Intravitreal Implant Options for Patients With Diabetic Eye Disease

The following articles discuss the use of the two intravitreal corticosteroids approved for treatment of diabetic macular edema, as well as other indications.

Treatment of DME With the 0.19-mg Fluocinolone Acetonide Implant

By Scott W. Cousins, MD

As part of this review of sustained-release steroid implants, I will discuss the 0.19-mg fluocinolone acetonide intravitreal implant (Iluvien, Alimera Sciences) in the setting of managing patients with diabetes. But first, let us acknowledge that the multiple comorbidities associated with diabetes often limit patients’ abilities to receive the optimal course of anti-VEGF therapy that adequately manages diabetic macular edema (DME).

LIMITED RESPONSE TO ANTI-VEGF TREATMENT

Unfortunately, some patients with DME—even those who adhere to the burdensome treatment regimen of anti-VEGF injections—do not respond to anti-VEGF treatment. In fact, in the DRCR.net Protocol I study, approximately 50% of patients did not adequately respond to anti-VEGF therapy. A post-hoc analysis of the DRCR.net Protocol I study demonstrated that this disparity is not a function of the number of injections a patient received, as inconsistent responders and nonresponders averaged more injections than responders. The recently published DRCR.net Protocol T study data also illustrated that many (Continued on page 58)

Dexamethasone Intravitreal Implant: Pharmacology and Clinical Update

By Yoshihiro Yonekawa, MD; and Jeremy D. Wolfe, MD

The dexamethasone intravitreal implant (Ozurdex, Allergan) is approved by the US Food and Drug Administration (FDA) for the treatment of diabetic macular edema (DME), macular edema associated with retinal vein occlusion (RVO), and noninfectious posterior uveitis. It delivers a potent corticosteroid via a biodegradable polymer that gradually disintegrates into water and carbon dioxide while the medication is released in a sustained and safe dose over several months.

Corticosteroids have a broad spectrum of biologic action, including down-regulation of inflammatory cytokines, endothelial adhesion molecules, and growth factors such as VEGF, giving this class of drug anti-inflammatory, anti-vascular permeability, and antiangiogenic effects, respectively. These molecular mechanisms are dysregulated in many vitreoretinal diseases to varying degrees, making corticosteroids effective treatment options for a number of disease states. However, not all corticosteroids are the same, and their varying chemical structures result in different clinical properties. (Continued on page 55)
“In our practice, we most commonly use the dexamethasone intravitreal implant in patients with DME and RVO who respond poorly to anti-VEGF agents.”

**WATER SOLUBILITY**

Triamcinolone is minimally water-soluble and becomes a depot of crystals that release steroid, resulting in a long half-life. Conversely, dexamethasone has two additional hydroxyl groups in the acetone functional group, making it significantly more hydrophilic compared with triamcinolone and fluocinolone. Water solubility has two benefits: a shorter half-life, which makes it amenable as a sustained-release medication by allowing controlled and steady release; and less aggregation onto ocular structures such as the trabecular meshwork, which appears to result in lower rates of intraocular pressure (IOP) elevation.

**IOP CONSIDERATIONS**

When using intravitreal corticosteroids in our practice, we ensure that patients have a clear understanding of the risk for cataract progression and possible ocular hypertension. We find that patients are less concerned about cataract, viewing cataract surgery as a matter of when rather than if. Most patients are accepting of drops for ocular hypertension, but glaucoma surgery is always an undesirable course. Among the various intravitreal steroid options, the dexamethasone intravitreal implant has a favorable IOP profile.

In the MEAD trial, incisional glaucoma surgery was required in 0.6% of patients with DME treated with the 700-μg dose of the dexamethasone intravitreal implant. By comparison, 33.8% of patients treated with the 0.59-mg fluocinolone acetone implant (Retisert, Bausch + Lomb), 4.8% of patients treated with the 0.19-mg fluocinolone acetone implant (Iluvien, Alimera Sciences), and 1.2% treated with 4.0 mg of intravitreal triamcinolone required incisional glaucoma surgery in the respective large clinical trials evaluating these therapies in patients with DME.

