MANAGEMENT OF DIABETIC MACULAR EDEMA
APPLICATION OF CURRENT EVIDENCE TO PATIENT CARE

Highlights from a Roundtable Discussion

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Management of Diabetic Macular Edema
Application of Current Evidence to Patient Care

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**DIABETIC MACULAR EDEMA: OVERVIEW**

**Dr. Kaiser:** Diabetic retinopathy is the leading cause of blindness in the industrialized world among working-age people. Vision loss is often due to macular edema, which can develop at any stage of diabetic retinopathy. What biochemical changes lead to diabetic macular edema (DME)?

**Dr. Apte:** The pathogenesis of DME is multifactorial. Anatomic factors, which we do not completely understand, play a role. Pericyte death seems to be the earliest event; however, other underlying activity could be responsible for what we see anatomically and histopathologically as cellular death. It may involve cytokines that are known to be pro-inflammatory. It may involve cellular inflammation, perhaps the monocytic inflammation seen in other retinal vascular diseases or macular degeneration. Also, a combination of all these factors could result in DME. We have known for some time that vascular endothelial growth factor (VEGF) is associated with DME, but it may not be causative. It is possible the VEGF secreted by monocytic cells and retinal pigment epithelial cells is a cascade induced by inflammation.

**Dr. Kaiser:** The early DME studies, and the early studies by Dr. Anthony Adamis in particular, showed an inflammatory component to DME. Our patients can have different types of diabetes mellitus, which lead to complications such as macular edema at different rates and at different times. In general, when you work with primary care physicians or endocrinologists, how soon do you tell them that you want to see diabetic patients?

**Dr. Holekamp:** In the younger, insulin-dependent Type 1 patients, I like to see them within 5 years of diagnosis. In the older-onset Type 2 patients, I like to see them at the time of diagnosis.

**Dr. Kaiser:** What systemic risk factors for DME do you look for in these patients?

**Dr. Apte:** The systemic variables are important: long-term glucose control as well as blood pressure and lipid control. Uncontrolled hypertension is an independent variable for the development and worsening of macular edema. All of these variables influence not only incidence but also response to therapy. In addition, some of the diabetes treatments in use today can worsen macular edema or influence whether it is refractory to treatment. Therefore, especially for new patients, I want to know what their systemic risk profile looks like.

**Dr. Holekamp:** I make sure patients with DME are not taking pioglitazone or rosiglitazone because of their potential to cause DME, heart attack, or heart failure. In addition, I question patients about signs and symptoms of obstructive sleep apnea, which several studies have shown to be a risk factor for refractory DME. I have referred many diabetic patients for sleep studies. Retinopathy has improved in those who have been put on a continuous positive airway pressure machine, and they have been able to discontinue some systemic medications.

**Dr. Kaiser:** When you see patients for the first time and no DME is present, when do you want to see them back?

**Dr. Brown:** If they have absolutely no DME, I see them again within 2 years. If they have any background diabetic retinopathy, I see them yearly. If they have any DME, I have them come back in 3 to 4 months depending on how concerned I am about it progressing to the center of the fovea. I also explain to them the importance of blood pressure control, including how pressure lows can cause problems, and make sure they understand the significance of hemoglobin A1c levels and how beneficial it can be to lower it by even 1 percentage point.

**Dr. Reichel:** It is not clear why, but fluid overload is characteristic of patients who have diffuse macular edema. When that is the case, patients should be managed from that perspective. Also, based on my experience, cotton wool spots in the fundus of a patient who has diabetic retinopathy are more likely a sign of out-of-control hypertension than diabetic changes. When blood pressure is controlled the spots go away.

**Dr. Holekamp:** I agree, and I have found 4 to 6 cotton wool spots in a peripapillary pattern to be almost pathognomonic for obstructive sleep apnea. When breathing stops at night, blood pressure shoots up; this likely causes the cotton wool spots.

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**IMAGING AND THE DIAGNOSIS OF DME**

**Dr. Kaiser:** When you evaluate your diabetic patients, what diagnostic work up do you perform?

**Dr. Brown:** Diagnosis is a combination of clinical examination of the peripheral retina, central retina, and macula and by optical coherence tomography (OCT) imaging as well as fluorescein angiography (FA) in some cases.
Dr. Kaiser: Do you use contact lens examination in your patients to evaluate retinal thickening?

