Featured Cases: Diabetic Macular Edema

After participating in this activity, the participant will demonstrate the ability to:

- Formulate a treatment plan for diabetic macular edema utilizing intravitreal drug therapy and laser treatment;
- Describe the efficacy and safety outcomes of clinical trials investigating the use of anti-vascular endothelial growth factor (VEGF) therapies and corticosteroid treatments for DME; and
- Discuss potential drug-related adverse events clinicians should consider when selecting a treatment for patients with DME.

This discussion, offered as a downloadable audio file and companion transcript, covers the important issues related to diabetic macular edema, as reported from the 2012 annual meeting of the American Society of Retina Specialists in Las Vegas, Nevada, in the format of case-study scenarios for the clinical practice.

Unlabeled/Unapproved Uses
The author has indicated that this presentation will include discussions off label discussions of aflibercept, bevacizumab, ranibizumab, and corticosteroids for treatment of diabetic macular edema.

Faculty Disclosures
Dr. Huang discloses that he is a consultant to Bausch & Lomb, Notal Vision, Second Sight Medical Products and Sequenom.

Dr. Thompson discloses that he has received grants/research support from Genentech/Roche and Regeneron Pharmaceuticals.

Dr. Neil Bressler has disclosed he has served as a consultant for GSK and has received grants/research support from Abbott Medical Optics, Inc., Allergan, Bausch & Lomb, Bristol-Myers Squibb, Carl Zeiss Meditec, ForSight Labs, LLC., Genentech, Genzyme Corporation, Lumenis, Notal Vision, Novartis, Ora, Inc., QLT,Inc., Regeneron, and Steba Biotech.

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⇩ PROGRAM BEGINS BELOW

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STATEMENT OF NEED
The treatment of retinal diseases is an area of medicine where research and innovation are very strong. Newly presented information-and information due to come out very soon-will very likely change the ways clinicians provide optimal patient care. Many of these new trial results have not yet been published; the initial findings of much of the most important new data were first made public at key ophthalmology and retina specialist meetings in 2011. Trial updates, initial findings from ongoing trials, and guidance translating this critical information into practice protocols are expected to be presented at similar meetings throughout 2012.

Clinicians are either not aware of this new information and/or are not sure how they can best integrate it into their practices. Four key (interrelated) retinal treatment areas where increased clinician awareness will provide the most immediate patient benefit have been identified by the program directors.

- **Retinal Vein Occlusion:** New retinal vein occlusion treatment approaches have created uncertainty about choosing the most appropriate therapeutic option.
- **Macular Degeneration:** Newly released data may herald significant changes in the treatment of AMD that clinicians are unprepared to implement.
- **Diabetic Retinopathy/Diabetic Macular Edema:** Integrating ongoing research likely to change current diabetic retinopathy/diabetic macular edema treatment protocols has led to clinician confusion about best practices.
- **Vitreomacular Adhesion:** Clinician unfamiliarity with therapies currently in development may delay delivery of optimum benefit for patients with vitreomacular adhesion.

BOB BUSKER: Welcome to this Volume 2, Issue 1 *eOphthalmology Review* podcast. *eOphthalmology Review* is presented by the Johns Hopkins University School of Medicine, and is supported by educational grants from Alcon Laboratories, Genentech, Inc., and Regeneron Pharmaceuticals, Inc. This activity has been developed for ophthalmologists and retina specialists, and there are no fees or prerequisites to participate.

I'm Bob Busker, managing editor of eOphthalmology Review. Today's program comes from the 2012 annual meeting of the American Society of Retina Specialists in Las Vegas, Nevada, and is hosted by eOphthalmology Review course director Dr. Neil Bressler of the Johns Hopkins University School of Medicine. Dr. Bressler is the James P. Gills Professor of Ophthalmology, and chief of the Retina Division at the Wilmer Eye Institute at Johns Hopkins in Baltimore.

