Exploring the DME Treatment Decision Tree

Where do the various treatment options fit in managing patients with diabetic macular edema?

AN INTERVIEW WITH DAVID EICHENBAUM, MD

There is now a variety of options for treating patients with diabetic macular edema (DME), which at once is a benefit but also a source of potential confusion. What is the best approach to the patient newly diagnosed with DME? What about for patients with chronic, long-lasting edema? Does the inflammatory nature of the disease suggest a role for steroids? And although it has not been studied extensively, is there perhaps a role for combination therapy?

Finding definitive answers to these questions in the absence of a plethora of data from long-term, randomized clinical trials is a Herculean task—and it may well be a Sisyphean endeavor as new options are studied and become available. Yet, physicians are making treatment decisions every day in this information vacuum, decisions that have implications for the health of patients' vision immediately and into the future.

To begin to explore some of these questions, *Retina Today* interviewed David Eichenbaum, MD, of Retina Vitreous Associates of Florida, to seek his input on how he manages patients with DME.

Retina Today: What are your decision-making criteria for selecting treatment for a patient with DME?

David Eichenbaum, MD: My typical evaluation of a DME patient includes a dilated examination and optical coherence tomography (OCT), and I do angiography on all my new patients with diabetes to look for the location of leaks. I periodically repeat the angiography, but not very often. The most important thing I am looking for is the location of the edema. Historically, we would rely on criteria derived from the Early Treatment Diabetic Retinopathy Study to determine whether to start therapy, but I am really more concerned with whether the edema is center-involving. If it is center-involved symptomatic edema, I recommend starting with intravitreal therapy regardless of the level of Snellen or ETDRS eye chart acuity. I will sometimes observe asymptomatic mild center-involving DME. My usual first-line approach is to use antiangiogenic agents.

There are options in the choice of anti-VEGF agents with both ranibizumab (Lucentis, Genentech) and aflibercept (Eylea, Regeneron) approved by the US Food and Drug Administration for treatment of DME. Off-label use of bevacizumab (Avastin, Genentech) is an option as well. I usually start with ranibizumab, because the molecule is designed without an FC portion, which probably reduces antibody recirculation. That said, even though I start with anti-VEGF therapy, I am most likely going to use combination therapy with some mix of anti-VEGF, steroid, and laser, and surgical intervention as needed. For example, I use laser following anti-VEGF therapy in patients with persistent noncentral focal leaks, but I almost always use deferred laser because the DRCR.net showed a benefit for deferred laser, especially in longer follow-up. A lot of people still use prompt laser, but I prefer to defer laser at least 4 to 6 months because it is associated with improved visual outcomes.

***RT*:** How do you define treatment failure with anti-VEGF therapy?

Dr. Eichenbaum: There are 3 ways to think about treatment failure with regard to anti-VEGF therapy: (1) failure of response to monthly injections with regards to anatomic drying, which occurs in about 20% of patients; (2) recurrence with less than monthly therapy, which occurs in a higher proportion of patients; or (3) lack of willingness to come in for monthly therapy. The anti-VEGF agents work well, and there is a reduction in the treatment burden after the first 12 to 24 months of treatment, but if the patient cannot make it through those first 12 to 24 months of more frequent therapy there is often going to be chronic low-level edema. We know from the RISE and RIDE trials that if the edema is undertreated, if the macula stays edematous, the

probability of visual improvement diminishes over time.

***RT*:** When and why would you consider use of steroids in patients with DME?

Dr. Eichenbaum: Practically speaking, steroids are particularly important for patients with DME who are noncompliant with regular anti-VEGF injection therapy. Noncompliance, it should be noted, is a big reason why many patients develop uncontrolled diabetic center-involved edema in the first place. Many patients who are unwilling to undergo monthly anti-VEGF therapy are on dialysis, have ulcers or other nonhealing wounds, and have a host of other systemic issues going on at the same time. To my way of thinking, this is a primary reason to think about adding a steroid, especially 1 that has sustained release and is therefore not as dependent on patient compliance or associated with a high incidence of severe intraocular pressure elevation. If the patient cannot or will not return for frequent future visits, whether or not that is because he or she is under a huge burden of health care utilization, there has to be something on board to control the edema. Another practical in-the-clinic characteristic that affects my decision to use steroids is lens status. I am more likely to inject a steroid earlier in a pseudophakic patient.