Dr. Reichel: I do not, but I do use high-magnification lenses. With 78- or 90-diopter lenses, I can see clinically significant macular edema (CSME). That being said, in 10% to 15% of patients, even with normal visual acuity and no evidence of thickening on clinical exam, OCT reveals mild cystic changes that are relatively unobservable to the human eye.

Dr. Kaiser: At what point do you perform FA, or do you?

Dr. Brown: If there is minimal diabetic retinopathy or none at all, I do not do FA. If there is retinopathy, I typically do widefield angiography with a scanning laser ophthalmoscope (SLO) device or a widefield contact lens system, such as the Staurenghi lens. I want to ascertain the extent of capillary nonperfusion centrally and peripherally and look for microaneurysms, etc.

Dr. Reichel: I generally do not do FA. With the changes in laser technology and the new parameters we use for treating the macula in diabetic patients, the risk of subthreshold laser therapy, such as the Staurenghi device, is unclear what the clinical significance of that is, but I like to have a baseline OCT for my diabetic patients.

Dr. Kaiser: Does everyone on the panel agree with that?

Dr. Brown: I did until I started using an ultra-widefield SLO device and seeing neovascularization that I did not see before. I typically use the SLO in patients with cotton wool spots or other indications of ischemia or DME. In some cases, I see a relatively normal vascular pattern in the periphery, but in others I see huge areas of capillary nonperfusion. Using ultra-widefield SLO, I find I move up the timing of monitoring and perhaps treatment, sometimes significantly. In some cases, I find neovascularization and start discussing early panretinal photocoagulation (PRP) before high risk characteristics appear.

Dr. Holekamp: I still use FA if I am not quite sure exactly what is going on in an eye. However, if I see clinically significant DME and microaneurysms that are leaking, and think that I can do an adequate job without an FA, I may treat them focally. I use FA if I see a diffuse pattern and I want to see whether there is capillary dropout and foveal ischemia, which I do not think we can detect adequately with any other modality.

Also, I agree with Dr. Reichel that OCT can reveal cystoid macular edema that was not detectable clinically. It is unclear what the clinical significance of that is, but I like to have a baseline OCT for my diabetic patients.

Dr. Kaiser: Do you routinely obtain color fundus photographs in your diabetic patients?

Dr. Holekamp: It depends on the amount of diabetic retinopathy they have. If it is very mild, minimal background changes that we call nonproliferative disease, I see them once a year and do not get baseline fundus photographs. If they have moderate nonproliferative disease, I might get baseline photographs, particularly if I learn their diabetes is poorly controlled. If their hemoglobin A1c level is in the double digits, that changes my management. I would see them in 6 months rather than a year, communicate with their internist, and reinforce with them the importance of glucose control.

Dr. Kaiser: What features do eyes with DME exhibit on OCT? Do any features change your thinking about patient management?

Dr. Reichel: In newly diagnosed patients, OCT can show a variety of changes, including cystic changes within the inner retina, schisis, occasionally foveal schisis, and sometimes subretinal fluid as a form of macular edema. It is also important to recognize when chronic cystic changes are present. We are still learning to describe how those appear on OCT.

Dr. Kaiser: Another feature I look for on OCT is traction. In the presence of traction, medical therapies such as injections and lasers in general do not work.10,11 Thus, if I see true traction, a taut posterior hyaloidal membrane, even at the first visit, I am inclined to do surgery sooner rather than later.

Classically, the Early Treatment Diabetic Retinopathy Study (ETDRS) has defined CSME based solely on clinical examination. With the advent of OCT and the ability to see retinal edema not visible to the human eye, has OCT changed your definition of CSME?

Dr. Reichel: I rely on a combination of clinical exam and OCT. If a patient has CSME, I treat. If OCT picks up more subtle disease with edema near the fovea, whether I treat depends somewhat on visual acuity. If visual acuity is excellent and OCT shows minimal cystic changes and central foveal thickness of 250–270 μm or less—the actual numbers depending on which instrument is used—in my opinion it is reasonable to observe the patient. If I see more thickening than that, and acuity has dropped into the 20/30 to 20/40 range, I find it reasonable to consider treating with an intraocular pharmacologic treatment.