Dr. Bressler has disclosed that he has received grants and/or research support from Abbott Medical Optics, Inc., Allergan, Bausch & Lomb, Bristol Myers Squibb, Carl Zeiss Meditec, ForSight Labs, LLC., Genentech, Genzyme Corporation, Lumenis, No-tell (Notal) Vision, Novartis, Optovue, Inc., Pfizer, Inc., Quark Biotech, Inc., and Regeneron. His spouse has served as a consultant for GlaxoSmithKlien and has received grants and/or research support from Allergan, Bausch & Lomb, Genentech, Lumenis, Notal Vision, Novartis, Regeneron, and Thrombogenics.

Today's topic is Diabetic Macular Edema. Dr. Bressler's guests are Dr. SuberHuang from Case Western Reserve University School of Medicine in Cleveland, and Dr. John Thompson of Retina Specialists.

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Learning objectives are that after participating in this activity, participants will demonstrate the ability to:

- Formulate a treatment plan for diabetic macular edema utilizing intravitreal drug therapy and laser treatment;
- Describe the efficacy and safety outcomes of clinical trials investigating the use of anti-vascular endothelial growth factor; (VEGF) therapies and corticosteroid treatments for DME; and,
- Discuss potential drug-related adverse events clinicians should consider when selecting a treatment for patients with DME.

And now our host, Dr. Neil Bressler.

I'm **DR. NEIL BRESSLER:** Thank you, Bob. Let me start out by introducing my colleagues. Joining me today is Dr. Suber Huang, the Philip F. and Elizabeth G. Searle Professor of Ophthalmology at Case Western Reserve University, Vice Chairman of the Department of Ophthalmology, and the Director of the Center for Retinal and Macular Disease at the University Hospital's Eye Institute in Cleveland. He also is the current President of the American Society of Retina Specialists. Dr.Huang disclosed that he has served as a consultant for Bausch and Lomb, Sequenom, Second Sight, and Notal Vision. Dr.Huang, thank you for joining us today.

DR.HUANG: It's a pleasure to be here.

DR. BRESSLER: Also joining me is Dr. John Thompson, Program Chair and President Elect of the American Society of Retina Specialists. Dr. Thompson is also an Assistant Professor at the Wilmer Eye Institute at the Johns Hopkins University School of Medicine and a Clinical Associate Professor at the University of Maryland, and he also is in private practice with Retina Specialists in Baltimore. Dr. Thompson has disclosed that he has received grants or research support or both from Genentech, Roche, and Regeneron Pharmaceuticals. Dr. Thompson, thank you also for being part of today's program.

DR. THOMPSON: You're welcome.

DR. BRESSLER: And I do want to note that our discussion today will include the off label use of aflibercept, also known as Eylea, bevacizumab, known as Avastin, and ranibizumab, also known as Lucentis, as well as off label use of corticosteroids for the treatment of diabetic macular edema. Let's begin by describing one of our patient presentations. When a patient presents with diabetic macular edema

involving the center of the macula, let's say the OCT central subfield thickness is 425 microns on a spectral domain device, and you conclude that the edema has caused the best corrected visual acuity to have deteriorated to about 20/50. And let's say there are dot and blot hemorrhages and lipid and you think it's all consistent with moderate nonproliferative diabetic retinopathy.

What I'd like to go over is really what treatment in that situation that you prefer to recommend for DME. Now let me add further that the patient not only has diabetic macular edema but the patient is phakic in this instance, and the other eye is 20/25 and there is moderate nonproliferative diabetic retinopathy in that other eye, but there is no diabetic macular edema in that other eye.

So with this situation, let's say the recent hemoglobin-A1c was 7.8, good control, not great control, and the patient is attempting to maximize their glucose control and their blood pressure control, Dr.Huang, let me start with you, how would you go about treating that diabetic macular edema that it's thickened in the center and the visual acuity is decreased?

