A panel of experts gathered during the 2015 annual meeting of the Association for Research in Vision and Ophthalmology for a roundtable discussion on improving outcomes for patients with diabetic macular edema using pharmaceutical treatment, including vascular endothelial growth factor suppression and corticosteroid therapies, based on the most current research and clinical data.

I would like to thank the faculty members for their participation, as well as Alimera Sciences for supporting this OSLI RETINA supplement. For more information on this topic, visit Healio.com/OSLIRetina.

Carmen A. Puliafito, MD, MBA
Editor-in-Chief
OSLI RETINA

Introduction

MODERATOR

Scott W. Cousins, MD, is the Robert Machemer, MD, professor of ophthalmology and immunology, vice chair for research, and director of the Duke Center for Macular Diseases at Duke Eye Center, Duke University School of Medicine in Durham, North Carolina. Dr. Cousins received a modest honoraria from SLACK Inc. for his contribution to this supplement.

Pravin U. Dugel, MD, is managing partner at Retinal Consultants of Arizona and clinical professor at USC Eye Institute department of ophthalmology, Keck School of Medicine of the University of Southern California in Los Angeles. Dr. Dugel received a modest honoraria from SLACK Inc. for his contribution to this supplement.

Kirk H. Packo, MD, is professor and chairman of the department of ophthalmology, and director of the retina section at Rush University Medical Center, and he is a senior partner with Illinois Retina Associates in Chicago. Dr. Packo received a modest honoraria from SLACK Inc. for his contribution to this supplement.

Richard K. Parrish II, MD, is professor, associate dean for graduate medical education, and Edward W.D. Norton chair in ophthalmology at Bascom Palmer Eye Institute, University of Miami, Miller School of Medicine in Florida. Dr. Parrish received a modest honoraria from SLACK Inc. for his contribution to the supplement.

Elias Reichel, MD, is vice chair for research and education in the department of ophthalmology at the New England Eye Center in MA, and he is a professor of ophthalmology at Tufts University School of Medicine. Dr. Reichel received a modest honoraria from SLACK Inc. for his contribution to this supplement.

FACULTY

Alexander M. Eaton, MD, is founder and director of Retina Health Center in Fort Myers, Florida, and consulting associate in the department of ophthalmology at Duke University School of Medicine in Durham, North Carolina. Dr. Eaton received a modest honoraria from SLACK Inc. for his contribution to this supplement.

Szilárd Kiss, MD, practices at Weill Cornell Eye Associates and is director of clinical research and associate professor of ophthalmology at Weill Cornell Medical College in New York, New York. Dr. Kiss received a modest honoraria from SLACK Inc. for his contribution to this supplement.

doi: 10.3928/23258160-20151124-01
ABSTRACT: Diabetic macular edema (DME) is one of the most common causes of vision loss in patients who have diabetes, and all of these patients are at risk for developing DME. The onset is often painless, difficult to detect, and can occur at any stage of diabetes. Ideally, DME is preventable, but treatment must be considered when preventative methods fail. Although physicians have several different treatment options for patients with DME, some patients who receive treatment can respond poorly and may even lose vision. Until recently, laser photocoagulation was regarded as the standard of care for DME; however, pharmaceutical treatments are rapidly replacing this standard as the desire to maximize systemic treatment of DME increases. A panel of experts gathered during the 2015 annual meeting of the Association for Research in Vision and Ophthalmology for a roundtable discussion designed to focus on improving outcomes for patients with DME using pharmaceutical treatment, including the use of anti-VEGFs and corticosteroids, based on the most current research and clinical data.

[Ophthalmic Surg Lasers Imaging Retina. 2015;46:S5-S15.]

INTRODUCTION

Pravin U. Dugel, MD: Diabetes is an epidemic. In the United States alone, the growth rate of this disease is projected to be 165% by the year 2050.1 Perhaps one of the most devastating and impactful consequences of this disease is the loss of sight. Indeed, the main cause of blindness—diabetic macular edema (DME)—is progressive and insidious. Fortunately, recent therapeutic measures appear promising. In this roundtable symposium, we are here to discuss new paradigms in the treatment of DME.

What is your examination process for diagnosing a patient with DME?

DIAGNOSING DME

Szilárd Kiss, MD: For a patient with diabetes, I typically perform a comprehensive dilated examination with indirect ophthalmoscopy. In addition, for both diagnostic as well as documentation purposes, I obtain an optical coherence tomography (OCT) scan and an ultrawide-field fundus photograph. If the hemoglobin level is elevated above 10 g/dL and/or I suspect additional pathology on my examination, I also obtain an ultrawide-field fluorescein angiogram. It is amazing how much pathology is revealed on an ultrawide-field fluorescein angiogram that is not obvious from an examination or photography.

Dugel: What are the related risk factors for patients with DME?

Kirk Packo, MD: There are a great number of risk factors for DME, both proven and speculative. The only proven risk is that of glycemic control—the worse the control, the higher the risk of retinopathy.2-4 Other factors such as renal status, blood pressure control5 and lipid status6 all strongly suggest a role for DME development, but have lower than class I level of scientific evidence. Other less-proven, but potentially important, risks include hormonal imbalances, platelet function, and inflammation.

Elias Reichel, MD: The most significant risk factors associated with DME include glycemic control and duration of diabetes. Hypertension, dyslipidemia, and kidney disease are also important factors that

Improving Outcomes for Patients With Diabetic Macular Edema
contribute to the development of DME. Other factors to consider include whether the patient is pregnant, suffers from sleep apnea, or is taking thiazolidinedione.

