Featured Cases: Diabetic Macular Edema and Vitreomacular Adhesion

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

- Discuss the evidence regarding the treatment of diabetic macular edema with laser or intravitreous injections
- Describe safety considerations in the treatment of diabetic macular edema
- Summarize how new therapies fit into the management of vitreomacular adhesion abnormalities

This discussion, offered as a downloadable audio file and companion transcript, covers the important issues related to Diabetic Macular Edema and Vitreomacular Adhesion, as reported from the 2014 American Society of Retina Specialists (ASRS) annual meeting in San Diego, California. The format for this round-table discussion is case-study scenarios for the clinical practice.

Unlabeled/Unapproved Uses
The authors have disclosed that their discussion will include the unlabeled or unapproved uses of bevacizumab.

Faculty Disclosures
Dr. Neil Bressler has disclosed that, in the past year, he has served as a principal investigator of research projects at the Johns Hopkins University sponsored by Bayer, Genentech, Novartis, and Regeneron.

Dr. Judy Kim has disclosed that, in the past year, she has served as a consultant for Allergan. Her institution has received research funding from Regeneron and Genentech.

Dr. Lee Jampol, has no relevant relationships to disclose.

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INTENDED AUDIENCE
The activity has been developed for ophthalmologists and retina specialists.

There are no fees or prerequisites for this activity.

STATEMENT OF NEED
- Clinicians lack confidence that their knowledge of new AMD developments will allow them to provide optimal patient care.
- Clinicians are unprepared to integrate new diabetic retinopathy and diabetic macular edema research findings into their current treatment paradigms.
- On-going research into retinal vein occlusion treatments has created clinician uncertainty about choosing the most appropriate therapeutic options.
- Clinicians require additional knowledge about new therapies to develop best practices in treating vitreomacular abnormalities.

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Updated 4/09

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Pentium 800 processor or greater, Windows 98/NT2000/XP/7 or Mac OS 9/X, Microsoft Internet Explorer 5.5 or later, 56K or better modem, Windows Media Player 9.0 or later, 128 MB of RAM, sound card and speakers, Adobe Acrobat Reader, storage, Internet connectivity, and minimum connection speed. Monitor settings: High color at 800 x 600 pixels.

PROGRAM BEGINS BELOW

On-going research into retinal vein occlusion treatments has created best practices in treating vitreomacular abnormalities. Clinicians are unprepared to integrate new diabetic retinopathy and research findings into their current treatment paradigms. Continuing Medical Education at the Johns Hopkins University School of Medicine will keep your personal and credit information confidential when you participate in a CME Internet based program. Your information will never be given to anyone outside of the accredited provider’s CME program. CME collects only the information necessary to provide you with the services that you request.

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BOB BUSKER: Welcome to this Volume 3, Issue 2 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. There are no fees or prerequisites to participate.

I’m Bob Busker, managing editor of eOphthalmology Review. Today’s program comes from the 2014 Annual Meeting of the American Society of Retina Specialists, ASRS, in San Diego, California. Our host is eOphthalmology Review course director Dr. Neil Bressler, the James P. Gills Professor of Ophthalmology and Chief of the Retina Division at the Wilmer Eye Institute at the Johns Hopkins University School of Medicine in Baltimore.

Dr. Bressler has disclosed that in the past year he has served as a principal investigator of research projects at the Johns Hopkins University sponsored by Bayer, Genentech, Novartis, and Regeneron.

His topics today are diabetic macular edema and vitreomacular adhesion. Dr. Bressler is joined by Dr. Judy Kim of the Eye Institute at the Medical College of Wisconsin and Dr. Lee Jampol of the Northwestern University Feinberg School of Medicine.

Dr. Judy Kim has disclosed that she has served as a consultant for Allergan and has received research funding from Genentech and Regeneron.

Dr. Lee Jampol reports that he has no relevant financial interests or relationships with a commercial entity.

Our faculty today have disclosed that their discussion will include the unlabeled or unapproved uses of bevacizumab for the conditions discussed.

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Learning objectives for this audio program are, that after participating in this activity, the participant will demonstrate the ability to:

- Discuss the evidence regarding the treatment of diabetic macular edema with laser or intravitreous injections;
- Describe safety considerations in the treatment of diabetic macular edema; and
- Summarize how new therapies fit into the management of vitreomacular adhesion abnormalities.

And now, from the 2014 ASRS meeting in San Diego, our Host, Dr. Neil Bressler.