The rationale for using steroids in patients with DME is that, at a microbiologic level, diabetes is a lot more than a VEGF-driven disease like an acute vein occlusion or age-related macular degeneration. There are many inflammatory factors, interleukins, and adhesion molecules in

EXAMPLE CASE

A 66-year-old white man with a history of diabetic macular edema first diagnosed in 2011 presented to my office. He had previously been treated with laser and unspecified injections in both eyes.

I started the patient on monthly anti-VEGF therapy in his left eye with ranibizumab (Lucentis, Genentech) in July 2013. The patient subsequently received 12 ranibizumab injections through August 2013 with no tolerance for extension of the interval. I continued the patient on monthly injections.

In April 2014, the patient underwent cataract extraction with placement of an intraocular lens, after which visual acuity in the left eye improved to 20/20. In August 2014, however, acuity dropped to 20/40 and there was a mild increase in central edema despite ongoing monthly anti-VEGF therapy with ranibizumab (Figure 1). The patient reported to me that he had grown frustrated with the monthly injections, especially because of the loss of acuity.

In September 2014, the patient chose to receive a dexamethasone intravitreal implant (Ozurdex, Allergan) after imaging showed continued progression of the edema despite another injection the month before (Figure 2). The intraocular pressure (IOP) at that time was 14 mm Hg. During a follow-up examination in October 2014, the patient reported a subjective improvement in acuity and decreased metamorphopsia. The ophthalmic examination revealed stable Snellen acuity at 20/40. The examination and optical coherence tomography showed resolution of the edema and a mild epiretinal membrane (Figure 3). The IOP in the left eye of this patient had risen 20 mm Hg. However, despite the IOP rise, no antihypertensive therapy was prescribed and the patient is scheduled to return in 1 month for evaluation of the treatment response and for an additional IOP check.

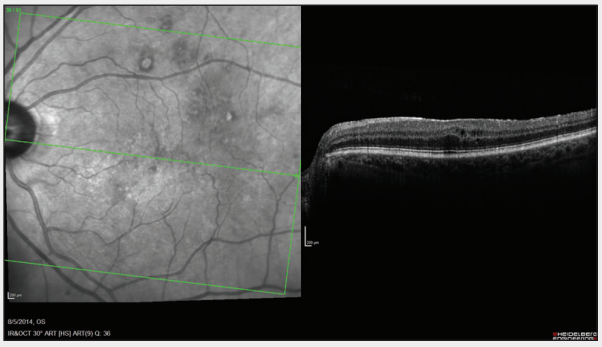
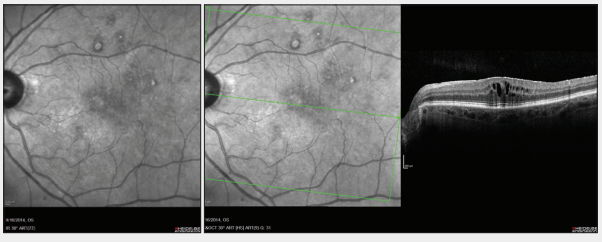


Figure 1.



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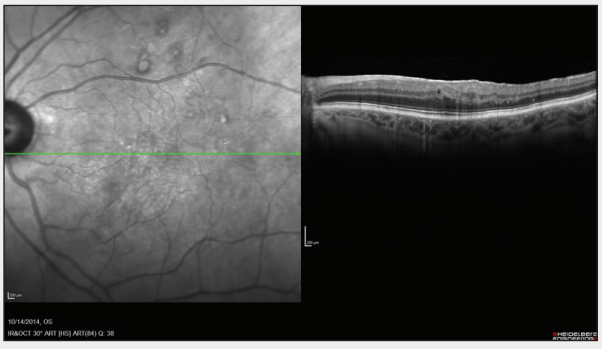

Figure 3.

ADDING CONTEXT TO SAFETY CONCERNS

About a third of patients in the MEAD trial developed a rise in intraocular pressure (IOP) after receiving a dexamethasone intravitreal implant (Ozurdex, Allergan), but what is the clinical significance of the IOP elevations observed in the clinical trial and in real-world practice, and how should this alter the management of patients? In an attempt to add context to the safety concerns associated with the implant, *Retina Today* interviewed Michael Levitt, MD, a glaucoma specialist in Tampa, Florida, and David Eichenbaum, MD, who contributed the retina specialist's perspective on this important topic.