**Dugel:** It is well known that inflammation is a major component of diabetic retinopathy. In fact, there is evidence of a direct relationship between the severity of diabetic retinopathy and DME and inflammation as measured by an increase in inflammatory cytokines. Microvascular inflammation may represent the natural evolution of this disease that requires more than vascular endothelial growth factor (VEGF) suppression.

**Alexander M. Eaton, MD:** A large body of evidence suggests pro-inflammatory cytokines, such as interleukin-6, chemokines, and other key inflammatory proteins contribute to the development of diabetic retinopathy. Left untreated, these mediators can lead to persistent low-grade inflammation and the influx of leukocytes, which contributes to retinal vasculature damage, ischemia, hard exudates, and the development of DME. The complexity of the process warrants the need for effective therapies that target more than one signaling cascade.

**PATIENT SELECTION FOR TREATMENT**

**Dugel:** DME is a potentially blinding disease if left untreated, and with its multifactorial origin, it is difficult for specialists to determine exactly who to treat. What are the treatment guidelines for patients with DME, and how do you determine if a patient has clinically significant macular edema?

**Packo:** Previously, results from the Early Treatment for Diabetic Retinopathy Study (ETDRS) provided anatomic definitions of edema that were driven by ophthalmoscopy. These definitions included retinal thickening or presence of hard exudates at or within 500 µm from the center of the macula or an area or areas of retinal thickening at least 1 disc area in size. Today, spectral-domain OCT (SD-OCT) has changed the definition of what is considered clinically significant macular edema by dividing patients into those with central-involved edema and those with non-central-involved DME. I think medical therapy is the starting point. I recommend single-injection therapy when there is significant edema beneath the fovea, even in a patient who has good vision. Patients with non-central-involved edema are more difficult to treat because more factors must be considered.

The size of the edema, presence of lipid exudates, concomitant retinopathies such as neovascularization and progressing cataract, and status of the other eye all guide the decision to treat as much, or even more so, as does visual acuity. Previously in the ETDRS era, clinical examinations and fundus photography were used exclusively to judge clinical edema. However, now that OCT scans can show intraretinal edema when the examination and color fundus photographs look normal, physicians realize that both OCT and the examination are necessary. Conversely, the examination may suggest threatening rings of lipid and leakage, and yet the central OCT looks normal. Treatment decisions for DME require a multifactorial evaluation process.

**Eaton:** If a patient has 20/20 vision, I am less inclined to treat unless I see a juxtafoveal area of thickening that meets the ETDRS treatment guidelines, in which case I would initially consider focal laser photocoagulation. However, I consider the whole picture and use a combination of therapies from laser to VEGF inhibitors to corticosteroids.

**Scott W. Cousins, MD:** Some patients are candidates for laser as initial therapy. If the fluorescein shows focal microaneurysms amenable to laser treatment, I will discuss laser rather than injections even if the patient’s vision is 20/20 and the examination reveals juxtafoveal threatening lipids or clinically significant DME appropriate for grid laser.

**Reichel:** Specialists do not often adhere to the old ETDRS definitions now that they can use OCT scans to see pathology that was previously undetected. So, it is important to consider visual acuity with OCT. SD-OCT plays a significant role in evaluating patients. I consider location and amount of thickness on the central subfield and would consider performing laser treatment. Finally, I select drugs based on central retinal thickness and visual acuity. They all play a role in my decision-making.

**Kiss:** SD-OCT is the mainstay of diagnosis of DME, and noted edema on SD-OCT has replaced traditional clinically significant macular edema that may have been observed during a dilated exam. SD-OCT is an important tool not only for diagnosing, but also for educating the patient about how vision is affected. If cystic changes involving the fovea are responsible for a patient’s decreased vision, I initiate treatment...
immediately, starting with anti-VEGF therapy. SD-OCT is also important when injection fatigue sets in and the patient may not fully understand why more treatment is required. Reiterating the clinical diagnosis of DME with the visual provided by the cystic changes (and even noting when those changes improved with injections) on an SD-OCT image often helps with patient compliance with their intravitreal injections.

**CONTROL AND COMPLIANCE**

**Dugel:** Systemic interventions, such as controlling blood sugar, blood pressure, and lipid levels, can be effective ways to manage therapy for patients with DME. Can managing systemic controls improve outcomes for patients with mild macular edema?

**Cousins:** Yes, systemic interventions can improve outcomes for some patients. I have shown patients printouts of their electronic medical record, highlighting one copy for the patient and sending another to their primary care physician, and for some patients, the diagnosis of DME triggered a reality check and pushed patients to begin to take care of themselves. By their next visit with me, they have decreased their HbA1c level to 7% and have lost 50 lbs, and their retinopathy has improved.

**Dugel:** How do you approach systemic control in patients with DME?

**Kiss:** Systemic control is paramount to the long-term treatment of patients with diabetes. I have access to past examinations and laboratory results, and because communication with the entire medical team is important, all of my notes and imaging are sent automatically to the referring physician. I emphasize the importance of hemoglobin levels, blood pressure, and blood lipid control with the patient, and I find some patients begin to pay attention to systemic control after a few intraocular injections. I stress that this control may reverse or prevent damage, but that the existing damage to the retina requires ongoing treatment.

**Eaton:** First, I check the patient’s blood pressure and request a test to determine the HbA1c level to obtain an idea of the diabetic regulation. I review the importance of diabetic control and send a note to the internist explaining the patient’s condition and emphasizing the importance of controlling blood pressure, glucose, and cholesterol.