As reflected in the MEAD study results, we find that IOP elevation with the dexamethasone intravitreal implant is mild and predictable. These elevations peak at 6 to 8 weeks after injection and then return to close to baseline by 3 or 4 months. In our practice, we have not experienced the so-called staircase progressive IOP elevation with repeated injections as is sometimes seen with triamcinolone. IOP elevation with triamcinolone also appears to be less predictable in terms of timing (several days to many months) and severity (between 70-80 mm Hg). On the other hand, 89% of patients who developed ocular hypertension at any point during the MEAD trial did so within the first three injections, and 99% of patients who developed ocular hypertension did so within the first four injections. This means that if a patient has not demonstrated an IOP spike by the third or fourth injection, it is unlikely that he or she will do so after future injections.

**CLINICAL APPLICATION**

Clinical application of the dexamethasone intravitreal implant is broad, and many studies have reported on uses beyond FDA-approved indications. Its efficacy has been demonstrated in use for macular edema after cataract surgery, retinal detachment repair, epiretinal membrane peeling, radiation maculopathy, retinitis pigmentosa, and in combination with anti-VEGF agents for neovascular age-related macular degeneration. Pediatric uses have also been described.

In our practice, we most commonly use the dexamethasone intravitreal implant in patients with DME and RVO who respond poorly to anti-VEGF agents. The literature supports the efficacy of the dexamethasone intravitreal implant as rescue treatment for recalcitrant DME as well as branch and central RVO. The controversial question is when to switch to the dexamethasone intravitreal implant—in other words, after how many ineffective anti-VEGF injections do you consider a patient to be a poor anti-VEGF responder?

**SWITCHING THERAPY**

It has been demonstrated that if central retinal thickness does not decrease by at least 25% after the first anti-VEGF injection in patients with RVO, the patient is likely to be a poor responder regardless of the number of injections. Similar findings have been reported in DME patients (Shah AR, et al, unpublished data). We are therefore comfortable switching to the dexamethasone intravitreal implant relatively early, and these patients often respond well (Figure).

**VITRECTOMIZED EYES**

There is controversy over the faster clearance of anti-VEGF agents and triamcinolone in eyes that have undergone vitrectomy. The dexamethasone intravitreal implant, as well as other sustained-release products, have theoretical advantages in vitrectomized eyes because cleared corticosteroid is immediately replaced by more elution of medication. Studies have shown the efficacy of the dexamethasone intravitreal implant in vitrectomized eyes with uveitic cystoid macular edema, DME, and RVO.
ADVANTAGE OF A DRAWBACK

The dexamethasone intravitreal implant and the two fluocinolone acetonide implants are all sustained-release devices, but they differ in their durations of action. The fluocinolone implants were designed to last for 3 years. Significantly fewer injections are required, but, once the implant is placed, the eye is committed to potentially 3 years of steroid exposure and accompanying IOP complications. On the other hand, the dexamethasone intravitreal implant, while initially designed to last for 6 months, usually provides clinically meaningful effects for 3 to 4 months based on our experience with refractory edema. The drawback of requiring more injections becomes an advantage when managing IOP issues, because the steroid effects subside sooner.

CONCLUSION

The dexamethasone intravitreal implant is an efficacious steroid delivery system that provides sustained release of a safe and potent steroid in a controlled and predictable manner. It has played an important role in our practice’s treatment paradigms for retinovascular disorders and posterior uveitis.

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2. Fuller M, Bandello F, Belfort R, et al. Dexamethasone intravitreal implant in patients with macular edema related...
patients did not adequately respond to anti-VEGF therapy. In Protocol T, approximately half of the patients had persistent edema and required rescue laser at week 24 after monthly anti-VEGF injections.

**FAME STUDY OVERVIEW AND RESULTS**

The 0.19-mg fluorocinolone acetonide intravitreal implant was studied in two randomized, multicenter, double-masked, parallel-group, 36-month clinical trials (FAME A and FAME B) in patients with DME previously treated with laser. Entry criteria required at least one previous laser treatment and BCVA between 19 (20/50) and 68 (20/400) letters in the study eye as measured on the Early Treatment Diabetic Retinopathy Study chart. Patients with a history of uncontrollable intravitreal pressure (IOP) elevation with steroid use that did not respond to topical therapy were excluded from participation. The most common AE was cataract, with 82% of patients in the FAME A study and 78% in the FAME B study. Cataract surgery was performed in 80% of these patients, compared with 50% in the control group. The most common AE was cataract, with 82% of patients in the FAME A study and 78% in the FAME B study. Cataract surgery was performed in 80% of these patients, compared with 50% in the control group.