***Retina Today*:** How significant is an IOP elevation in a nonglaucomatous eye into the 25 to 30 mm Hg range?

Michael Levitt, MD: In a nonglaucomatous eye, a rise of that magnitude is not a concern as long as the pressure is being checked. If there are other risk factors that lead the treating physician to think there may be potential to damage the optic nerve, a topical antihypertensive can be added. But in looking at the MEAD data, where about a third of patients had an IOP elevation, only 1 patient required incisional glaucoma surgery, so I do not think is an overwhelming concern.

***RT*:** Does this change at all in a patient with diabetes who also has glaucoma? Is it feasible to offer the implant to patients with a known history of glaucoma?

Dr. Levitt: There were patients enrolled in the prospective MEAD trial and retrospective SHASTA trial who received the dexamethasone implant despite concomitant glaucoma. As with all glaucoma patients, risk stratification is important. There are 3 things to key on: (1) the optic nerve appearance and the integrity of the nerve fiber layer; (2) the visual fields, assuming the visual fields are not affected by something else and are interpretable; and (3) the age of the patient. A 90-year-old with a cup-to-disc ratio of 0.6 is not too concerning, but a 55-year-old with a cup-to-disc ratio of 0.95 is a different story. A steroid, regardless of its formulation or mechanism of delivery, might not be my first choice if there was something else I could do for that patient.

David Eichenbaum, MD: A lot of patients with diabetes who come into retina clinics are in their 50s to 60s, many will be Hispanic or black, many will have vascular disease, and some will have coexisting glaucoma that is being controlled with 1 or more drops. Is there a role for pretreating patients with certain risk factors for glaucomatous progression? Or would you suggest waiting to see if there is a steroid response before initiating treatment?

Dr. Levitt: I think it is important to look at how far along the patient is on the medication spectrum in treating his or her glaucoma before needing incisional surgery. What I mean by that is, if the patient is using 1 medication, he or she is far from the maximum tolerated topical medication before needing incisional glaucoma surgery. However, if you have a patient already on 4 topical eye drops to get to the target IOP, and the glaucoma is only minimally controlled, then I might be more concerned, because the next step is trabeculectomy or a tube. Obviously we would rather not have to go there.

I would not pretreat with a topical antihypertensive, especially when thinking about the dexamethasone implant. Even with triamcinolone (Kenalog-40, Bristol-Myers Squibb), there is only about a 50% chance of developing elevated IOP, and studies with the dexamethasone implant suggest a rate of about 25% to 30%. Although that is high, there are still 70% of patients who do not have a pressure rise. Putting them on another medication may not harm them, it would counteract the elevation of pressure, but it does not reduce the likelihood of becoming a steroid responder.

Dr. Eichenbaum: I think that is an important point that most of us in the retina world do not think about: The current thinking on steroid responders is that, if a patient is a steroid responder, he or she will be a responder regardless of whether a second drop is used or not. On top of that, because the rate of IOP increase is lower and more predictable with the dexamethasone implant than with triamcinolone, you may not have to pretreat patients with an antihypertensive.

What if a patient does have a pattern of increases in IOP after receiving intravitreal steroids? Should we talk with that patient about getting a topical medication prophylactically at the time of injection?

Dr. Levitt: I think in that situation it might be a good idea to consider topical medication, and certainly if there is a history of response to the dexamethasone implant in particular.

***RT*:** Is there a role for a steroid challenge for patients who might be at risk for a response?

Dr. Levitt: I do not think it is necessary. You may consider it in a patient with advanced glaucoma in whom you really wanted to use a dexamethasone implant. But the vast majority of patients have mild to moderate glaucoma, and if you look at the data, there is only a 25% to 30% risk of elevation

ADDING CONTEXT TO SAFETY CONCERNS (Continued)

and only 1 patient in MEAD had to go to a surgical intervention. In theory, it might make sense to use prophylactic antihypertensives in academic medicine, but in practice I do not think it would be necessary.

Dr. Eichenbaum: Does optical coherence tomography (OCT) have a role in stratifying the risk to the optic nerve? A lot of retina specialists will take an OCT to evaluate the nerve. I think the problem with that, however, is that they do not know how to correlate it because, in retina, we usually do not use visual field machines frequently to follow and treat glaucoma, and we do not often have years of longitudinal pressure readings on the patient. What do you think? Is there a role for a baseline optic nerve OCT or is it not useful data?

