Status of Sustained-release Steroids for Diabetic Macular Edema

WITH DAVID S. BOYER, MD

Retina Today: Where do corticosteroid sustained-release devices fit in the treatment armamentarium for diabetic macular edema (DME)?

David S. Boyer, MD: Anti-VEGF therapy is extremely effective in treating DME, at least in the short term.[1] However, some patients do not have a full response or take a long time to respond to anti-VEGF therapy, and these patients might be able to achieve improved visual acuity if their edema could be resolved earlier with more aggressive treatment. Diabetic eye disease is truly multifactorial, including a significant inflammatory component in DME.[2] This is in contrast with age-related macular degeneration (AMD), in which inflammation plays a relatively small role, except in the initiation of the process of neovascularization.[3] Anti-VEGF therapy is able to control the edema in AMD fairly well. But in DME, anti-VEGF therapy alone does not always control it. Because of its multifactorial nature, the use of steroids of any type can be advantageous in the paradigm of treatment of DME.

Because of the long-acting nature of durable steroid implants, patient selection must be fairly rigorous. This is particularly true with the fluocinolone acetonide implant (Iluvien, Alimera Sciences), which provides sustained delivery of the drug for up to 3 years. In the FAME studies, in phakic patients, over 3 years there was an 80% to 90% chance of cataract development.[4] Therefore, you might not want to put this long-acting delivery system into a young person with a clear lens. Also in those trials, filtering surgery to lower intraocular pressure (IOP) was needed in 4.8% of patients receiving the low-dose implant. Therefore this might not be the best option in a patient who has an existing issue with IOP control, because you will not have the reserve option of topical therapy to address IOP rise due to the implant.

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On the other hand, the dexamethasone implant (Ozurdex, Allergan) is much shorter acting, with a duration of action of approximately 3 to 4 months. This has advantages and disadvantages. One advantage is that it can be use intermittently as needed. Also the safety profile is more favorable; at 36 months, the incidence of cataract formation is about 60% to 70%, and incisional glaucoma surgery was needed in very few patients: 0.3%.[5,6] Generally, elevated IOP with the dexamethasone implant can be controlled with topical or systemic antiglaucoma medication. The implant has US regulatory approval for use in treatment of retinal vein occlusion and noninfectious posterior uveitis.

The device is potent and provides a fast response, and its treatment effect can be fairly long-lasting, although not on the order of the fluocinolone implant. In vein occlusions the effect lasts 2 to 3 months, sometimes longer. In uveitis it can provide a nice treatment response for up to 6 months. In diabetes, my clinical impression is that the treatment effect is on the order of 3 to 4 months.

A phase 3 clinical trial of the dexamethasone implant in patients with DME has been conducted (the MEAD study), and the results have been presented,[7] but the data have not yet been published so I cannot share details. I will say that in that study, the dexamethasone

implant demonstrated a rapid and durable treatment benefit in patients with DME, and that it was safe and well-tolerated in observations over a period of 3 years.

Multiple serial implants did not seem to cause a continued increase in IOP, so it does not appear to have a cumulative effect. But certainly with multiple implants the risk of cataract development increases over time.

The long-lasting implants have distinct advantages over intravitreal injection of triamcinolone acetonide. The biggest advantage is the low increase in IOP with the dexamethasone implant compared with triamcinolone, with which the steroid response is totally unpredictable. It is important to note that the dexamethasone implant does have a bolus effect, although not as pronounced as that of intravitreal injection of triamcinolone. The effect of the implant does diminish over a period of time, so it's not a constant release mechanism. The fluocinolone implant has more of a chronic release mechanism, with delivery lasting 2 to 3 years.

There is another fluocinolone intravitreal steroid implant, the Retisert (Bausch + Lomb), which is sutured in the posterior segment in a surgical procedure. That device has been shown to deliver steroid for up to 3 years in patients with noninfectious uveitis, the indication for which it is approved. The incidence of glaucoma is high, and cataract is almost ubiquitous. For a patient with chronic uveitis, that kind of safety profile might be justified, but it would not be recommended for patients with DME.