DR. HUANG: Neil, this is a, you've done a great job in setting up this patient and describing some of the things that you need to have before you decide what the proper course of treatment is. You've talked about the patient's glucose control, you've talked about what is going on in the fellow eye, and all these things play a role in our decision.

I talk with the patient about what diabetes is and how it causes damage to the eye, and then we proceed with what can we do about it to treat their vision. There has been a large study sponsored by the National Eye Institute involving a large group of doctors, retina specialists around the country, comparing three different modes of treatment, focal or grid laser photo coagulation, intravitreal anti-VEGF injections, and the use of intravitreal corticosteroids. And in this study they indicated that intravitreal anti-VEGF using ranibizumab or Lucentis was found to be superior to focal grid photocoagulation and to corticosteroids in the majority of cases.

With this knowledge, I would have a discussion with the patient about the risks and the benefits and the alternatives, including observation with the patient, and together we decide on how we would proceed. The results of that study would indicate, and my current mode of treatment is to use intravitreal anti-VEGF treatment as an initial step.

DR. BRESSLER: So Dr. Thompson, let me turn to you, would you also start with intravitreal anti-VEGF medication in this scenario, and, if so, do you start it in combination with laser or do you just start with anti-VEGF? So let me go to my first question and that is, you know, do you agree, in this situation would you typically consider that as your first line therapy, anti-VEGF therapy?

DR. THOMPSON: Yes, I think that the treatment of diabetic macular edema has really changed enormously over the past several years as a result of the, several studies of different anti-VEGF agents that have shown efficacy. So for the particular patient you describe, my first line treatment would definitely be intravitreal anti-VEGF, and the reason is that the patient has center involved thickening of the macula, the visual acuity is decreased, and I think in that situation neither the focal grid photocoagulation or the corticosteroids in a phakic patient are very good options. So I definitely would go with the anti-VEGF agents.

DR. BRESSLER: So John, let me turn to you, would you also start with an anti-VEGF medication, and if so, would you consider doing it a lone or do you like to combine it with laser when the person walks in like this?

DR. THOMPSON: I would start with an anti-VEGF agent because given the scenario that you presented with the center involved, the visual acuity has decreased some and the retinal thickness is up in the 400 range on speckle domain OCT, I think that the anti-VEGFs are clearly the way to go.

The use of laser, we're trying to figure this out as retina specialists because there have been some studies that have used anti-VEGF with immediate laser, anti-VEGF with deferred laser, or laser only arms, and the anti-VEGF agents were clearly superior to the laser only arms, but it's not clear whether laser still has a role with the anti-VEGF agents. But in looking at trials where laser photocoagulation was done in addition to anti-VEGF agents versus the anti-VEGF agents alone, there really was not a clear additional advantage with using the laser photocoagulation.

Now it is conceivable that maybe by doing laser you could get by with fewer anti-VEGF injections and that has not been extensively studied but I think as it stands right now, my primary treatment would be the anti-VEGF agents and laser would be a secondary consideration.

DR. BRESSLER: I think I would agree with you, I don't find any evidence so far that adding laser is better than just starting with the anti-VEGF alone, and we, as you said, have not seen any evidence to suggest it decreases the number of injections even though we'd like that, in fact, the number of injections seems to be very few in the second year, two or three.

So Suber, let me ask you, in this same scenario, is there anything about the appearance that changes your approach? Sometimes I hear from some of our colleagues, well, you know, if the edema looks predominantly focal, I'd like to just laser those simple micro aneurysms that are causing the edema in the center. Should we consider laser in those situations given the same clinical presentation?

DR. HUANG: Well one of the interesting things about the trial that was done, and one of the most surprising findings was that focal laser really had very little effect, at least compared to the anti-VEGF agents. I think what is so striking from our clinical experience is that we have all had cases where we see micro aneurysms that are leaking fluid and affecting central vision and we've done a single spot of laser and all the fluid's dried up. And it's such a dramatic and such a good effect that we would have not intuitively found out or expected that focal laser did not have that additive effect. That being said, the power of the clinical trial in having a large number of patients that are distributed from all backgrounds and all around the country, is very compelling. And since it doesn't and since we know that laser can or sometimes does damage the retina near the central vision, that is something that I tend to hold in reserve.