Dr. Levitt: I do not think it is garbage data, but I also do not think you can make a decision based on an OCT of the optic nerve rim by itself. There are limitations inherent to each platform that can be used to image the optic nerve. For instance, the normative databases on most machines are not huge, and many devices arbitrarily set the location of the nerve fiber layer. So, if you take an OCT and it is "abnormal," how does that change your information?

Dr. Eichenbaum: Sometimes retina specialists I talk to take an OCT of the optic nerve to see whether it is "safe" to elevate the pressure.

Dr. Levitt: There really is not any good data that you can accurately predict progression in a glaucoma patient with OCT, but if you phrase the question as "how much nerve is there left?" it gets a little interesting. If the cupping is advanced, I would argue against the value of an OCT image. Once someone has a 0.9 cup-to-disc ratio, I rarely do an OCT because it really does not add any information. If the cup-to-disc is 0.9 to 0.95, you do not need an OCT to make a diagnosis of glaucoma. I think you need a good evaluation of the eye and hopefully visual fields if you have them.

Dr. Eichenbaum: Visual fields and an evaluation by a glaucoma specialist might be a good referral in patients with a high suspicion of undiagnosed or undertreated glaucoma prior to exposing them to the risk of intraocular steroids. Perhaps good advice to physicians thinking about adding a steroid to their armamentarium is that, if there is a question of a glaucoma diagnosis, or if there is uncertainty, it would be a good idea to refer for a baseline glaucoma evaluation based on the nerve appearance rather than relying on the OCT. Whereas most patients can tolerate these pressure rises, and even though many of the pressure rises that occur are not very clinically significant and can be treated appropriately with topical medications, it might be better to have an expert evaluation.

Dr. Levitt: There is no way you can just look at the optic nerve and judge how susceptible it is to an IOP elevation of a certain amount. Glaucoma is really a spectrum disease with a variable presentation, and so 2 identical patients with the same cup-to-disc ratio may respond differently to a steroid. It is difficult if not impossible to tell who will respond, so working in conjunction with a glaucoma specialist who has a lot of experience in risk stratification of these patients might be prudent. The other advantage to this is that, if the patient does ultimately require intervention of some sort, you are already working with a glaucoma specialist. The pressure rise and its attendant potential to cause irreversible damage can happen rapidly, so it is a good idea to work closely with someone if you do not have a glaucoma specialist in your office already.

Dr. Eichenbaum: What about the systemic health of patients in the context of glaucoma? Are patients with diabetes and glaucoma more likely to have glaucoma progression if they have poor systemic glycemic control?

Dr. Levitt: That is seen as a weak risk factor. The relationships between diabetes and glaucoma and between hypertension and glaucoma are not well understood or established.

Dr. Eichenbaum: There is a much more established role of systemic health in diabetic macular edema (DME). If one can improve the overall health of the patient, one will probably reduce the patient's treatment burden and exposure to VEGF, steroids, laser, and incisional surgery.

Dr. Levitt: How do you work with the primary care physician to ensure the systemic health is being monitored?

Dr. Eichenbaum: I send letters to the primary care physician to keep him or her informed, and, in return, I ask for lab results and I encourage patients to share lab results with me. I do not make any specific medical suggestions based on the labs, but teaching patients to know their hemoglobin A1C and lipid levels is a way to engage them in their care and call them to account. Occasionally, I will call the primary care physician or endocrinologist to talk about progression of disease, because progression of disease is an indication of loss of systemic control. The other time I will call the primary physician

ADDING CONTEXT TO SAFETY CONCERNS (Continued)

is when a pregnant patient is developing progression to neovascular diabetic proliferation, because I really cannot use anti-VEGFs routinely in that patient population.

***RT*:** Are there risk factors in a patient that would steer you away from steroid use altogether?

Dr. Levitt: For anybody who has severe optic nerve head cupping or is on the verge of needing incisional surgery, I would think twice about using a steroid. Certainly this would be true in those who have increased risk factors for being a steroid responder: anyone who has primary open-angle glaucoma and who has responded to steroid previously, who has a family history of steroid response, or who is on maximum medical therapy. The decision really relies on risk stratification, and advanced cupping and maximum medical therapy are 2 big risk factors in my mind. For a patient with both of those, if there is another way to treat, then I would steer away from steroid.