CHOICE AND TIMING OF TREATMENT

Dr. Kaiser: At what point do you consider therapy for DME?

Dr. Reichel: It is a matter of debate whether focal edema and diffuse edema are the same and how that should impact choice of treatment. I think there are some differences and identifying the pattern of macular edema on clinical exam is important. If I see a small, discrete area of focal edema or just an island of edema that is away from the center of the fovea, I expect the patient will respond well to laser treatment. When disease has progressed beyond that pattern, I begin to consider alternative treatments.
Dr. Kaiser: Do you have a vision cutoff in your mind before you start treating, or would you treat an eye with perfect 20/20 acuity?

Dr. Apte: I would treat a patient with good vision.

Dr. Kaiser: What are your definitions of focal and diffuse edema? Do you use any other definitions to characterize DME?

Dr. Holekamp: Focal and diffuse are part of our history of treating DME, part of our lexicon. I think we have a general understanding that if we can identify microaneurysms, we classify that as focal leakage. There may be circinate lipid around it, and we expect that to respond well to focal laser, meaning we treat the aneurysms and the edema goes away and, over time, the lipid becomes reabsorbed. I also think we consider diffuse to mean a generalized thickening throughout the central macula where we cannot clearly identify the individual leaking microaneurysms. Historically, that has been the type of macular edema that is more difficult to treat and where pharmacotherapy has helped us.

Dr. Kaiser: When you are evaluating your imaging studies and clinical exam, are you thinking focal vs. diffuse, or is that more of a historical footnote that you do not use anymore?

Dr. Holekamp: I have changed my DME classification/treatment algorithm to think more along the lines of early-, mid-, and late-stage macular edema. Early-stage macular edema tends to be more focal with some microaneurysms still visible. The purpose of treatment in that scenario is to stop the leakage before it affects vision. I agree with Dr. Apte that it is fine to treat a 20/20 eye because the landmark diabetic retinopathy studies codified clinically significant DME as the kind of thickening that puts vision at risk. With that in mind, I will certainly treat an eye in which I think the lipid is tracking toward the fovea and it looks focal. I consider that to be early DME. Medium- or mid-stage macular edema would be more diffuse, but with vision still around 20/50.

From some of the clinical trials we have had recently, we have a new term, “center-involved” macular edema. It seems we are beginning to think more in terms of 20/50 vision and center-involved macular edema as being what might respond well to treatment with an intravitreal steroid or an anti-VEGF agent. Lastly, I consider late-stage macular edema to be what would be described as chronic, persistent, or resistant to treatment. This is the most challenging type to treat, whether it is with surgery, combination therapy, or emerging options.

EVALUATING ANTI-VEGF THERAPY FOR DME

Dr. Kaiser: In the European Union, the anti-VEGF agent ranibizumab was approved for the treatment of diabetic macular edema. In a recent Diabetic Retinopathy Clinical Research (DRCR) Network study, Protocol I, intravitreal ranibizumab was reported to be superior to laser therapy for preventing vision loss due to DME. This has led some retinal specialists to advocate anti-VEGF therapy as the first-line therapy for DME, which in the United States is still off-label use. Do you agree?

Dr. Apte: Broadly, I agree. The DRCR study showed ranibizumab plus deferred laser or prompt laser to be superior to laser alone for DME in terms of visual acuity. (Figure 1) Several other clinical trials, including RISE and RIDE phase 3 studies (Ranibizumab Injection in Subjects With Clinically Significant Macular Edema With Center Involvement Secondary to Diabetes Mellitus), READ-2 (Ranibizumab for Edema of the Macular in Diabetes: a Phase 2 Study), and RESTORE (A Randomized, Double-Masked, Multicenter, Laser-Controlled Phase III Study Assessing the Efficacy and Safety of Ranibizumab [Intravitreal Injections] as Adjunctive and Mono-Therapy in Patients With Visual Impairment Due to Diabetic Macular Edema), have shown ranibizumab to be an effective monotherapy against center-involving DME or superior to laser alone either as monotherapy or combined with laser. However, in the DRCR Protocol I study at 1 year, visual acuity in the group that received steroid plus prompt laser and were pseudophakic at baseline (n = 273) was comparable to visual acuity in the ranibizumab groups. (Figure 2) So, yes, as a broad statement, anti-VEGF therapy is superior to laser or steroids according to the DRCR trial, but the discussion is far more nuanced than simply taking the results at face value.