For recalcitrant cases, cases where it doesn't seem to be responding, I always remember that this was our first line weapon in our armamentarium for 20 years or more.

DR. BRESSLER: Sure, I think we always have cases that did well with laser, it's just we cannot identify a case that we could predict ahead of time that is actually going to do better with laser than with anti-VEGF, and, in fact, it's the other way around. Even in the predominantly focal appearances, it seems that the anti-VEGF is more likely to preserve vision, less likely to cause deterioration.

So, John, one of the hardest parts is, okay, we're all in agreement here, we say there's DME and let's start with an anti-VEGF agent, my question is can you identify which agent you are going to recommend to the patient? Let's say the patient has insurance that would cover completely aflibercept, or bevacizumab, or ranibizumab, and they turn to you and they say, I don't know, what do you recommend, you're the expert, what do you recommend to them?

DR. THOMPSON: Well I think there's a clear gap in knowledge here which will hopefully be filled in in the next several years with the DRCRNET (phonetic) study which will be comparing these three different agents. At this point we've all seen efficacy, when we participated in the clinical trials with aflibercept or with ranibizumab they clearly work, we've treated patients with off label bevacizumab and that clearly works. And so I don't have a good sense that one of these agents is superior to another.

I have had some patients that I have had on bevacizumab just because it was covered by insurance or it wasn't costly to the patient who has not responded, who I have then changed with the agreement of the insurance to ranibizumab, and some of those patients have shown an enhanced response. But in my macular degeneration experience, I have also had the opposite type of thing where one drug seemed to work better than another for no clear reason.

So I cannot predict that one drug would be superior, but they all work very well, but I can't say whether one is better than the other.

DR. BRESSLER: You know, when we only had one choice I think it was pretty easy, that was the choice we gave them. What I'm learning from I think experience now is usually everything isn't equal. I agree with you that the evidence would suggest that all of these are beneficial anti-VEGF agents among the three, and usually something comes out in the conversation with the patient. Maybe someone says, oh, that one is FDA approved, I want to go with that one. Oh, that one, you know, is less expensive overall, I don't know what is going to happen to my insurance,

I want to go with that one. And by presenting the three nuances that may exist among them I sometimes get a feel where I say, okay, it sounds like you might prefer X and then they're very happy to go with that position. But as you said, I really am looking forward to this next government sponsored study that will compare all three and maybe give us greater science rather than just the nuanced discussion with the patient.

Well, Suber, let me turn to you and again with this scenario of our typical patient walking in with this vision impairment and with edema, a lot of our colleagues also ask, okay, you've got this OCT, it's over 400 microns thick, do you need a fluorescein angiogram or do you typically recommend to the patient getting a fluorescein angiogram when you see they have edema, the center is thickened, you have the measurement on OCT, how do you approach the question of fluorescein angiography?

DR. HUANG: Well the use of fluorescein angiography has become, has changed over the years. It was our primary diagnostic tool for many decades and now it's become very much of an ancillary test, much more secondary. The use of OCT gives us anatomic confirmation of the net amount of leakage in the macula, but the fluorescein angiogram is a very useful tool, especially in cases where it is not responding in the way that I think it ought to.

When that happens, we wonder whether there may be some other reason. One other reason might be there is global ischemia, which, as we know, is not visible by OCT and is not easy to spot on clinical examination in many aspects, in many cases. We also could have occult neovascularization, and we know that each of those conditions can stimulate vascular endothelial growth factor to a greater degree, and perhaps that is overwhelming our anti-VEGF therapy.

In the instances where I have recalcitrant therapy – I have recalcitrant fluid that is not resolving, it does not seem to be acting in a way that we think is clinically appropriate, I think a fluorescein angiogram is very useful.