**Reichel:** I directly communicate with the patient’s primary care physician or endocrinologist. When a patient with diabetes has proliferative disease, a long discussion regarding next steps, including immediately seeing the primary care physician or internist, is needed. HbA1c is actually individualized per patient now, so it is important to ask the patient, “What is your targeted HbA1c level?”

**Packo:** If I encounter difficulty maintaining a targeted HbA1c level long term, I start the discussion with the internist. I think it is a mistake to wait for patients to decrease the HbA1c level before beginning treatment. Data show that the response to anti-VEGF therapy is still viable regardless of HbA1c control, although it may not be quite as good when control is poor.

**Dugel:** Do you make therapeutic decisions based on your assumption of patient compliance?

**Richard K. Parrish II, MD:** Physicians understand that with respect to multiple treatments with a drug, the more that a patient is asked to use a medication, the less likely that he or she will comply with the regimen. Assuming patients are compliant is the first hurdle to overcome, and then physicians must be both realistic and noncritical, while considering treatment burden.

**Reichel:** I directly communicate with the patient’s primary care physician or endocrinologist. When a patient with diabetes has proliferative disease, a long discussion regarding next steps, including immediately seeing the primary care physician or internist, is needed. HbA1c is actually individualized per patient now, so it is important to ask the patient, “What is your targeted HbA1c level?”

**Packo:** If I encounter difficulty maintaining a targeted HbA1c level long term, I start the discussion with the internist. I think it is a mistake to wait for patients to decrease the HbA1c level before beginning treatment. Data show that the response to anti-VEGF therapy is still viable regardless of HbA1c control, although it may not be quite as good when control is poor.

**Dugel:** Do you make therapeutic decisions based on your assumption of patient compliance?

**Richard K. Parrish II, MD:** Physicians understand that with respect to multiple treatments with a drug, the more that a patient is asked to use a medication, the less likely that he or she will comply with the regimen. Assuming patients are compliant is the first hurdle to overcome, and then physicians must be both realistic and noncritical, while considering treatment burden.

**Kiss:** I try to determine the best plan for a patient’s specific condition independent of my initial evaluation of possible compliance. If I notice that a patient misses multiple appointments for unexplainable reasons, I take that into consideration when making potential treatment decisions.

**Eaton:** First, I check the patient’s blood pressure and request a test to determine the HbA1c level to obtain an idea of the diabetic regulation. I review the importance of diabetic control and send a note to the internist explaining the patient’s condition and emphasizing the importance of controlling blood pressure, glucose, and cholesterol.

**Reichel:** I directly communicate with the patient’s primary care physician or endocrinologist. When a patient with diabetes has proliferative disease, a long discussion regarding next steps, including immediately seeing the primary care physician or internist, is needed. HbA1c is actually individualized per patient now, so it is important to ask the patient, “What is your targeted HbA1c level?”

**Packo:** If I encounter difficulty maintaining a targeted HbA1c level long term, I start the discussion with the internist. I think it is a mistake to wait for patients to decrease the HbA1c level before beginning treatment. Data show that the response to anti-VEGF therapy is still viable regardless of HbA1c control, although it may not be quite as good when control is poor.

**Dugel:** Do you make therapeutic decisions based on your assumption of patient compliance?

**Richard K. Parrish II, MD:** Physicians understand that with respect to multiple treatments with a drug, the more that a patient is asked to use a medication, the less likely that he or she will comply with the regimen. Assuming patients are compliant is the first hurdle to overcome, and then physicians must be both realistic and noncritical, while considering treatment burden.

**Kiss:** I try to determine the best plan for a patient’s specific condition independent of my initial evaluation of possible compliance. If I notice that a patient misses multiple appointments for unexplainable reasons, I take that into consideration when making potential treatment decisions.

**Eaton:** First, I check the patient’s blood pressure and request a test to determine the HbA1c level to obtain an idea of the diabetic regulation. I review the importance of diabetic control and send a note to the internist explaining the patient’s condition and emphasizing the importance of controlling blood pressure, glucose, and cholesterol.

**Reichel:** I directly communicate with the patient’s primary care physician or endocrinologist. When a patient with diabetes has proliferative disease, a long discussion regarding next steps, including immediately seeing the primary care physician or internist, is needed. HbA1c is actually individualized per patient now, so it is important to ask the patient, “What is your targeted HbA1c level?”

**Packo:** If I encounter difficulty maintaining a targeted HbA1c level long term, I start the discussion with the internist. I think it is a mistake to wait for patients to decrease the HbA1c level before beginning treatment. Data show that the response to anti-VEGF therapy is still viable regardless of HbA1c control, although it may not be quite as good when control is poor.
**Kiss:** When making treatment decisions, I use both visual acuity as well as SD-OCT findings. The discordance between the two can be striking—sometimes a patient is 20/25 with extensive cystic changes, whereas other times, a patient is 20/50 with a small centrally-located cyst found on the OCT scan. If OCT findings show edema that affects a patient’s vision, I recommend initiating treatment. The same holds true when I make decisions about whether to continue or stop the treatment—I consider OCT and visual acuity equally.

**Eaton:** I also tend to rely on both OCT and visual acuity. Although visual acuity is the most important factor guiding treatment, if there is significant edema, I tend to treat patients even if they have good vision.

**Parrish:** DME affects central acuity and typically leaves peripheral vision intact. However, in glaucoma, which is my specialty, visual acuity is a poor indicator of visual function because patients with advanced glaucomatous damage may maintain excellent central acuity but have difficulty getting around because of loss of peripheral vision. Therefore, central visual acuity may be good while peripheral vision is significantly affected.