DR. NEIL BRESSLER: Thank you for joining us. I have Dr. Judy Kim from the Medical College of Wisconsin and Dr. Lee Jampol from Northwestern University Feinberg School of Medicine. I’d like to discuss first perhaps cases of diabetic macular edema. So Lee, why don’t I start with you. If you have a patient who has diabetic macular edema, you see in the right eye that it involves the center of the macula. And then you get an OCT, and the thickness is let’s say 425 microns in the central subfield. The vision is impaired; it’s about 20/50, the retinopathy level seems to be mild to moderate nonproliferative retinopathy, and the eye is phakic. The patient is bothered by the vision and has noticed it’s been deteriorating for several months. Even though the other eye is 20/20, that eye also has mild to moderate nonproliferative retinopathy. There is no macular edema. Can you walk me through what you typically recommend to the patient? Do you just observe them because the other eye is 20/20? Do you consider doing focal grid photocoagulation? Are you going to consider anti-VEGF therapy or corticosteroids?

DR. LEE JAMPOL: Up until very recently the standard of care was focal laser treatment of microaneurysms and areas of thickening. But a whole series of studies, perhaps a major one, Protocol I of the Diabetic Retinopathy Clinical Research Network, has shown that the use of anti-VEGF treatment is very much better than focal laser as the initial approach. So I would definitely recommend the initiation of anti-VEGF treatment in that type of patient.
use aflibercept that goes by the trade name Eylea, bevacizumab which is Avastin, or ranibizumab, Lucentis? Which anti-VEGF would you consider for this person? Let’s assume the patient’s insurance company indicates they’ll cover the costs of intravitreous injections for their diabetic macular edema. What do you discuss with the patient, which one do you recommend?

DR. JUDY E. KIM: Before recommending medical therapy I will talk to them about controlling blood sugar and blood pressure first and see what type of medications they may be on. I want to look at those before I go on to any kind of treatments. If the patient needs treatment with an anti-VEGF agent, there are several options. Fortunately, we now have aflibercept added to our armamentarium to ranibizumab and bevacizumab.

At this time, if insurance was covering the patient and money was not a problem, I would recommend ranibizumab 0.3 mg, only because if it were my eye that’s what I would want. I would want it because numerous clinical trials show safety as well as efficacy. We can use bevacizumab, but until DRCRnet Protocol T shows that is as good as ranibizumab or aflibercept, I may be less inclined to use it. If insurance is a problem, I do start patients with bevacizumab. I have not had much opportunity to use aflibercept yet, since it’s only been recently approved.

DR. BRESSLER: Lee, maybe you have a comment on that because I’m also curious that in one of the trials looking at bevacizumab versus laser, there was a gain of 5 letters, whereas with ranibizumab and aflibercept in different studies, there was a gain of 9 or 10 letters if you adjust for starting visions. I don’t think we know yet if one is better than the other or equivalent to the other, maybe you could give me your opinion on that. And I understand the DCRR Network is looking specifically at a head-to-head trial comparing these. How would you approach that?

DR. JAMPOL: I think it’s somewhat dangerous to compare the results of different clinical trials. The patient populations are different, the management styles are different. We are very fortunate in that very shortly Protocol T of the DRCRnet has a beautiful head-to-head comparison of all three drugs. The one-year results will be available probably in early 2015, maybe a little sooner, but we’re expecting that will clearly show which of the three drugs following the DRCRnet algorithm is better for treating in this situation. Maybe they are all the same or maybe one or more is superior.

DR. BRESSLER: So even as people are listening to this podcast, there may be updates we’ll have to look into to see if it affects that, because we really do need comparative information to know.

Judy, one of the differences among those trials that Lee was saying make it dangerous to compare is that they use different regimens in terms of getting the outcomes that they achieved. So as I understand it, RIDE and RISE for the first two years applied ranibizumab monthly. I know that in the VIVID and VISTA trials looking at aflibercept, they gave five consecutive monthly injections of aflibercept and then went every two months out to two years, which is different from monthly. And then the DCRR Network did something entirely different: they started with four injections monthly before they knew how that might be superior to laser. They started with four injections monthly and then looked at the OCT and visual acuity and kept injecting as long as the person was improving, but would withhold injections once stability was reached beyond six months. Even if there was residual edema, as I understand it, they only retreated if it began to worsen at some point, leaving some people with perhaps improvement but persistent edema.

So given all those regimens, which one do you discuss with a patient as to how you want to follow up?

DR. KIM: We are very fortunate in our field to have all of these clinical trials to help us guide our patient management, but once again, clinical trial is different than real life, and as physicians I think we all need to deal with that. Our patients do not want to come every month for monthly injection, nor monthly evaluations, so I do use some judgment in how I take care of my patients.