DR. BRESSLER: So, John, how do you approach the angiography and then what do you tell the patient in terms of why you're getting it?

DR. THOMPSON: I think the angiogram is especially useful when you are getting ready to embark upon therapy because I've certainly had patients where I thought I was dealing primarily with diabetic macular edema, but it happened to be a pseudophakic patient and, in fact, it was pseudophakic cystoid macular edema. And Suber alluded to the fact that some of these patients have diabetic retinopathy with micro aneurysms but they have actually developed choroidal neovascularization as a secondary complication.

So I think that it's important to get the angiogram initially, see what you are dealing with and then I don't use the angiogram much after I get my baseline angiogram, except as Suber said, when the patient doesn't seem to be responding. But I do think it's important to get that first angiogram to make sure that you truly understand the pathophysiology of the macular edema.

DR. BRESSLER: I would agree, I believe we've learned maybe it's not essential if you didn't have it, you can still take care of the patient, but it might facilitate your understanding of what's going on. Sometimes I decide maybe four, six, nine months into treating the person with anti-VEGF that I still have some edema that I might want to now add laser to as well, and often I find that angiogram a good roadmap to identify where it is going to be. So I think this is all very helpful in what we want to do.

Well I want to go in after our break to some other scenarios rather than this typical patient who we have I think discussed very well in terms of having edema in the center with impaired vision. So we'll do that after we have a little break. So I want to thank you both for starting us off on this.

BOB BUSKER: And we'll return to Dr. Bressler and his guests in just a moment.

Hello, I'm Bob Busker, managing editor of eOphthalmology Review.

eOphthalmology Review is a CME-certified program presented by the Johns Hopkins University School of Medicine. Volume 2 of the program features Dr. Neil Bressler in case-based discussions with leading retina specialists, presented as both podcasts and downloadable transcripts.

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DR. BRESSLER: Welcome back to this eOphthalmology Review Podcast. I'm Dr. Neil Bressler from the Johns Hopkins University School of Medicine. My guests today are Dr. Suber Huang from Case Western Reserve University, and Dr. John Thompson, also from Johns Hopkins University, and our topic is diabetic macular edema.

We have just discussed the patient who has substantial thickening of the macula, diabetic macular edema with vision impairment, I'd like to go to a different patient description now. I'd like to talk about the patient that also presents with edema that is in the center of the macula but let's say it's only a little thickened, it's 350 microns on an OCT. And let's say the best corrected visual acuity in this case is actually 20/20.

Now there's still our dot and blot hemorrhages, and there's lipid, consistent with moderate nonproliferative diabetic retinopathy. Now if the patient if phakic, the other eye is also 20/20, also has moderate nonproliferative diabetic retinopathy and has no DME, let's say the patient has fair control of their diabetes, their hemoglobin-A1c is 7.8, and again the patient is still attempting to maximize their glucose control and blood pressure control, let me turn to you, Dr. Thompson, and say how do you manage this patient who is 20/20 and yet has definite thickening of the central macula from diabetic macular edema?

DR. THOMPSON: This is a situation where the fluorescein angiogram and the OCT becomes very important because if this patient has some micro aneurysms in the temporal macula and some edema surrounding the micro aneurysms, and the edema happens to get into the fovea, but there really isn't a lot of leakage from the fovea in the fovea directly, then this is a case that I might consider focal photocoagulation for.

I still reserve that for patients that are threshold or borderline clinically significant diabetic macular edema. However, if I saw in the fluorescein angiogram and the OCT that there was more diffuse edema, even though the retinal thickness is not that great, then in that situation I would initiate treatment with anti-VEGF. But I do think there is some role for focal photocoagulation in these very early cases.

DR. BRESSLER: So, Suber, how about you, what do you do with a patient who is asymptomatic, 20/20, but the central subfield is definitely thickened, do you consider starting with focal grid laser? Let's say there are obvious micro aneurysms that you think are contributing to the edema and they're not in the very center of the retina, or do you observe or do you start with anti-VEGF therapy?