Dr. Eichenbaum: I think a good summation of the glaucoma risk is that, even with repeated doses—in the MEAD trial there were a little over 4 mean treatments given over 3 years, and in the SHASTA trial there were about 4 to 5 mean injections given—the safety of the dexamethasone implant from a glaucoma perspective is consistent, and it does not become more of an issue the more injections are given. If you have a close working relationship with a glaucoma subspecialist, you may be able to treat even glaucoma suspects with fewer injections overall, or if they do not respond to anti-VEGF therapy you can add the steroid and manage the pressure. But it sounds like we are both saying that vigilance is important.

Dr. Levitt: Agreed.

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addition to VEGF and related vascular proteins affecting the pathogenesis of DME.

The injectable suspension of triamcinolone acetonide (Kenalog-40, Bristol-Myers Squibb) used to be my go-to agent in these cases, but I backed away from that primarily because of the risks of poorly predictable pressure elevations. Plus, it hazes patients' vision because it is a suspension. I moved away from triamcinolone as soon as anti-VEGF agents became widely used.

However, the availability of the dexamethasone intravitreal implant (Ozurdex, Allergan) has changed my thinking, because it has controlled pharmacokinetics and a predictable release of steroid attributable to the biodegradable Novadur implant. Now, if I have a patient who does not do well with monthly visits or cannot tolerate monthly visits for the first several months, there is a role for dexamethasone therapy in that patient.

***RT*:** Does your thinking change at all for patients with chronic or recalcitrant edema?

Dr. Eichenbaum: There is some literature supporting the notion that patients with chronic edema may have a disease process that is more inflammatory than vascular, so the addition of a steroid may come sooner for a patient with center-involving chronic edema. Most of the patients with DME I see do not have chronic edema, so I am upfront in telling them that they are going to need a lot of anti-VEGF shots in the first 1 to 2 years if the plan is to utilize anti-VEGF monotherapy. I give these patients a trial with anti-VEGF injections without laser, but if the patient has recurrent or persistent center edema and cannot or will not come in for that first 12 to 24 months of higher-burden anti-VEGF therapy, then adding the dexamethasone implant is a reasonable choice.

***RT*:** What do you use to determine the efficacy of treatment response? Do you rely more on functional correlates such as change in visual acuity, or is the anatomic response more important?

Dr. Eichenbaum: I treat toward vision improvement. The OCT is a guide, and it is helpful to know the anatomic response; I want to reduce the burden of the overlying pathology to the give the patient the best chance of a functional improvement. However, as we know in many components of medicine, structure and function do not always align, and I am primarily concerned with visual acuity improvement and vision maintenance more so than with a bone-dry macula. I do go for both, and I will change the treatment plan to dry the macula, but functional vision improvement is my primary goal.

***RT*:** Are there differences in the steroid formulations currently available for use in clinical practice?

Dr. Eichenbaum: There are differences, and they are quite significant. One of the big problems I have with triamcinolone in this indication is that, because it is a suspension, the actual drug volume being injected is unknown. Therefore, the risk of steroid-induced side effects is also unknown because the dose is irregular and the pharmacokinetics are irregular.

In a simple example, if I have a patient whose intraocular pressure (IOP) rose to 30 mm Hg after an injection, I would not really be able to predict if the patient would have a similar response or if the IOP would go up to 35 or 40 mm Hg with the next injection. There is published data showing that the actual injected dose of the triamcinolone suspension is variable in the real world.

With the dexamethasone intravitreal implant, what you get is a predictable and repeatable dose response with regard to increased IOP changes. That is a tremendous benefit from a safety standpoint, and the efficacy seems to be parallel if not slightly longer in duration than triamcinolone.

Another advantage of the dexamethasone implant is that it reduces the treatment burden, and that means not just reducing the number of injections, it also means reducing the patient's burden of coming to the office. The reason I withhold the dexamethasone implant as an initial treatment is that I want to get to know the patient and the eye(s), and steroid injection does have some risks that anti-VEGF injection does not. I want to know if he or she will come back for follow-up.

If patients are having trouble with follow-up or do not want to come in for regular injections early in their treatment, I tell them I can give them the dexamethasone implant as an option to reduce their overall treatment burden.

***RT*:** It has been suggested that there are different pharmacokinetics among the steroid formulations in addition to a difference in mechanism of delivery. What is the "bolus effect" and what are the implications for safety?