I recommend that because diabetes is a chronic disease, they will need chronic treatment. I set up the patient to know that it is not a one-time deal; it’s not fix it all like in surgery, so they know that they’ll have to come and see me for a long period of time. I will initially give three loading doses of whichever anti-VEGF I’m using and I will monitor with OCT as well as visual acuity, and then from
there I will modify my treatment based on how they’re doing.

**DR. BRESSLER:** Lee, do you do this as needed or do you think it’s easier to just give a set number of injections every month or every other month?

**DR. JAMPOLO:** I think this disease is quite different from age-related macular degeneration where very often you have to continue to inject monthly to get the absolute best response. There certainly are exceptions, but many patients require that. In the DRCRnet studies the algorithm they follow in a very simplistic review is that if the eye continues to improve after the loading doses, then you continue to give shots. If it stabilizes after six months or so, then you can hold off and extend your treatment intervals or examination intervals, and if it worsens you reinitiate the injections. I think that’s a good idea.

Now following that — and this is very important for your listeners to understand — the number of injections in the first years is substantial, eight or nine, but the second year it drops down significantly to about three, and then the third, fourth, and fifth years it goes down almost to none, zero to one injections a year. This is very different; you are not committing the patient to injection every month, and therefore the drug company studies that have shown results with monthly injections I don’t think apply to our patient group. We’re going to start out with this, some sort of an algorithm monitoring the improvement, and once it stabilizes the patients remain stable after five years in almost every case.

**DR. BRESSLER:** I think this is important and at the ASRS meeting we are recording from right now in San Diego, I think we learned from the Network that, as you said, Lee, in the third year there was a median of two injections over the whole group and they maintained their vision, and in the fourth year one injection median, and the fifth year zero. So it does take a lot of work in the beginning I think to get this under control and get improvement in many of the people, but we see less and less.

I want to come back to what we learned also about lasering those eyes in a few minutes, Judy, but perhaps I could ask, if you are monitoring these people to decide rather than just treating them every month, what do you look for on the OCT to decide whether it’s improving or worsening?

**DR. KIM:** On OCT I look at the thickness first of all, and second I will look at how many cysts are present, and then whether there’s also associated subretinal fluid. Those are three things I would look at on OCT to see whether they’re changing.

**DR. BRESSLER:** And Lee, two things that the network used to monitor whether they should consider withholding or continue treatment were OCT and visual acuity. If you look at a patient whose OCT, after let’s say, three consecutive injections over a year into has not budged, it’s staying at about 325 microns but it’s just persistently thickened, do you look at the visual acuity as well to decide if it’s improving? If somebody goes from 20/50 to 20/25 would you inject them again that next month, even if the OCT did not change?

**DR. JAMPOLO:** One very important thing is, we don’t have to dry out every macula. We would like to do that, and in some patients the macula dries out completely, but if the retina stabilizes in thickness and the vision is stabilized or better, we will often follow the patient and not give an injection at that point.

If data from one of the modern OCT machines increases or decreases more than about 10 percent, that’s outside the range of variation from the machine and the situation. So I think if thickness increases 10 percent, that’s probably a worsening, and that would be an indication to treat.

But we also look at visual acuity. if the OCT is stable and the vision is dropping, and there is no other reason for it, cataract or whatever, I think decreasing visual acuity is also an indication, and usually we look for more than five letters change as being significant, particularly if it’s reproducible on two visits.

**DR. BRESSLER:** that’s about a line on a chart or more than a line, let’s say.

**DR. JAMPOLO:** About a line.

**DR. KIM:** And I want to point out also —

**DR. BRESSLER:** Please, Judy.
DR. KIM: That as you said, Lee, this disease is different from AMD, where we really have to be very vigilant about drying out if possible, but in patients with diabetic macular edema do seem to tolerate a little more fluid than AMD patients do. So we don’t have to be as aggressive.

DR. BRESSLER: And Judy, do you ever add laser when you’re doing this anti-VEGF and the edema no longer going away, do you then add laser at some point in the macula?

DR. KIM: In patients with extrafoveal thickness I will add laser as probably first-line treatment, but those with fovea-involving edema I will start with anti-VEGF. And after let’s say six monthly injections and they have not improved one iota, those will be the patients I would consider adding laser, just as DRCR I had recommended.

DR. BRESSLER: How about you, Lee: do you add laser? I know you’ve been writing about whether it’s falling to the wayside in our community of retina specialists?

DR. JAMPOL: When you have a circinate ring with thickening and exudate extended into the fovea caused by very localized aneurysms, it’s very tempting to do laser. I’ll point out that we don’t have a good study comparing laser with anti-VEGF treatments. The DRCRnet is going to try to figure that out based upon Protocol V looking at patients who do have very focal leakage and seeing if laser might do better in those eyes. But right now for initiating treatment, I think in almost every case anti-VEGF is the first way to go.