DR. HUANG: I talk the situation over with the patient. I think is tress that this is a condition that has been in slow evolution over a long period of time, one, two, maybe ten or even twenty years, and if they are asymptomatic, one of our goals is, of course, not to give them a complication and make them worse. But I agree with Dr. Thompson that there are obvious times when there is vision threatening or near vision threatening retinopathy where the patient may benefit from treatment that is just applied at the right time.

There are other considerations such as whether the patient may come back for follow-up, whether their treatment, their medical treatment is worsening or perhaps improving. If they're improving a lot, they're on a course of therapy, perhaps they newly had insurance and had reentered the medical arena, we could also consider observation, but I think what Dr. Thompson has proposed is very reasonable.

DR. BRESSLER: You know, when we only had laser and that takes months to work sometimes, I was afraid of letting that person deteriorate. Now that we have this more rapidly working anti-VEGF therapy, I am a little more comfortable now watching that asymptomatic 20/20 person and saying, you know, if you start to notice something or if I start to notice that your vision is worsening, we could always go in, I don't have to worry so much that when it was laser or nothing, we don't necessarily have the luxury of an immediate responsive treatment. Now we do, so

I find myself more often than not watching these, but there is no right answer.

And I agree with what you were saying in terms of you have to really discuss with the patient and see what they want to do.

DR. HUANG: I think another point is that the advent of OCT has allowed us to have actual quantitation of how much edema is present. Certainly if we show that there is progression of disease that may change how the patient feels about it, as well. John, what do you think?

DR. THOMPSON: I agree that observation certainly has a role in some of these very mild patients with early macular edema. And I think that understanding the patient and what their beliefs and what their sentiments are about the treatment is very important. And some patients would, of course, just rather go ahead and get it taken care of, and there are some that are very fearful of treatment, where it is really best to establish a rapport with a patient, and by the second or third or fourth time you recommend possible treatment they may be much more accepting of the treatment than when you surprise them for the first time and recommend treatment.

DR. BRESSLER: I think that makes a lot of sense. Suber, let's take another example, again, a patient with diabetic macular edema, this time again they're impaired, they have 20/50 vision, they notice that it's blurry. But this time the patient is pseudophakic. I wonder if that makes you want to consider corticosteroids or do you still start with anti-VEGF therapy as recommendation to them, and what makes you decide which way to go?

DR. HUANG: This is a great case to illustrate the benefit of a fluorescein angiogram. Not all macular edema is created equal, there are cases where there are focal micro aneurysms, where the vasculature is diffusely impaired and then there are cases where that is not primarily from diabetic macular edema at all, but the cystoid spaces that we see sometimes following cataract surgery. It doesn't have to be recent, it can be quite late and macular edema from that scenario is different.

The study we alluded to previously did, in fact, show that intravitreal steroid injection was as efficacious as anti-VEGF therapy in the short-term, over three months. Unfortunately, this effect was not sustained out to two years and generally was found to be a less favorable treatment option. However, in this case, I think making the differentiation between pseudophakic, cystoid macular edema and diabetic macular edema is very important.

DR. BRESSLER: John, before I get to how you might treat that patient, I would ask you do you think you're comfortable or can reliably tell the difference between pseudophakic post surgical, Irvine-Gass, cystoid macular edema in someone who has also definite diabetic macular edema?

DR. THOMPSON: Sometimes it can be difficult, but if the patient ahs diffuse petaloid type of leakage on the fluorescein angiogram and there are very few micro aneurysms around the macula, then that would suggest to me that the pseudophakic cystoid edema is the major problem while if there's lots of micro angiopathy around the macula and the leakage appears to be arising from that micro angiopathy, then I'm more likely to label it as diabetic macular edema.