**Safety**

Safety was studied over 36 months in the FAME trials. Adverse events (AEs) were consistent with other ocular corticosteroids and were manageable in nature. The most common AE was cataract, with 82% of patients in the fluorocinolone acetonide treatment group reporting cataract compared with 50% in the control group. Cataract extraction was performed in 80% of these patients, compared with 27% of the control group. Increased IOP was reported in 20% of the fluorocinolone acetonide patients compared with 4% in the control group; however, only 5% of patients experiencing increased IOP required incisional surgery. The study

(Continued from page 54)
DISEASE MEDIATION

It is well established that DME is multifactorial and that it may be mediated by multiple cytokines—not strictly VEGF. Differential responses to immediate versus delayed therapy in the RISE and RIDE trials indicated that delayed treatment, which perhaps allowed other disease-mediating factors to contribute to disease progression, resulted in poorer visual outcomes at multiple time points. A similar differential response to therapy was observed in the FAME study. A subanalysis of FAME data examined response based on duration of DME diagnosis and compared patients with short-duration DME (< 1.73 years) with patients with long-duration DME (> 1.73 years). In patients with short-duration DME, the subanalysis showed that both control patients treated with standard of care (laser, anti-VEGF, and intravitreous triamcinolone acetoneon) and the 0.19 mg fluocinolone acetoneon–treated patients had similar outcomes: Approximately 25% of patients in each group achieved a 3-line improvement in BCVA at month 36. However, in patients with long-duration DME, the response in the standard of care control group was diminished, with only 13.4% of patients achieving 3 or more lines of BCVA improvement at month 36 compared with 34% of 0.19 mg fluocinolone acetoneon–treated patients gaining 3 or more lines (P < .001). Patients treated with 0.19 mg fluocinolone acetoneon in FAME responded similarly regardless of disease duration; however, the standard of care offered in the sham control group performed significantly worse in the long-duration disease group.

This clinical response reflects the differences in the retinal microenvironment. When patients with DME do not respond adequately to selective anti-VEGF therapy, it may indicate that multiple cytokines, not strictly VEGF, are the primary disease mediators. Duration of DME appears to influence this increase in cytokine activity. The differential treatment effect seen in long-duration versus short-duration DME in FAME appears to be related to the continuous delivery of low-dose steroid.

THE IMPLANT IN A NUTSHELL

When patients do not respond adequately to anti-VEGF therapy, it may be an indication that their disease has evolved into a more inflammatory-based state, thus requiring a shift in treatment paradigm. New multifactorial steroids are proving to be promising therapeutic options. The FAME study illustrated the potential value of continuous steroid therapy in long-term disease patient populations. The 0.19-mg fluocinolone acetoneon intravitreal implant received approval from the US Food and Drug Administration (FDA) in September 2014. The drug is indicated for patients who have been previously treated with a course of corticosteroids and who did not have a clinically significant rise in IOP. As a corticosteroid, fluocinolone acetoneon may address multiple cytokines.

The 0.19-mg fluocinolone acetoneon intravitreal implant is a nonbioerodible implant made of polyimide, the same nonbioerodable material used in the haptics of many intraocular lenses. The cylindrical implant measures 3.5 mm × 0.37 mm and holds 190 µg of fluocinolone acetoneon. A small 25-gauge needle places the device through the pars plana into the vitreous, creating a self-sealing wound and eliminating any need for tunneling. The implant delivers a continuous, low dosage (0.2 µg/day) over the course of 36 months. Fluocinolone acetoneon levels peak 1 week after implantation and level off by the third month.

CONCLUSION

As physicians come to better understand the nature of DME as the disease matures, they must calculate the burden that their patients feel, as frequent injections may present diminishing returns. Sustained-release steroid options have emerged as a viable and effective treatment option for patients with DME. In my practice, the 0.19-mg fluocinolone acetoneon intravitreal implant has shown positive outcomes since it received FDA approval, and I will continue to recommend it to patients with mature, multiple cytokine–mediated DME.

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