Dr. Eichenbaum: The bolus effect describes a sudden burst following the injection followed by a taper thereafter. There is a bolus effect of triamcinolone or triamcinolone acetonide injectable suspension (Triesence , Alcon), with an initial jolt of steroids and rapidly reduced effect thereafter. With the dexamethasone implant, the Novadur polymer component, which dissolves to glycolic acid and water, is biodegradable; as it degrades, it effects a steady and predictable release of steroid over time. As a result, there is a much more predictable steroid response.

There may not be that initial punch up front,,but often, in real-world settings, this implant is going to be used as 1 element of combination therapy. When used with anti-VEGF injections, the result is a rapid antiangiogenic effect up front combined with durability in treating the inflammatory component with steroid. The dexamethasone implant by itself will deliver a more sustained effect than a bolus injection, but in the context of combination therapy it starts to make even more sense.

***RT*:** What do you tell patients about the safety of the dexamethasone implant?

Dr. Eichenbaum: There are 2 things, really, to be concerned about with the dexamethasone implant: cataract formation and IOP elevation. In the MEAD study, a significant number of patients developed cataracts, and IOP elevation occurred in about a third of patients. These are real, and the discussion of potential side effects has to occur with each and every patient. However, I do believe there is important context to add to both of these items.

There was an appreciable risk cataract progression, especially with multiple injections, in the MEAD trial. There is often an improvement in acuity with cataract extraction that far exceeds baseline visual acuity, and this was shown in the group requiring cataract surgery in the MEAD trial, where the dexamethasone implant was used as monotherapy. I think we can extrapolate from that data that cataract extraction can lead to very good results in patients who are phakic and require steroid therapy as part of a combination therapy approach, as many patients in the clinic will have the dexamethasone implant as part of a treatment regimen with anti-VEGF injections and/or laser as well.

As for IOP response, that 33% incidence of IOP response sounds concerning, but there is important context to that figure as well (see Sidebar). First of all, that IOP response is less significant than we might expect compared with a drug like triamcinolone. Second, a great number of the IOP elevations among subjects in MEAD were subclinical events, meaning they were self-limiting, transient, or otherwise required no action. We have to remember that it was a clinical trial, so the investigators had to report any IOP elevation and lump it into 1 category of "IOP elevation." Third, even cases in which IOP rose to a concerning level were largely treatable with a single antihypertensive medication. Only 1 patient in the MEAD study required glaucoma surgery.

***RT*:** What do the major clinical trials (MEAD, SHASTA) say about the most likely postinjection timeframe for an IOP elevation to occur?

Dr. Eichenbaum: The interval is well studied. In the MEAD and SHASTA trials, the increase in IOP was most likely to occur around 6 to 8 weeks after the injection. When I inject patients with the dexamethasone implant, I bring them back in 6 to 8 weeks for a pressure check.

***RT*:** What role does the systemic health of patients have in managing their DME?

Dr. Eichenbaum: Paying attention to the systemic health of patients is crucial for 2 reasons. First, in my thinking, the steroid has an especially important role in the patient who has a history of an acute thromboembolic event. I do think about the systemic health of the patient with respect to antiangiogenics. If the patient has had an acute event, I tend to steer clear of anti-VEGF injection, especially if there was a heart attack, stroke, or amputation. The level of systemic distribution of anti-VEGF agents after local injection to the eye is controversial, and there are not good data among patients with DME to parse out the potential risk in patients with recent acute events. The fact that many patients with DME already have a vascular component to their overall disease process leads me to operate on the side of caution. Local injection of a steroid will have some level of systemic distribution, but vascular pathology in the human body would potentially be much less affected by a steroid compared with an antiangiogenic agent.

The other reason I pay attention to the systemic health is that it affects both the systemic and ocular health of that patient. As retina specialists, our purview is the ocular health of the patient, but we are also physicians first, and if we can encourage a patient to attend to his or her blood glucose levels, we are helping that patient along the path to better overall health. Yet there are ocular implications here as well. As I alluded to earlier, poor systemic control is a primary reason patients develop ocular consequences of their disease. Patients have to pay attention to their blood glucose and blood pressure, otherwise there could be chronic or worsening edema despite treatment. Study after study shows that this persistent edema can rob patients of the ability to ever recover visual acuity. Overall improvement in systemic health is how patients see well for decades; the few months to a year during which patients undergo intensive treatment with a retina specialist is really about affording the patient a chance to tune up his or her systemic health to ensure life-long good vision. ■

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