Dr. Brown: My first-line treatment for patients with relatively early center-involving DME depends on the individual and FA. If I see obvious microaneurysms, I will treat them with laser unless, for example, the patient drives a truck for a living and cannot afford not to pass his interstate license test. In a case like that, I will treat with an anti-VEGF agent, which I expect to resolve interstitial edema and get the patient functioning normally much faster.

Dr. Kaiser: When you use laser, do you follow the classic ETDRS guidelines for laser application to produce a light burn?

Dr. Brown: I use predominantly a micropulse laser, so I titrate the power. It is much less power than classic ETDRS, a very light white burn as opposed to hot white. I am a lot more cautious about using a laser for anything near 500 microns from the fovea because I do not want to cause a noticeable scotoma, and I now have other options in the armamentarium. I am comfortable with the safety and effectiveness of using an anti-VEGF agent off-label. As I mentioned, I do use laser for microaneurysms and for areas of capillary nonperfusion if they are well outside the 500 microns.

Dr. Kaiser: Has anyone on the panel used any of the sub-threshold lasers? What is your experience?

Dr. Reichel: Subthreshold treatment has been shown to be efficacious. I think it is a paradigm shift in how laser
treatment is performed, but I am not sure it requires a special micropulsing laser. My colleagues and I are currently conducting a small pilot study to try to determine whether, using a standard laser, it is possible to treat the retinal pigment epithelium, not within 500 microns of the fovea but farther out, by “painting” at a very low, subthreshold endpoint. The spacing of the treatment is important.

Dr. Apte: I would like to see more evidence that any of the new lasers are any more effective than the conventional lasers. Often for the initial treatment course, I use an anti-VEGF agent prior to laser. Then I can place barely visible burns. I use a small spot size and do not feel pressure to treat with a grid or a multitude of spots. I can always treat more later. The anti-VEGF agent lightens the laser load in terms of power and spots.

Dr. Brown: I agree. When I decide to treat microaneurysms in a very thick retina, I deturgescence first. If the collimation of the laser beam is not spread by edema, a lot less power can be used.

Dr. Kaiser: How soon after an anti-VEGF injection, do you bring patients back?

Dr. Brown: I bring them back in 1 week.

Dr. Apte: It depends on the individual patient, but definitely within weeks.

Dr. Brown: Our current anti-VEGF dose does not keep edema away for a full month in some patients. I do not want to wait too long to bring them back or we will not get much benefit.

Dr. Kaiser: How soon after laser treatment, do you see patients again?

Dr. Apte: I see them in a few weeks. As we have seen in many of the recent studies, laser treatment is not going to work right away.

Dr. Holekamp: That is correct, but we can now improve visual acuity immediately with injections. So instead of returning in 4 to 6 months for follow-up of their laser treatment, patients are coming back in a month for their second anti-VEGF injection. We are seeing our patients more frequently but we are still giving laser treatment because it will help them in the long-term.

Dr. Reichel: Using the DME classification Dr. Holekamp described—early, mid, and late—I treat early-stage patients with laser and have them come back in 2 months. Mid-stage patients, even though they have decent visual acuity, I might also treat with laser but bring them back sooner for an anti-VEGF injection because the laser is not going to work immediately. Late-stage patients return to the office as frequently as every other week because they have not been responding well to treatment and are receiving injections, steroids, and laser.

Dr. Holekamp: It really is a paradigm shift in how frequently we are seeing our DME patients. We now know from multiple clinical trials involving anti-VEGF agents that we had been undertreating these patients. They need multiple monthly shots to reverse the diabetic retinopathy.