DR. BRESSLER: Now what do you do if you're not sure? So you look in and the angiogram says, oh, there's some petaloid appearance but there is also many micro aneurysms around there and you're thinking maybe they have both the optic nerve is staining with fluorescein, how do you approach that patient? Do you just treat them for both conditions, for just one of the conditions, how do you go about that?

DR. THOMPSON: I think it's reasonable to consider treating them for pseudophakic cystoid macular edema since many of those patients will respond to topical drops, nonsteroidals and steroid drops. And so in that situation I might try them on a course of a month of treating pseudophakic CME and then again the OCT is very helpful if they show a response which some patients do, then you're home free. On the other hand, if they are showing now response, then I might say well maybe the diabetic macular edema is a more important component or it's an eye that is just not as responsive with pseudophakic CME that is severe.

DR. BRESSLER: You know, I think we have the luxury with diabetic macular edema, unlike the choroidal neovascular form of macular degeneration, we have the luxury of waiting perhaps a couple of

months to see if we can get rid of post surgical cystoid edema, and not worry that there might be permanent vision loss. I don't want to wait a year with diabetic macular edema, but we might have a little advantage there.

I wonder, sometimes my colleagues like to consider starting with corticosteroids in someone with diabetic macular edema who is pseudophakic because they think there will be less injections and they think the subgroup analysis from one of the government sponsored studies showed it might end up with similar vision gains and loss compared with anti-VEGF. Does that sway you, Dr. Huang, into considering corticosteroids, or do you still start with anti-VEGF therapy when it's pseudophakic with DME?

DR. HUANG: Well I think that the approach to trying to understand the various component parts of what is causing the retina to be thickened is very important and I think we just discussed that. I think in general, because pseudophakic cystoid macular edema often responds to topical therapy or periocular or noninvasive therapy, if you will, I think that at least that deserves a try. So in my practice I treat rather aggressively using these noninvasive techniques first. Any amount of improvement will tell us not only whether or not we're on the right track, but also potentially have a great effect on the vision as well.

DR. BRESSLER: And, you know, in terms of trying to decrease the number of injections, I'm not certain we decrease the total number of visits in cases that we start with corticosteroids, because they still can have a pressure problem. And we learned with the anti-VEGF medications, although there may be an average of six treatments in the first six months for diabetic macular edema and an average of two to three treatments in the second six months, there is only an average of two to three treatments in the second year with anti-VEGF therapy. But if we start with corticosteroids and over half of the people need either monitoring or drops to treat that, they may end up with the same or even more visits to the ophthalmologist. So I'm still comfortable without evidence that corticosteroids are superior, I'm still comfortable starting with anti-VEGF in these conditions.

DR. THOMPSON: I agree, Neil, that the intravitreal steroids can be very problematic, because not only do a substantial percentage, perhaps 20 to 40 percent of patients have some elevation of their intraocular pressure, but the elevation of the intraocular pressure can occur at various times, it doesn't always occur within three weeks of administering the intravitreal steroids. So these patients, in my hands, often require more intensive monitoring, especially if they've developed a pressure problem. And I think that in patients with diabetic macular edema, if they are the small percentage in the studies typically in the range of 1 to 2 percent with some of the intravitreal steroids that end up with incisional surgery, they can end up with a situation where they have hypotony for a while that worsens the macular edema.

So I think in many ways the anti-VEGF agents, if you look at the profile of the anti-VEGF agents versus the safety profile of the steroids, the anti-VEGF agents usually win out in terms of the safety profile.

DR. BRESSLER: So, Suber, let me extend the corticosteroid discussion one more time and that is if you have someone who doesn't respond to anti-VEGF therapy, so they have typical diabetic macular edema, whether they're phakic or pseudophakic, but we'll say pseudophakic in this case, and you're convinced there is no post surgical or Irvine-Gass type of macular edema, you think it is all diabetic macular edema, but you have given them these anti-VEGF injections for six, nine months, you have added focal grid laser, and it just didn't budge, it's still there. You look at the vitreous interface and you say you don't think that's causing traction or contributing to that. Do you consider corticosteroids in those cases when you have gone this route of anti-VEGF for six, nine months, you've added laser, you don't think the vitreous is involved, how do you handle that, would you consider it in that case?