DR. BRESSLER: Yes, certainly I’m not aware of any definitive data we have to suggest that that will help, and we certainly have plenty of people with peripheral areas of nonperfusion who do very well with anti-VEGF treatment to their edema. Even if the edema persists and doesn’t completely go away, they often maintain excellent vision.

Speaking about imaging, Lee, in the case we presented, we didn’t mention anything on fluorescein angiography. For our patient who has macular thickening and 20/50 vision, and you’re planning to initiate anti-VEGF medication, do you get a fluorescein angiogram?

DR. JAMPOL: Certainly fluorescein was the mainstay of our evaluations in the past, but I think OCT has diminished that greatly in terms of its importance. I think if you strongly suspect ischemia in the macula, the fluorescein could be helpful if you are not sure if there’s proliferative disease either posteriorly or peripherally, but I don’t find it really helpful in managing these patients with DME that we’re talking about.

DR. BRESSLER: And a couple of safety issues I’d like to go to before we go on to our next case, so Judy, let’s start with you. We know sometimes that patients might complain bitterly of irritation or swelling of their eye after an intravitreous injection, and we find out that it’s some reaction or as a result of antiseptic or Betadine that was placed on their eye. Do you ever not use Betadine over an injection site, and what do you do about the patients who complain of irritation after antiseptic to their eye?
DR. KIM: Study after study has shown that antiseptic with povidone iodine is important in preventing or reducing the risk of endophthalmitis. So I always use povidone iodine on all of my patients. The allergy to iodine is really not true allergy to povidone iodine, so I reassure the patient that it is necessary and I will use it. If patients have a lot of irritation I may use a little less and also consider 5 percent instead of 10 percent, for instance.

I ask my patients to irrigate the eye with artificial tears after the injection throughout the day, and that seems to have helped the patients, as well.

DR. BRESSLER: I think a lot of our colleagues have agreed, no Betadine, no injection. And they do try to make sure at least they get it over the site, at least let that dry and make sure that’s in.

Speaking of safety, I’d like to talk a little bit, Lee, about systemic safety. One of the concerns about these drugs theoretically as intravitreous drugs, is when they were given intravenously, let’s say anti-VEGF medications for metastatic colon cancer, there was a definite but slight increased risk of cerebrovascular or cardiovascular events. So if our patient had had a heart attack or stroke let’s say two years ago, does that change your management?

DR. JAMPOL: Given systemically the drugs can cause hypertension, they can affect renal function, and there’s increased incidence of arterial thrombotic events and also GI events, but the dose we’re giving into the eye is much, much smaller, which is somewhat reassuring.

So many patients have now been treated with anti-VEGF that the evidence is that if there is an increased risk of arterial thrombotic events, it’s a very small one. And whether there’s any difference between the three drugs is also controversial. Some studies show them to be about the same, while others showing slight differences. So I think we can safely say that it’s a very low incidence of increased arterial thrombotic events.

On the other hand, if you have a patient who has had seven strokes, including one a month before, then that certainly is very worrisome. I’m concerned about that still, and I think about it very carefully in patients who do have severe atherosclerosis or thrombotic events. But I think in the average patient, in most patients it’s a very small increased risk, if any.

DR. BRESSLER: Very good.

BOB BUSKER: We’ll return with Dr. Bressler and his guests in just a moment.

I’m Bob Busker, managing editor of eOphthalmology Review. If you found this program on iTunes or on the web, please be sure to subscribe. This podcast is part of the Johns Hopkins eOphthalmology Review, an educational program providing case-based discussions with leading retina specialists. Presented as both podcasts and downloadable transcripts, eOphthalmology Review activities are certified for CME credit by the Johns Hopkins School of Medicine, and are presented without charge. For more information or to subscribe to receive our podcasts directly to your email, please visit www.eophthalmologyreview.org.

DR. NEIL BRESSLER: Welcome back to this eOphthalmology Review. I’m Dr. Neil Bressler from the Johns Hopkins University School of Medicine. My guests today are Dr. Judy Kim from the Medical College of Wisconsin and Dr. Lee Jampol from the Northwestern University Feinberg School of Medicine.