Dr. Apte: The one category of patients (which includes only a minority of patients) for which I would recommend surgery

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**Fig. 1.** In a recent study conducted by the Diabetic Retinopathy Clinical Research Network in patients with diabetic macular edema, intravitreal ranibizumab with prompt or deferred focal/grid laser produced visual acuity outcomes superior to focal/grid laser treatment alone. Reprinted with permission from Diabetic Retinopathy Clinical Research Network.33

**Fig. 2.** In the Diabetic Retinopathy Clinical Research Network’s Protocol I study of patients with diabetic macular edema, in the subset of eyes that were pseudophakic at baseline (n = 273), visual acuity improvement in the triamcinolone plus prompt laser group was comparable to visual acuity improvement in the ranibizumab-treated groups. Reprinted with permission from Diabetic Retinopathy Clinical Research Network.33
very early is DME and vitreoretinal surface abnormality. If a patient clearly has DME and vitreomacular traction, I might use an anti-VEGF agent but would start discussing surgery.

**Dr. Brown:** The hesitancy I have in those patients is that anti-VEGF agents seem to clear vitrectomized eyes more quickly, which could compromise how well they work if you need these agents for that patient in the future.

**Dr. Kaiser:** Obviously, anti-VEGF agents block VEGF. Do you think there are any other effects of an anti-VEGF agent in diabetic macular edema?

**Dr. Brown:** In blocking VEGF, we may also be upregulating other factors, such as hypoxia-inducible transcription factors or erythropoietin. There is a “teeter-totter” effect with the various biochemical entities. Blocking one of the main factors likely upregulates or downregulates others. We do not really know at this point whether that is beneficial.

**Dr. Reichel:** What about systemic considerations? There is the potential issue of a link between pan-VEGF blockade and increased risk of stroke or cardiovascular events, and diabetics are already high-risk. Furthermore, in general, our diabetic patients are getting more anti-VEGF injections than our age-related macular degeneration (AMD) patients. The REAP-3 study evaluated two different doses of ranibizumab for DME, 0.5 mg and 2.0 mg, and there were more hospitalizations in the higher dose group.

**Dr. Kaiser:** Does that concern affect your choice of anti-VEGF agent? It has been suggested that pegaptanib, because it specifically blocks just VEGF isoform 165, poses less systemic risk.

**Dr. Reichel:** I do not think it is unreasonable to consider pegaptanib. It appears it may have an effect in DME.

**Dr. Holekamp:** An issue with bevacizumab is that we do not have safety data from a large diabetic population, which is the same situation we had in AMD until CATT (Comparison of Age-Related Macular Degeneration Treatment Trials). Therefore, bevacizumab safety is an unanswered question at this time for diabetic patients with vasculopathy and therefore at higher risk for heart attacks and strokes.

**Dr. Reichel:** The risk of bacterial infections with repeated exposure is a question with anti-VEGF agents and diabetics as well.

**Dr. Apte:** According to the results from all trials of multiple injections, the risk of endophthalmitis can approach 1% which is considerably higher than AMD trials. That may be a concern in macular edema patients who have bilateral disease and who, according to recent trials, may require 11 to 24 injections over a 2-year period.

**Dr. Kaiser:** What has been your experience with elevated intraocular pressure and anti-VEGF injections?

**Dr. Reichel:** It seems to develop as the number of injections increases, usually with more than a dozen injections. It is also my sense that it is more likely to occur with monthly as opposed to as-needed treatment.

### MONTHLY VS. AS-NEEDED DOSING OF ANTI-VEGF ANTAGONISTS

**Dr. Kaiser:** When you are treating DME patients with an anti-VEGF agent, do you use a monthly regimen as was used in, for example, the RISE study, or a regimen more similar to what was used in DRCR Protocol I? (Figure 3)

**Dr. Brown:** I inject the patient monthly until the foveal anatomy returns to fairly normal. I do not necessarily have to eliminate every tiny cyst, but I want to get from no foveal depression to a foveal depression with improvement in visual acuity.

**Dr. Apte:** For me, the choice of regimens is patient-dependent. I typically bring patients back after 1 injection and discuss next steps with them. Some patients whose acuity has improved may not want another injection, even when I explain studies indicate that monthly injections are likely the most effective approach. Which of the available agents I use depends on the patient’s overall profile, including what their insurance covers.