**Packo:** I believe both visual acuity and SD-OCT are necessary, but in a specific order. I rely on SD-OCT findings in most settings to first stimulate the decision to treat a patient with DME. The acuity may then temper that decision into observation instead.

**LASER PHOTOCOAGULATION VERSUS ANTI-VEGF**

**Dugel:** If a patient has good visual acuity, yet the SD-OCT scan reveals non-central-involved macular edema, is there still a role for laser photocoagulation?

**Packo:** In research studies including the RESTORE study and Protocol I, anti-VEGF therapy versus laser was studied both as monotherapy as well as in combination with different drugs, but none of the studies concluded that laser alone is superior. If I obtain a fluorescein angiogram and find focal microaneurysms, I use laser photocoagulation to save the patient the burden of anti-VEGF therapy. After a series of anti-VEGF injections, a deferred focal therapy to localized areas of microaneurysm formation may decrease the number of required subsequent injections. Still, I rely on the medical therapy to reduce the edema as much as possible before the potential addition of any destructive laser therapy.

**Reichel:** For patients with presence of significant foveal fluid, I would perform focal/grid photocoagulation. I now use micropulsing laser for those patients, treating in the fovea, with good results.

**Dugel:** Most patients, however, present with center-involved edema. For these patients, do you begin treatment with anti-VEGF therapy?

**Reichel:** Depending on the patient’s presenting visual acuity and central subfield thickness, I would begin treatment for these patients with anti-VEGF therapy, using either aflibercept as indicated for DME or bevacizumab, even though it is not indicated for DME.

**Kiss:** My patients rarely require focal/grid laser photocoagulation as the initial form of treatment. Anti-VEGF therapy works extremely well, and patients with small amounts of edema typically require only a few injections. I am concerned with laser as the first line of therapy because the procedure may not provide patients with the most optimal vision even if OCT shows resolution of the edema.

**Eaton:** Physicians need to look at the entire clinical picture, noting the patient’s age and whether he or she is pseudophakic or has glaucoma. Patients with diabetes who also have a history of strokes are at an increased risk for stroke. For these patients, I would recommend an intravitreal corticosteroid, which is not associated with that risk. For young, phakic patients with no or limited arterial thromboembolism risk factors, particularly those with significant concomitant proliferative diabetic retinopathy, I would start with anti-VEGF therapy.

**Packo:** Patients who have experienced a central thromboembolic phenomenon, stroke, or transient ischemic attack are not appropriate candidates for anti-VEGF therapy until, perhaps, after a few months. Theoretically, this delay allows the body to utilize natural VEGF to repair central nervous system damage and mitigates the risk of systemic VEGF reduction from an intraocular injection. Because DME is a multifactorial disease, this is a time to consider a non–anti-VEGF therapy such as an intraocular corticosteroid, as well.
ANTI-VEGF SELECTION

Dugel: The results of Protocol T showed intravitreous injections of aflibercept, bevacizumab, and ranibizumab all improved visual acuity in patients with central-involved edema in general. In patients with vision of 20/40 or better, all drugs worked equally well. However, 1-year results demonstrated a distinction in patients with poorer vision. As visual acuity worsened, the greatest effect was seen with aflibercept. The impact of these results, and particularly of the subanalysis group, showed participants had a significantly higher chance of improved vision with aflibercept. However, these results remain controversial. Have the results of Protocol T changed which anti-VEGF you administer?

Packo: I had virtually given up on bevacizumab for the treatment of diabetic edema, and the results of Protocol T have changed my practice, as I now more readily use aflibercept to treat DME. It will be interesting to see whether retina specialists move straight to administering aflibercept without looking at that distinction of subset analysis on visual acuity.

Cousins: Before Protocol T, I usually started with bevacizumab. Now, I start with aflibercept. However, there is no downside to starting therapy with bevacizumab for several injections and then reassessing the need to change anti-VEGF agents based on DME response.

Kiss: After learning Protocol T’s first-year results, I started to use aflibercept for my patients with DME.

Reichel: I was fortunate to have used aflibercept for DME for a considerable amount of time beforehand, and Protocol T confirmed my results. If visual acuity is 20/50 or worse I prefer to use aflibercept. I also factor in central subfield thickness with a preference to use aflibercept if the OCT measurement is greater than 400 μm. For patients who have 20/40 or better visual acuity and factoring in an OCT central subfield thickness as well, any of the three anti-VEGF agents are suitable. However, if I treat a patient with recalcitrant DME—even with good vision and mild thickening—I tend to use aflibercept.

DETERMINING EFFECTIVENESS OF ANTI-VEGF THERAPY

Dugel: The results of the RIDE and RISE twin trials support that anti-VEGF therapy is not effective in every patient. From a physiologic point of view, why might a patient not respond to anti-VEGF monotherapy?

Cousins: Research on the pathobiology of diabetic retinopathy indicates that both VEGF and inflammatory mediators can drive DME. In addition, Müller cells, the retina’s fluid pump, are sensitive to both VEGF and inflammation. Patients with Müller cell pump dysfunction caused by inflammation might not respond to anti-VEGF monotherapy. Finally, new information suggests that the retinal neurons are also a target of hyperglycemia and may be susceptible to inflammation.

Dugel: The results of the Protocol I subanalysis showed that a substantial population of patients treated with anti-VEGF monotherapy did not gain significant visual acuity, therefore requiring additional treatment. Patients were treated every 4 weeks in the beginning, yet almost 26% were labeled as “non-responsive.”

Additionally, Protocol T data are consistent with this finding. Patients enrolled in Protocol T were the most anti-VEGF-starved patients ever studied. Even in this biased, pre-selected patient population, 37% of aflibercept-treated eyes, 46% of ranibizumab-treated eyes, and 56% of bevacizumab-treated eyes still required more than anti-VEGF monotherapy.

