THE EVOLVING LANDSCAPE OF DIABETIC MACULAR EDEMA MANAGEMENT

An interview with David M. Brown, MD; and Baruch D. Kupperman, MD, PhD
The introduction of new treatment options for diabetic macular edema (DME) has raised the bar on visual acuity and anatomic gains retina specialists can provide their patients. Diabetic retinopathy, however, is a disease filled with complexities and there are multiple targets that can be addressed to improve outcomes. An additional confounding factor is that these targets respond differently depending on the patient being treated.

There are several developments that are expected to come to fruition in 2014, and many more on the horizon. With this in mind, New Retina MD spoke with 2 retina specialists who have a high volume of patients with diabetes, David M. Brown, MD, and Baruch D. Kuppermann, MD, PhD, to gain insight on how their management of these patients is changing.

**New Retina MD:** When you see patients with diabetes, what is your approach to determining what to do next?

**David M. Brown, MD:** When a patient with diabetes comes into my office, I want to know his or her systemic health, which includes HbA1c levels, blood pressure, lipid profile, and any systemic medications the patient is on. These facts must be established no matter what treatment decisions I make. I need this information to help educate the patient on what he or she can do systemically to help the eye.

Next, I attempt to establish the status of the eye. In my opinion, widefield angiography is critical for evaluating the amount of capillary nonperfusion and microaneurysms, as well as the status of the edema.

**Baruch D. Kuppermann, MD, PhD:** Diabetes is a complicated disease and each patient is different, so there is no one correct approach. There is more individualization in therapy for patients with diabetes than in any other disease that we treat. I consider the status of the disease and whether the underlying proliferative diabetic retinopathy (PDR) is mild or more severe. I also consider whether the patient has been treated previously, along with his or her HbA1c and metabolic control.

It is not often that we talk about the systemic health of patients, but this is an important discussion, particularly in patients with diabetes. There are many factors in play with these patients and it is critical to know where they stand systemically and to discuss with patients how they can help their eye health with their lifestyle choices.

**NRMD:** How has the availability of anti-VEGF agents and steroids changed your approach to treating DME?

**Dr. Brown:** The anti-VEGF clinical trials demonstrated an average of 15 letters gained, and patients continued to do well with more injections over time. Unlike in other diseases, like age-related macular degeneration (AMD), the vision did not regress. In patients with diffuse edema, there is not much of a choice in how to treat; we have to give these patients anti-VEGF injections early and often to quiet the edema. The RISE and RIDE studies demonstrated that waiting 2 years to address edema is too long. The visual acuity gains achieved with ranibizumab (Lucentis, Genentech) were not nearly as robust as in the patients who were treated early.

In regard to steroids, I use these as a second-line treatment for DME, and mostly in patients who I am not worried about cataract formation.

**Dr. Kuppermann:** I have a very similar approach to treating DME, but I use intravitreal steroids frequently. Many of the patients in whom I use steroids have chronic DME, but I also have found that ethnicity plays a role. I have a lot of Latinos in my practice and I find that I do not get the response from anti-VEGF injections that was seen in the RISE, RIDE, VIVID, and VISTA clinical trials. I usually start my patients out with 3 to 6 monthly injections with anti-VEGF. When it becomes available, I will inject the dexamethasone intravitreal implant (Ozurdex, Allergan) in eyes in which the visual acuity does not change or if there is persistent fluid. When the fluocinolone acetonide implant (Iluvien, Alimera) becomes available, I would not implant it immediately after a nonresponse to anti-VEGF injections, because I want to evaluate how steroids work first with the dexamethasone implant because it is a shorter acting steroid. If I can inject a dexamethasone implant every 6 to 9 months with success then I will stay with this strategy. If, however, I have to inject a dexamethasone implant every 3 months, I will consider the fluocinolone implant due to its longer release of steroid. I will continue to treat this way over the next 1 or 2 years until I can manage the backlog of patients with chronic DME for whom we have not had success. As more people have access to earlier treatment with anti-VEGF, hopefully we will see fewer patients with chronic treatment-naïve DME.