DR. HUANG: In my practice, the use of intravitreal corticosteroids is very rare. I am frankly afraid of the risk to the eye, both in terms of glaucoma and cataract formation in those patients who are phakic. I would tend to reach more for the laser first, but one important step is to consider why an anti-VEGF agent might not be working.

Often we forget that fluorescein angiography might reveal widespread areas of ischemia which may have progressed, even during the course of treatment, and even from the initial angiogram if one was obtained at that time. So they may be overproducing VEGF and there may be other reasons, and even without retinal

neovascularization, in some instances scatter photocoagulation may reduce the amount of VEGF that is being produced by the sick and diabetic retina, and therefore anti-VEGF therapy, in addition to that form of laser, might, in fact, treat that very difficult case.

DR. BRESSLER: Well I think it will be interesting to learn. John, let me end with one other systemic safety issue, and that is our patients with diabetes are, unfortunately, at risk for other macro vessel problems such as a cerebrovascular accident, or myocardial infarction. If they have a history of either a stroke or a heart attack, does that change your management when they also have diabetic macular edema and you otherwise would be recommending an anti-VEGF therapy?

DR. THOMPSON: I think this is an issue that we don't have final answers on because none of the studies have shown convincing evidence that intravitreal anti-VEGF agents substantially increase the risk of stroke or myocardial infarction. But it is certainly a concern that the physician needs to have in the back of their mind.

So in patients like that I have a conversation and I say there may be an increased risk, it appears to be a very small increased risk. The risk of you losing vision if we don't treat your diabetic macular edema is much greater and so much of the time the patients are comfortable going ahead and having the anti-VEGF treatment. But I think it does require a discussion since there may be some increased risks.

DR. BRESSLER: Well, Dr. Thompson and Dr. Huang, thank you so much for sharing your expertise on our management, which is rapidly changing, on diabetic macular edema.

What I would like to do now is quickly summarize our discussion today, so let's return to our learning objectives. The first learning objective was to formulate a treatment plan for diabetic macular edema utilizing intravitreal drug therapy and laser treatment. We had consensus in this case that all of us would strongly recommend considering an anti-VEGF agent to start treatment for diabetic macular edema.

We would do this over and above our choice of laser which has been excellent for over 25 years since it started being used; however, we found that the anti-VEGF therapies were superior in both increasing the chance of vision improvement and decreasing the chance of vision loss.

The second learning objective was to describe the efficacy and safety outcomes of clinical trials investigating the use of anti-vascular endothelial growth factor therapies and corticosteroid treatments for diabetic macular edema. We had a nice discussion to realize that the anti-VEGF therapies are, indeed, superior, especially in phakic patients, to using corticosteroids either alone or in combination with laser, but we still have more to learn about using corticosteroids.

Our last learning objective was to discuss potential drug related adverse events that clinicians should consider when selecting a treatment for patients with diabetic macular edema. With corticosteroids we have to consider the increased risk of cataract formation and the need for cataract surgery. With corticosteroids we also have to consider the increased risk of raising the intraocular pressure and having to deal with glaucoma issues.

With the anti-VEGF therapies we don't have any definitive systemic issues at this time, but we look with caution about the possibility that there may be a small increased risk of cerebrovascular accidents or myocardial infarctions and this requires further study.

So I really want to thank Dr. Suber Huang, Dr. John Thompson, for participating in this eOphthalmology Review podcast on diabetic macular edema.

DR. THOMPSON: Thank you very much, Neil, thank you Suber.

DR. HUANG: Neil, I appreciate it, thanks very much.

BOB BUSKER: This podcast is presented in conjunction with eOphthalmology Review, a peer-reviewed, CME-certified program developed by the Johns Hopkins University School of Medicine for ophthalmologists and retina specialists.

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