In both of these trials, patients were routinely treated in controlled environments. Do these findings indicate that even the most compliant patient population might need additional treatment beyond anti-VEGF therapy?

Packo: I think that when patients have more chronic edema, as the patients had in Protocol I at trial entry, it is more common they will need multiple injections. Diabetes is a complex disease with many signals, and a single drug is not the answer. Rather, it is necessary to develop combination therapies that have multiple signals for patients, and physicians are already starting to combine anti-VEGF therapy with corticosteroid therapy.

Eaton: The data exemplify that additional therapy would be beneficial. I have a number of patients who maintained persistent DME even with monthly treatments. In these patients there is a role for corticosteroids and/or laser.

Dugel: How do you identify the 50% of patients who require more than anti-VEGF treatment?

Reichel: I administer anti-VEGF injections until OCT shows stabilization over two or three injections and
visual acuity is about the same. However, if OCT shows less than 10% change after 1 month, the patient may not be a responder to the anti-VEGF, and laser photocoagulation or corticosteroid therapy can then be considered.

Packo: RISE and RIDE reported a great response from anti-VEGF therapy within 7 to 10 days, but improvement beyond that time is minimal. I recommend physicians bring patients back after 1 week and conduct OCT to determine what is occurring.

“**A sustained-release device rapidly achieves a steady state of optimal drug levels.”**

--- SCOTT W. COUSINS, MD

Dugel: I always start with anti-VEGF treatment, not knowing whether a patient has monofactorial or multifactorial DME. However, I consider corticosteroid therapy if there is no measurable vision improvement after three or four anti-VEGF injections. I consider a patient’s OCT scan, but I am more influenced by vision because I recognize a disconnect between OCT and visual acuity, particularly in patients with chronic, multifactorial DME.

Eaton: I typically try two or three VEGF inhibitor treatments; if one does not work, I try another one. If I observe persistent edema, I consider corticosteroids or laser photocoagulation.

Dugel: How does the consideration of inflammation factor into your decision for treatment of patients with DME?

Kiss: DME is a multifactorial disease that has different driving components, depending on severity and duration. VEGF is a major contributor, but inflammation also can play a significant role. I start with a series of three to four anti-VEGF injections. If I do not observe improvement on OCT and/or in vision, I switch to an intravitreal corticosteroid, either alone or in combination with the anti-VEGF injection. I do not switch among the anti-VEGF drugs as I have found little value in going beyond aflibercept for my anti-VEGF regimen.

Dugel: Is there concern that laser photocoagulation will cause additional inflammation in patients with inflammation-driven DME who do not respond to anti-VEGF therapy?

**Cousins:** It may be a tradeoff, but the new micropulse laser techniques are more likely to physiologically improve patients rather than trigger inflammation. The goal is to activate physiologic process in cells without damaging retinal pigment epithelium cells or photoreceptors.

**Kiss:** Traditional focal/grid laser photocoagulation in the treatment of DME is obsolete, especially for patients with chronic DME. Micropulse laser shows some potential, although long-term, prospective, randomized, multi-center data are lacking with this particular modality.

**Dugel:** With inflammation-driven DME, is it more reasonable to treat patients with corticosteroids?

**Reichel:** It is reasonable, but if there is unsatisfactory response to anti-VEGF therapy, I will at least evaluate the patient with a fluorescein angiogram for the role of laser. Protocol I’s 5-year data support deferring laser, and it makes sense to minimize the destruction with anti-VEGF therapy. Most specialists do not use micropulse laser, so there is still some level of destruction.

**Eaton:** Corticosteroids are a reasonable option for patients who do not respond to anti-VEGF injections because data show that corticosteroids target the inflammatory component of DME, in addition to VEGF, which is not addressed by anti-VEGF therapy alone.

Dugel: The results of Protocol T showed that all three drugs improved visual acuity in patients with central-involved edema when initial vision loss was “mild.” If you are using one anti-VEGF and the patient’s vision plateaus, would you consider switching to another anti-VEGF?

**Packo:** I do switch anti-VEGF therapies. Visual improvement is slow with DME, but there is continued response to anti-VEGF therapy up to 1 year. However, it is important to note that in clinical trials, therapy is aggressive with patients receiving monthly treatment. In clinical practice, retina specialists and patients are more impatient, commonly giving up after three injections. As long as I see improved results on OCT, I am likely to wait out the year and then switch to a corticosteroid if edema is still present. As long as the edema is regressing and the vision improving, I wait out my original anti-VEGF choice. If I started with bevacizumab or ranibizumab, and either metric stalls after three injections, I will switch to aflibercept. My transition to corticosteroid is almost **A sustained-release device rapidly achieves a steady state of optimal drug levels.”**

--- SCOTT W. COUSINS, MD

Dugel: I always start with anti-VEGF treatment, not knowing whether a patient has monofactorial or multifactorial DME. However, I consider corticosteroid therapy if there is no measurable vision improvement after three or four anti-VEGF injections. I consider a patient’s OCT scan, but I am more influenced by vision because I recognize a disconnect between OCT and visual acuity, particularly in patients with chronic, multifactorial DME.

Eaton: I typically try two or three VEGF inhibitor treatments; if one does not work, I try another one. If I observe persistent edema, I consider corticosteroids or laser photocoagulation.

Dugel: How does the consideration of inflammation factor into your decision for treatment of patients with DME?