**Dr. Holekamp:** In all of the clinical trials for AMD and DME, the best anti-VEGF results came with monthly injections. Therefore, from the outset, I tell patients with center-involved edema and 20/50 vision or worse that they are going to get 4 monthly injections, possibly 6. I prefer to push the envelope with monthly injections to determine how good I can make their vision, rather than stop after an improvement from 20/80 to 20/60, for instance.

**Dr. Kaiser:** When widefield angiography reveals peripheral nonperfusion, what is your strategy?

**Dr. Brown:** When diffuse edema and peripheral ischemia are present, it is tempting to assume that PRP might be advantageous. We have no evidence to support that, but we are currently conducting a randomized trial at our site to compare PRP plus ranibizumab vs. ranibizumab alone to see if it matters. The study includes only patients with extensive ischemia. Our hypothesis is that by decreasing VEGF drive, we may be able to reduce the amount of anti-VEGF suppression that is necessary.

**Dr. Holekamp:** I bring these patients back in 1 or 2 weeks to check if they have responded to the injection. If they have not, in my mind, their macular edema has declared itself to be more complex than only VEGF-mediated. Therefore, additional VEGF treatment and PRP may have limited utility. My algorithm is to use laser for focal and early DME, anti-VEGF for center-involved, diffuse DME, and then steroids if there is no response to a series of anti-VEGF injections.
Dr. Kaiser: Increasing anti-VEGF dosing frequency to every 2 weeks to improve efficacy has been suggested. What are your thoughts on that idea?

Dr. Brown: It was surprising to me that in the READ-3 study the two different doses produced similar visual acuity results.

Dr. Kaiser: I agree, the READ-3 results move me away from the idea of treating more frequently than monthly and move me toward switching to a different treatment option sooner.

Dr. Reichel: In the HARBOR trial of ranibizumab for neovascular AMD,33 no significant difference in outcomes was shown for the two doses studied, 0.5 mg and 2.0 mg. That raises the question of whether lower doses in some patients might produce a better result with less potential toxicity.

Dr. Apte: I am happy to now have at least some guidelines from READ-3 and HARBOR. I had been underwhelmed with the results of higher doses as well as with more frequent dosing. I am not saying it was never effective, but in my practice I never saw a convincing pattern.

THE ROLE OF STEROIDS

Dr. Kaiser: What is typically the next step for patients who do not respond well to anti-VEGF agents?

Dr. Apte: If vision is not improving with anti-VEGF therapy, or if frequent injections are too burdensome for a particular patient, steroids can be considered. I am not using periocular steroids, which I never expected would be very effective. The network toxicity.

Dr. Reichel: I am not using periocular or if frequent injections are too burdensome for a particular patient, steroids can be considered. I am not using periocular steroids, which I never expected would be very effective. The results of a small DRCR trial confirmed that. The network toxicity.

Dr. Brown: They could be acting on inflammation, suppressing VEGF or other contributory factor, or increasing tight junctions between cells, which would reduce vascular permeability.

Dr. Kaiser: Why would steroids not be used as first-line treatment?

Dr. Reichel: In general, I see the patient 2 to 3 weeks later.

Dr. Brown: I see patients 1 week after an intravitreal steroid injection because I am more concerned about endophthalmitis than I am after treatment with an anti-VEGF injection, given that the inside of the eye is being immunocompromised.

SUSTAINED-RELEASED STEROID DELIVERY

Dr. Kaiser: The FDA has approved a surgically implanted, sustained-release fluocinolone delivery device for the treatment of chronic non-infectious posterior uveitis and a biodegradable injectable dexamethasone-based device for the treatment of macular edema associated with retinal vein occlusion. Two large, 3 year, Phase 3 clinical trials of an injectable fluocinolone-releasing device specifically for DME have been completed successfully, and the device has been approved in the European Union but will require additional studies before approval in the United States. If a sustained release steroid option for DME becomes available, how do you foresee using it in your practice?