RT: You mentioned use of multiple implants in MEAD. What can you tell us about repeated use of the implant in real-life practice?

Dr. Boyer: In the MEAD study, the implants were given no more frequently than every 6 months. The most a patient could get was 7 implants over the 3-year study. In the real world, in practice, you may be giving these implants more frequently early in the treatment course and less often later, probably combining it with laser and with anti-VEGF therapy.

The dexamethasone implant can be given fairly frequently. For CRVO it can be given every 4 or even 3 months without an apparent cumulative effect.

In real world practice for patients with DME, we will have to wait and see how it is going to play a role. It will not be a primary treatment because of the side effect profile compared with anti-VEGF therapy, but it will be an additive alternative for patients who do not experience a good response to anti-VEGF treatment. As you know, it can take anti-VEGF therapy a long time to achieve improvement in vision in DME; visual acuity continues to

improve over a 16- or 17-month period, unlike in AMD, in which vision improves in 3 to 4 months and then begins to plateau. So the addition of the dexamethasone implant in patients who do not respond well initially to anti-VEGF therapy can be beneficial.

The dexamethasone implant can also be beneficial in patients undergoing laser. The PLACID study compared the implant plus laser to laser with sham implant in patients with DME.[8] More patients achieved an initial 2-line gain of visual acuity with the implant-laser combination than with laser alone.

So I think in the real world physicians will find multiple uses for the dexamethasone implant to reduce DME more rapidly in combination with anti-VEGF therapy, and in some cases it may prove as efficacious as or more efficacious than using anti-VEGF on a monthly basis.

RT: What about systemic control? What role does that play in managing DME?

Dr. Boyer: Probably the most important thing we can do as physicians is explain to the diabetic patient that tight control of blood sugar, blood pressure, and lipids can significantly reduce DME, significantly reduce patients' need for laser, and even, over a long period of tight control, reverse some of the changes in the eye.

It is common for ophthalmologists, especially retina specialists, to sit in front of the computer and show patients imaging results that illustrate their changes. We explain that these changes can cause visual loss if the patient doesn't get his or her diabetes under control. That is a wakeup call in many cases for patients because they can actually see the damage in front of them, whereas they cannot see the damage being done in their heart or their kidneys. They hear the numbers, but they feel fine and it doesn't make the same impression. The eye physician can use this information to emphasize how important systemic control is.

We can also alert the patient's internist that the systemic control may not be optimal, that there may be other factors they need to control for, perhaps sleep apnea or some medication interaction. As physicians, we need to be asking questions about what medications the patient is taking and help the treating physician by emphasizing how important control of blood pressure and blood sugar is.

RT: The reason we bring up systemic control is the recent finding that, in patients with diabetes, bariatric surgery plus 3 years of intensive medical therapy resulted in better outcomes than medical therapy alone, with superior glycemic control and weight reduction.[9]

Dr. Boyer: That is correct. More than 90% of these obese patients with uncontrolled diabetes, after undergoing surgery, had glycemic control without the use of insulin.

There are several bariatric procedures. In this study, patients were randomly assigned to Roux-en-Y gastric bypass, sleeve gastrectomy, or medical therapy. Patients in both surgical groups had greater reductions in weight from baseline, with a 24.5% reduction in the gastric-bypass group and 21.1% in the sleeve-gastrectomy group, as compared with 4.2% in the medical-therapy group ($P <$ .001 for both comparisons).

Bariatric surgery is a major lifestyle event, and I would leave those decisions up to the patient in consultation with his or her primary physician and surgeon. It is encouraging that we now know there are treatments available for obese people who just cannot control their disease any other way. If we can get these types of people—who are obese, cannot lose weight, are not exercising, and have poor eating habits—to lose weight by any means that is a benefit, but bariatric surgery seems to have an additional component that is causing some hormonal or endocrine changes, allowing patients to become nondiabetic. It is very interesting, very exciting for patients with uncontrolled diabetes. ■

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