Kiss: DME is a multifactorial disease that has different driving components, depending on severity and duration. VEGF is a major contributor, but inflammation also can play a significant role. I start with a series of three to four anti-VEGF injections. If I do not observe improvement on OCT and/or in vision, I switch to an intravitreal corticosteroid, either alone or in combination with the anti-VEGF injection. I do not switch among the anti-VEGF drugs as I have found little value in going beyond aflibercept for my anti-VEGF regimen.

Dugel: Is there concern that laser photocoagulation will cause additional inflammation in patients with inflammation-driven DME who do not respond to anti-VEGF therapy?

**Cousins:** It may be a tradeoff, but the new micropulse laser techniques are more likely to physiologically improve patients rather than trigger inflammation. The goal is to activate physiologic process in cells without damaging retinal pigment epithelium cells or photoreceptors.

**Kiss:** Traditional focal/grid laser photocoagulation in the treatment of DME is obsolete, especially for patients with chronic DME. Micropulse laser shows some potential, although long-term, prospective, randomized, multi-center data are lacking with this particular modality.

**Dugel:** With inflammation-driven DME, is it more reasonable to treat patients with corticosteroids?

**Reichel:** It is reasonable, but if there is unsatisfactory response to anti-VEGF therapy, I will at least evaluate the patient with a fluorescein angiogram for the role of laser. Protocol I’s 5-year data support deferring laser, and it makes sense to minimize the destruction with anti-VEGF therapy. Most specialists do not use micropulse laser, so there is still some level of destruction.

**Eaton:** Corticosteroids are a reasonable option for patients who do not respond to anti-VEGF injections because data show that corticosteroids target the inflammatory component of DME, in addition to VEGF, which is not addressed by anti-VEGF therapy alone.

Dugel: The results of Protocol T showed that all three drugs improved visual acuity in patients with central-involved edema when initial vision loss was “mild.” If you are using one anti-VEGF and the patient’s vision plateaus, would you consider switching to another anti-VEGF?

**Packo:** I do switch anti-VEGF therapies. Visual improvement is slow with DME, but there is continued response to anti-VEGF therapy up to 1 year. However, it is important to note that in clinical trials, therapy is aggressive with patients receiving monthly treatment. In clinical practice, retina specialists and patients are more impatient, commonly giving up after three injections. As long as I see improved results on OCT, I am likely to wait out the year and then switch to a corticosteroid if edema is still present. As long as the edema is regressing and the vision improving, I wait out my original anti-VEGF choice. If I started with bevacizumab or ranibizumab, and either metric stalls after three injections, I will switch to aflibercept. My transition to corticosteroid is almost **A sustained-release device rapidly achieves a steady state of optimal drug levels.”**

--- SCOTT W. COUSINS, MD
always from aflibercept. If a patient’s vision plateaus, however, I will not wait a year to switch a therapy.

Dugel: If anti-VEGF therapy is delayed, vision may not improve to its full potential. One may deduce that the same might occur with a delay in switching to corticosteroids in multifactorial DME, as well. When should physicians consider switching from anti-VEGF monotherapy to corticosteroids?

Cousins: According to the RISE/RIDE study, waiting 2 years without intervening is too long, but information about tolerating persistent DME for shorter periods is unknown. I attempt three injections, and if I see improvement, I continue for three more. If I do not observe significant improvement after the sixth injection, I will consider another therapy for my patients.

TREATMENT WITH CORTICOSTEROIDS

Dugel: If you surmise that a patient is in the 50% group that requires additional treatment because he or she is not responding to anti-VEGF monotherapy, the next step would be to move into corticosteroid treatment. How do you distinguish between intravitreal corticosteroid treatments approved for treating patients with DME?

Eaton: Currently, two synthetic corticosteroids are indicated as intravitreal treatment for DME—dexamethasone implant (Ozurdex; Allergan, Irvine, CA) and fluorocinolone acetonide implant (Iluvien; Alimera Sciences, Alpharetta, GA). Although not indicated for the treatment of DME, triamcinolone acetonide, a synthetic corticosteroid suspension injection (Triescience; Alcon Laboratories, Fort Worth, TX), is often used and shows detectable levels for approximately 3 to 4 months. This treatment is less expensive than the intravitreal implants, but it can cause a snow-globe effect and a sterile endophthalmitis in rare cases. The bioerodable, extended-release dexamethasone intravitreal implant containing 700 µg of the corticosteroid was detectable primarily in the first 2 to 3 months. The much smaller, non-bioerodable, extended-release fluocinolone acetonide intravitreal implant (0.2 µg/day) has shown sustained intraocular release for 24 months and up to 36 months (Figure) at a slow, continuous and relatively constant level as opposed to the pulsed and significantly higher, short-term levels delivered by the other two.

Physicians should review the different properties of each of these corticosteroids and optimize them for the patient. The dexamethasone and fluocinolone acetonide implants are better tolerated by patients with less risk, but they are more expensive. When presented with the advantages and disadvantages of the different corticosteroids, I have found most patients have preferred the advantages of longer-lasting implants over the shorter-duration options.

Packo: All synthetic corticosteroids bind the same glucocorticoid receptor (albeit with different binding affinities), which in turn activates similar physiologic effects irrespective of which specific corticosteroid compound is administered. The major difference is whether the corticosteroid is administered as a bolus, providing a high level of the drug intermittently, or eluted over a long period of time. The complications profile is different, depending on the manner of corticosteroid administration.

Cousins: Furthermore, a bolus injection of corticosteroid provides a massive, concentrated dose of the drug—more than needed to saturate cellular glucocorticoid receptors—whereas a sustained-release device rapidly achieves a steady state of optimal drug levels.