Dr. Holekamp: These devices are designed to release steroid into the eye for a substantial duration. As has been seen with the approved devices, the treated eyes are prone to develop-

Fig. 3. The underlying rationale of the treatment algorithm in the Diabetic Retinopathy Clinical Research Network’s Protocol I was to deliver 4 mandatory monthly injections and then continue treatment prn until stabilization or lack of further improvement occurred. Reprinted with permission from Diabetic Retinopathy Clinical Research Network.33
ing cataract and intraocular pressure rise. Before utilizing this option, I would want to ensure it would be effective and that the patient is not a steroid responder. If the DME is beyond focal and not responding to anti-VEGF and I have made a commitment to use steroids, I would talk to the patient about a steroid challenge with a drop and then an intravitreal injection. If the edema clears, and I know whether there is going to be an intraocular pressure response, I would feel comfortable proceeding with a sustained-release device.

**Dr. Reichel:** A sustained-release steroid option should be beneficial in late cases involving severe edema already requiring laser and anti-VEGF treatment where vision is still poor.

**Dr. Kaiser:** Would you prefer that the patient already have a cataract or is pseudophakic before using a sustained-release device?

**Dr. Reichel:** I am not overly concerned about that.

**Dr. Kaiser:** Even in a 25- or 30-year-old patient?

**Dr. Reichel:** No, they are facing the possibility of going blind and would likely be having cataract surgery relatively early in life regardless of a sustained-release device.

**Dr. Holekamp:** With steroid on-board, cataract surgery tends to go well with minimal inflammation. We also know that filtering surgery for glaucoma tends to be successful for patients who have the FDA-approved fluocinolone device for uveitis.27

**Dr. Brown:** I have presented DME data from our cases in the FAME study of the yet-to-be-approved, injectable, fluocinolone sustained delivery device.28 Many of our patients, who are now 3 years out, have said they would like to have the device inserted in their other eye. From their perspective, rather than repeated injections of steroid or anti-VEGF, they received just one “shot,” and it improved their lives for 3 years. Even those who required filtering surgery are doing well and are happy.

**Dr. Apte:** The longer patients are required to undergo multiple injections, the more the risk/benefit equation favors sustained-release steroids.

**Dr. Brown:** Also, repeated injections are a heavy burden, in particular for working-age patients. It is difficult to keep a job if they have to take time off once every month.

**INDICATIONS FOR SURGERY IN THE SETTING OF DME**

**Dr. Kaiser:** It is generally accepted that surgery for DME in the presence of obvious traction is a reasonable option.29 It is far less clear, however, whether surgery should be done when no obvious traction is seen with OCT.30 When a patient has diffuse retinal thickening and has failed both steroid and anti-VEGF treatment, do you consider surgery?

**Dr. Reichel:** I have opted for surgery in that scenario. Macular anatomy has tended to improve, but not necessarily vision.

**Dr. Holekamp:** The goal of vitrectomy would be to increase intraocular oxygen,31 which is believed to have a potent anti-VEGF effect. To accomplish that, extensive PRP is also needed.

**Dr. Apte:** It is difficult to assess vitrectomy outcomes in DME based on the trials that have been done so far because they have involved worst-case scenarios in which patients have failed all previous therapies and are likely to be highly ischemic. That may be why in the DRCR Protocol D trial, for example,32 patients had anatomic improvement but not significant vision improvement.

**Dr. Kaiser:** I agree. It is worth noting that earlier surgery is more common in other parts of the world, especially in Japan, than it is in United States.

**Dr. Holekamp:** I suspect that early DME may be more strictly VEGF-mediated. By the time it is chronic, so many other factors are playing a role, perhaps making a favorable response less likely. Therefore, further exploration of earlier surgical intervention would be helpful.

**EVOLVING TREATMENT PARADIGMS**

**Dr. Kaiser:** Certainly, the number of options vitreoretinal specialists have for managing patients with DME has been growing. Trials by the DRCR.net and others have been helpful in providing guidance on the relative effectiveness of the available therapies and patient selection. Given the heavy burden diabetes and diabetic eye disease places on patients and society as a whole, work in this area will continue. Key areas of focus will be how best to apply the results of these trials to patient care, whether combined treatment delivers advantages over monotherapy, and new therapies capable of improving outcomes as well as reducing the treatment burden for patients.

**References**