Judy, I’d like to spend a few minutes now switching gears to an entirely different area of retina treatment that we’ve been exposed to over the last year or so, and that’s the concept of abnormal vitreomacular adhesions. Let’s say we have a patient who comes in with decreased vision. You see some sort of elevation of the macula and you get an OCT, which clearly shows some structural abnormality that looks like the retina and the macula is being tented up, maybe the thickness is over 500 microns, and the vision is 20/50. You can’t see any obvious epiretinal membrane, the eye is phakic, the other eye is 20/20, but the patient tells you it’s really been bothering her over the past year or so and it’s not getting any better. It interferes when she’s trying to read, she has to close that eye when she’s trying to drive, and she gets a little confused. What do you do with that patient? Do you just observe the eye to see if it gets better on its own and maybe the patient didn’t realize what was going on, do you start with intravitreous ociriplasmin, or do you go to vitrectomy?

DR. KIM: In the past we have been able to go right to surgery if the eye is truly, truly symptomatic and this has been going on for a while. If it is with an eye that is not symptomatic, I will recommend observation
and have the patient come back for a follow up. But if as you have described, this patient’s daily activities or work are compromised, I go over the risk/benefit alternatives of the options of surgery vs ocriplasmin. Whether I recommend injection in the office vs surgery depends on what the OCT shows. If there’s broad traction I will not go into injection but instead will recommend surgery; but if it’s a focal adhesion that’s causing the traction, and there’s no epiretinal membrane — which is sometimes a little difficult to tell — and the patient is younger, then injection in the office is an option.

DR. BRESSLER: Lee, would you like to comment on Judy’s response there?

DR. JAMPOL: I would say that ocriplasmin’s efficacy in many places in many reports has been very disappointing. It doesn’t help many patients; even when you follow the indications for which situations you should use it, the results are disappointing. And there is a very grave concern about toxicity to the retina, where there are well-documented cases of fairly frequent abnormalities of the outer retinal elements on OCT and loss of vision and visual field. The use of this drug at our institution is almost nil right now until the situation is further sorted out in terms of how frequent the side effects are and how persistent they are and how serious they are. I think if the patient needs something done right now, I would be in favor of vitrectomy, because with modern instrumentation the complication rate is fairly low. But we observe a lot of patients who are minimally symptomatic where it’s just found on a routine OCT, we definitely observe them first. Some of them will release, some of them remain persistent for long periods of time but will become symptomatic. If their symptoms progress, then you can do vitrectomy at that point.

DR. BRESSLER: Certainly I know from the studies that cases with broad epiretinal membranes had no obvious benefit, or if they hoped that this might work in a larger macular hole, let’s say anything even over a few hundred microns, it would not work as well.

Judy, did you have another comment?

DR. KIM: Because of the things that you mentioned, Lee, the use of ocriplasmin is quite limited even in our institution or even in my hands because very few patients do meet those criteria. But I do think that in a young patient whose eye is phakic and who is really symptomatic and I’ve been observing and it’s not changing at all, then given the potential side effects of the surgery, injection is an option, but the number of people who meet that criteria is very, very small.

Surgery and smaller gauge surgeries, do give good results with these patients, but they can have other side effects. So having been a surgeon with anything that can go wrong having gone wrong, I do take surgery very seriously.

DR. BRESSLER: I think certainly we want to be cautious in the cases we’re taking because it’s not going to work in everyone, but there may be some, and we’re going to need more experience, and hear more about it at this meeting and others in the future. I want to thank both of you for sharing your thoughts, this was a superb discussion of what’s going on, and to give us a little update from the meeting here. So Lee, thank you.

DR. JAMPOL: Thank you.

DR. BRESSLER: And Judy, thank you again.

Now I would like to quickly summarize our discussion today, so let’s return to our learning objectives. The first learning objective was to discuss the evidence regarding the treatment of diabetic macular edema and whether we should approach that with laser or intravitreous injections. And I think we learned both from our panelists and at the ASCRS meeting that intravitreous injections clearly increase your chance of improvement in vision that can be sustained out to five years, as we’ve learned from the DRCR Network, without the need for continued injections because the number of injections has gone down from one in the fourth year for the median to zero in the fifth year, with over half of the cases never even needing laser.

The second objective was to talk about the safety in diabetic macular edema, and we’ve learned you really do need to apply Betadine before any injection. There are some theoretical systemic concerns, but the dose going into the vitreous is so small that if there is a systemic risk it’s probably very small in these patients.

And our final learning objective was to think about how new therapies fit into the management of vitreomacular adhesion abnormalities. I think we’ve learned that while ocriplasmin may be considered in...
some cases, we still have more to learn about it. There are certain circumstances where perhaps it should not be considered with broad adhesion or epiretinal membranes or larger macular holes. But certainly we’re going to have to learn from more experience in the future about the safety of this drug in more and more people and when it might be indicated versus observing versus going to vitrectomy.

So thank you very much again.

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