Dugel: If you decide to switch to corticosteroid treatment, with which one do you begin therapy?

Packo: I use the dexamethasone implant first because changes in a patient’s intraocular pressure (IOP) are predictable with this treatment. This, as well as my own clinical experience, shows that IOP can be managed for the majority of patients.

Kiss: If I have decided to use a corticosteroid in a patient’s DME treatment regimen, I will start with the...
dexamethasone implant. This implant has demonstrated clinical benefit with a favorable safety profile.38 My familiarity with the implant for patients with retinal vein occlusion and uveitis adds to my comfort with this corticosteroid.

**Cousins:** I begin treatment with the triamcinolone acetone injection because of my comfort and experience level with it. In my experience, I have not found a significant difference between the clinical durability of triamcinolone acetone and dexamethasone implants.

**Eaton:** If a patient has had a stroke, then I am cautious about using a VEGF inhibitor first, so I use dexamethasone implants if immediate therapy is needed. However, for other patients, if edema has not responded to multiple VEGF inhibitor treatments, then topical corticosteroid challenge can be helpful. To conduct a challenge, I follow the technique used by Hollands et al.39 in which patients are treated with prednisolone acetate 1% four times a day for 6 weeks. I check their pressure at 2 weeks, and again at 6 weeks. A positive response is defined as a difference in IOP between the treated eye and the contralateral eye of more than 8 mm Hg or more than 25 mm Hg in the treated eye. In the study, none of the patients who passed the topical challenge and were treated with triamcinolone acetone injection required incisional glaucoma surgery. As a result, if the patient has a negative topical corticosteroid challenge, then I recommend treatment with the fluocinolone acetone implant due to its 3-year duration of action and favorable risk profile.

**Physicians should consider multiple factors, including frequency of injections.”**

—KIRK H. PACKO, MD

**Dugel:** If a patient responds to corticosteroids, but then the effect wears off after 2 to 4 months, would you inject the dexamethasone implant again or would you switch to the fluocinolone acetone implant?

**Packo:** The number of dexamethasone implants administered to patients in clinical trials is significantly less than that administered in clinical practice. For example, in the SHASTA trial,38 patients were dosed every 6 months. In practice, dexamethasone implants do not last that long, and so patients are dosed more frequently than the clinical trial suggested. Physicians should consider multiple factors, including frequency of injections, if patients tolerate dexamethasone implants without IOP increase, and the economics. If fluocinolone acetonide implants maintain a patient’s retinal dryness for 3 years, then that corticosteroid is preferable to multiple dexamethasone implants. Generally, I attempt several dexamethasone implants in a row before I switch the patient to the fluocinolone acetonide implant.

**Kiss:** I typically initiate treatment with anti-VEGF therapy even in patients who have a history of stroke or heart attack, although I prefer to wait 6 months after an acute event. If I do not find the anatomical or visual function results I expect, then I move to the dexamethasone implant, followed by the fluocinolone acetone implant. I always keep in mind that surgeons are not restricted to monotherapy, so I will combine corticosteroids with anti-VEGF injections.

**Dugel:** The paramount reason for using the fluocinolone acetone implant in this patient population is that they do not respond appropriately to anti-VEGF monotherapy, presumably because they have a primarily inflammation-driven disease. This represents approximately 50% of our patient population,38 which is a considerable unmet need.

**Packo:** Many specialists assume that after switching from anti-VEGF therapy to corticosteroid therapy they should give up on anti-VEGF therapy entirely. However, patients may have had a response to anti-VEGF therapy that lasted for several injections and then stalled, indicating that for a time, the therapy worked. While the corticosteroid implant is still in the patient’s eye, the specialist should consider conducting another anti-VEGF injection challenge to see if further improvement is possible. Typically, retina specialists start with anti-VEGF therapy and then move to a corticosteroid, but making that change back again is important to keep in mind. Anti-VEGF therapy and corticosteroids not only attack the edema from different biochemical directions, but they can work together synergistically too. Combining them both may provide better results than monotherapy.40

**Eaton:** The FDA approval guidelines for fluocinolone acetonide implants help me to predictively select patients who will have a corticosteroid response.41 If dexamethasone implants or triamcinolone acetone injections are used first, then approximately 1% of patients might undergo surgery they could have avoided had they been given a topical corticosteroid challenge. A topical corticosteroid challenge can help physicians predict which patients will have a strong response to the treatment and determine if the only treatment that is working is a corticosteroid, possibly reducing the burden of surgery.
For patients who pass the corticosteroid challenge or who have received previous corticosteroids without a significant rise in IOP, most welcome the option of transitioning to the fluocinolone acetonide implant because of the potential to reduce frequency of injections. In patients whose edema clears after the first 3 months of the fluocinolone acetonide implant treatment, it is likely to remain cleared for a while. Therefore, with subsequent 3-month visits, these patients could simplify their follow-up by seeing a local ophthalmologist to monitor their IOP and perform OCT and retinal examination.

POSSIBLE ADVERSE EFFECTS AND COMPLICATIONS

**Dugel:** Diabetes is a complex disease, and there are many associated complications. One of the complications in patients with diabetes is the development of a cataract. DME is a potentially permanently blinding disease. If blindness from DME can be averted, but the price paid is an acceleration of cataract formation from corticosteroid exposure, then I think that is an acceptable compromise. Does a concern for cataracts affect your decision regarding which treatment to use?

**Eaton:** My decision to use a corticosteroid in a younger, phakic patient depends on the severity of the diabetic retinopathy and previous response to treatment. If the patient already has or is close to developing a cataract, or is unresponsive to anti-VEGF therapy, then I would consider corticosteroid therapy.