One of the true advantages with the drug delivery systems is that they work well in vitrectomized eyes. Often we are faced with the consideration of whether to surgically remove the hyaloid in patients with DME, and the sustained-delivery implants do not require the vitreous for a reservoir. Although patients who have undergone vitrectomy can still receive anti-VEGF injections with some success, the half-life is reduced once the vitreous is gone.

**NRMD:** Is there still a significant role for laser?

**Dr. Brown:** The mainstay of treatment for diabetes since the ETDRS has been laser, which provided small gains—only 20% of participants in the study gained 6 letters of vision after treatment. The main reason that laser was considered the standard of care was because only about 10% of patients in the ETDRS study lost 3 lines of vision. The algorithm
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–Baruch D. Kuppermann, MD, PhD

has been to laser to the point where the patient’s vision improves but not so much that they would lose vision.

Laser is still an appropriate choice for patients with focal areas of circinate rings or big areas of microaneurysms that are not near the fovea. We have started using the Navilas navigated laser system (OD-OS), using fluorescein angiography to target microaneurysms in concert with the system’s eye tracker. We are currently participating in a clinical trial, TREDME (clinicaltrials.gov/show/NCT01934556), which is designed to test this laser system in conjunction with ranibizumab (Lucentis, Genentech) versus ranibizumab monotherapy for DME to evaluate whether combination therapy can reduce the frequency of injections required without compromising visual acuity gains.

The fluorescein angiography on the Navilas allows us to see at least 3 times more microaneurysms than we can see with a contact lens, allowing us to treat without collateral damage. My personal hypothesis is that when a patient is treated with anti-VEGF injections, the leakage may subside, but the microaneurysms do not go away if laser is not applied. This is a proof-of-concept trial with only 150 patients, so a larger clinical trial will be needed to confirm our results.

Dr. Kuppermann: I still use laser and have been experimenting with micropulse laser, which has yielded good effects with no damage that I can see. I do not yet have a handle on the role that micropulse laser will play, but it is an interesting concept.

Dr. Brown: Micropulse is an interesting concept, but the biggest problem that I have with it is that everyone who uses it does so with different parameters. This makes it difficult to get a good grasp of the best way to perform the treatment.

Diabetic macular edema, by its very nature, is a complicated disease. Systemic factors, such as those related to metabolism, fluid, and blood pressure, play a role in DME, so it is often hard to tell what treatment is effective. It is difficult to know how to titrate best for micropulse and which wavelength is most effective.

Dr. Kuppermann: There is definitely still a role for focal laser in combination with anti-VEGF agents. Theoretically, the leakage can be diminished with an anti-VEGF agent and that treatment supplemented with laser. I think there is a subset of patients who inherently will not respond as well to anti-VEGF agents, and for these patients I may add steroid.

Dr. Brown: If a patient has peripheral ischemia and neovascularization, I will apply panretinal photocoagulation (PRP). When the dexamethasone implant is approved, however, it will be my first-line therapy for patients with proliferative DME prior to applying PRP, because the steroid helps suppress the inflammatory macular edema that is created by laser.

NRMD: A part of the DME discussion has revolved around the differences between this disease and AMD, the difference in patient profiles, and the difference in response to therapy when considering the health of patients with diabetes. A smaller part of this discussion involves the safety of long term injections of anti-VEGF agents. Is there any cause for concern when applying therapies for this more vulnerable patient population?

Dr. Kuppermann: With any disease, we have to be conscious of the safety profiles of our treatments to ensure that we are not hurting our patients. It is true that some patients with diabetes are more likely to have concomitant conditions as a result of their systemic disease. There have been data presented that suggest the available anti-VEGF agents have different effects on systemic VEGF levels, but this issue is controversial and I do not think we have enough information at this point to come anywhere near a conclusion. We know that steroids cause cataracts and IOP rises—how these effects balance out against the benefits will help determine the appropriateness of their use whether in bolus injection or via sustained-delivery implants.