**Kiss:** The development of a cataract in an older patient with diabetes is not a concern. In a younger patient, I weigh the risk of cataract development with the need to control the retinopathy, so I may try other treatment modalities (eg, more frequent anti-VEGF injections, focal/grid laser) before injecting a corticosteroid.

**Reichel:** Cataract is one of the sight-related complications of diabetes and will be removed when it likely develops. Therefore, possible acceleration of cataract formation does not deter me from switching to corticosteroid therapy.

**Dugel:** One of the complications of corticosteroid therapy can be an increase in IOP that, if left untreated, can lead to permanent vision loss. However, an important and consequential distinction must be made: what is the difference between hypertension and glaucoma?

**Parrish:** IOP of about 20 mm Hg can be managed without referring the patient to a glaucoma specialist. Physicians should examine the disc for cupping or fresh disc hemorrhage. Elevated IOP after corticosteroid therapy is a type of secondary ocular hypertension, and if specialists feel anxious, then adding any of the available antiglaucoma medications would be appropriate. I recommend referring a patient to a glaucoma specialist if IOP elevates to 30 mm Hg.

**Dugel:** The SHASTA and FAME studies suggest it may be possible to predict when an increase in IOP would occur. It is interesting to speculate, with this knowledge, how post-clinical trial behavior may change. Physicians may not be as aggressive in considering laser or surgical intervention because there is a predictable pattern of how patients will respond and when IOP may decline spontaneously, following the drug pharmacokinetics.

**Parrish:** Today, the term glaucoma is reserved for patients who have evidence of injury to the optic nerve or retinal nerve fiber layer, functional damage, or visual field loss that fits with optic neuropathy. Patients who experience IOP elevations after corticosteroid therapy have secondary ocular hypertension, which is also known as corticosteroid glaucoma.

**Dugel:** When should retina specialists worry about an increase in IOP?

“Specialists should try to identify patients at risk for an increase in IOP.”

— RICHARD K. PARRISH II, MD
implants, IOP elevation would lag because it correlates to concentration of the corticosteroid in the eye. As that diminishes, specialists would usually expect to see IOP decrease; however, some patients may have an irreversible effect.

If a patient received the dexamethasone implant and experienced an IOP fluctuation, and then he or she needs another injection, then the physician must determine whether to continue with the corticosteroid considering an additional therapy would be necessary to manage IOP elevation. It is possible to sort out super-high responders using topical dexamethasone or topical prednisolone acetate 1% four times a day. If a patient does experience a high pressure response while on that dosage for 4 to 6 weeks, it is unlikely he or she may have one with a sustained-release corticosteroid. The amount of corticosteroid contained in the fluocinolone acetonide implant is small, less than the corticosteroid component in one drop of 1% prednisolone acetate. The fluocinolone acetonide implant is similar to using one drop of topical steroid for 3 years.

**Packo:** If a patient is put on a topical corticosteroid challenge and then experiences a significant rise in IOP, it is likely that a corticosteroid implant will cause a similar, if not worse, rise in IOP. However, negative predictability is modest, at best, from a topical corticosteroid challenge, and specialists may need to challenge patients for 3 to 6 months before observing a rise.

**Parrish:** The likelihood of a patient experiencing substantial IOP elevation with the fluocinolone acetonide implant is small. If IOP increases, then physicians manage it quickly because the typical plan is to see patients within 6 weeks and then quarterly thereafter.

If patients have loss of central vision and are not responding to traditional therapy (ie, anti-VEGF) but are experiencing improved vision with a corticosteroid, then specialists might need to treat patients for elevated IOP, as that elevation could cause damage. With patients who are super-responders to corticosteroid therapy, it is less likely an elevated IOP can be controlled with medical therapy. The benefit-risk ratio is tipped in favor of doing what needs to be done to maintain central vision with a corticosteroid and then managing the complications of glaucoma.

**CONCLUSION**

**Dugel:** With new discoveries of pathophysiology, innovations in treatment, and advances in ophthalmic technology, clinicians’ knowledge of DME continues to advance. Therefore, it may be time to refer to DME in terms of stages. For analogical purposes, one may consider the field of oncology. An oncologist does not just report, “Mrs. Jones has breast cancer.” Instead, the oncologist states, for example, “Mrs. Jones has stage IIIA breast cancer,” and other oncologists immediately understand not only the diagnostic, but also the therapeutic implications of that staging system. As in other disciplines in medicine, is it time to recognize the heterogeneity of DME and discuss the disease with more granularity?

**Eaton:** It may be a good time to look at defining the groups more specifically. I also like the concept of focusing on vision in addition to OCT findings because reduction in inflammation may improve vision before OCT results show improvement in some patients. Ultimately, retina specialists try to improve vision, and it is sensible to bring that back into focus.

**Dugel:** Ophthalmologists’ concept of DME has changed over the years, and it is now recognized that patients with DME fall into two groups: a permeability-driven group and an inflammation-driven group. The first will likely respond to the anti-VEGF monotherapy. The second will likely respond well to corticosteroids, particularly corticosteroids that are long-term devices.

DME evolves over time, demonstrating focal leakage then diffuse leakage, then pigmentary changes and fibrosis. Clinicians recognize these phenotypic changes. The next paradigm shift in the understanding and treatment of DME involves the physician correlating these anatomic changes with physiologic progression, particularly in defining the multifactorial switch that fundamentally changes this disease from a permeability-driven disease to an inflammation-driven disease.

I thank the panel for the comments, OSLI RETINA for organizing this symposium and Alimera Sciences for providing its support.

REFERENCES