Dr. Brown: For some of my patients who have chronic edema, there is not enough anti-VEGF in the world to reduce their edema and these are the patients who will benefit from the dexamethasone implant. I use it off-label for many of my patients who fit this profile, and although it is expensive, it works, and patients tend to not mind paying for something that works at this stage in their disease. In fact, the copay for injections of ranibizumab for 3 months would be about equal to the out-of-pocket cost for the dexamethasone implant. I prefer the idea of the dexamethasone implant rather than injecting triamcinolone acetonide because the implant delivers a lot of steroid faster in a pulsing fashion, improving the side effect profile.

NRMD: Do you actively comanage patients with diabetes along with patients’ primary care doctor, endocrinologist, or diabetologist?

Dr. Brown: My approach is not really comanagement as much as providing education and keeping all parties in the loop. It is the patients’ and their primary care doctors’ job to figure out the best way to manage their HbA1c levels and...
blood pressure; it is my job to stress to the patient that it is worth it to go through this every-minute, everyday struggle to maintain these levels.

**Dr. Kuppermann:** I agree. One thing that I am always struck by is only a small percentage of my patients even know their HbA1c numbers. They know they are being tested, they know that the doctor tells them they are in a good range or not, but they do not know the exact figures. I encourage them to be aware of their current status and to know what the goal is, because this knowledge will help drive their behaviors. This is one thing that I am surprised does not seem to be impressed upon them by their primary care doctors as heavily as it should.

**Dr. Brown:** What has helped me the most is to devise a simple way of telling patient how their systemic health relates to the overall picture. I tell patients that hemoglobin exists throughout the entire body and that in the average person, sugar adheres to about 5% of hemoglobin. Although 7% sounds good, it is not just 2% more, but 40% more. For every point that the blood sugar levels can be lowered, the incidence of retinopathy is lowered 28%. Patients can become discouraged if they are at 9% because it seems impossible to achieve 6%, but I tell them that if they can get to even 8%, it will lower their risk of worsening retinopathy by 28%. This encouragement seems to help many of my patients.

**Dr. Kuppermann:** I sometime speak in thirds and quarters rather than percentages because it can seem more tangible. But overall, I have the same approach when talking to patients. I tell patients not to be discouraged, and I agree that explanation and encouragement helps; however, it is interesting to me that many of our patients are not focused on their blood sugar levels.

**Dr. Brown:** It really is a team approach. Hopefully patients are hearing the same message from their podiatrists who are cutting off toes and the renal specialists who are hooking them up to shunts.

**NRMD:** What can we look forward to in new developments in the treatment of DME?

**Dr. Brown:** This is going to be a big year based on the assumption that we will have 3 new products approved for DME. Aflibercept (Eylea, Regeneron) will represent an additional anti-VEGF option and we will also have the results from the Diabetic Retinopathy Clinical Trials Network Protocol T study in late 2014 or early 2015, which will provide insight into how ranibizumab, bevacizumab (Avastin, Genentech), and aflibercept compare to one another in terms of efficacy and safety for the treatment of DME. We will also most likely see the US Food and Drug Administration approvals of the dexamethasone intravitreal implant and the fluocinolone acetonide implant. The introduction of these products into our algorithm for treatment will be exciting and rewarding. There are many therapies that are in the pipeline that will hopefully continue to increase the number of patients for whom we can offer better outcomes.

**Dr. Kuppermann:** Now that we have a foundation in which we can control edema and improve visual acuity, the next step is to look at other pathways, such as Tie-2. There are multiple trials exploring either Tie-2 or angiopoietin-2 agonists. There are other studies looking at antiinflammatory agents outside of steroids, and basic science is moving toward clinical trials that may give us even more options beyond anti-VEGF and steroids.

A whole other area that is emerging is the role of the vitreo-macular interface and the hyaloid. Surgery to remove taught hyaloid can be successful in resolving DME, and in the future, pharmacologic vitreolysis may be another option to alter the course of diabetic retinopathy in terms of inhibiting the progression of nonproliferative disease to proliferative.

All of this is years down the road, but the innovation is impressive when you consider that even just 3 years ago, we only had focal laser, which has minimal effects on visual acuity gains.

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