According to the American Diabetes Association, nearly 10% of the US population has diabetes, and this number rises to more than 25% among those 65 and older. These individuals are at an increased risk of developing eye problems. Between 2005 and 2008, 4.2 million (28.5%) Americans with diabetes aged 40 years or older had diabetic retinopathy (DR), which is the most common related eye condition and a leading cause of blindness in American adults. Diabetic macular edema (DME) can occur at any stage of DR. More than 560,000 Americans have DME and roughly 70% of people with proliferative DR will develop DME.

Because the incidence and prevalence of diabetes are on the rise, the incidence and prevalence of DME will also escalate. Thus, until a cure is discovered, patients and retina specialists alike must do all they can to prevent the disease, manage its signs and symptoms, and stop its progression. For retina doctors, that means keeping up to date on the latest treatments, techniques, and research to enhance the care they provide to their patients with DME. As part of that education, knowing what other clinicians are doing may provide valuable pearls that one may choose to adapt in one’s own treatment regimen.

This ongoing informational series provides insights from experienced retina specialists into the developing landscape of managing patients with DME. In Part 6 of the series, Anat Loewenstein, MD, of the Tel Aviv Sourasky Medical Center and Tel Aviv University in Israel, shares several cases in which she treated patients with DME using a corticosteroid implant.


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Treatment of DME With Steroids

A corticosteroid implant can be helpful in both treatment-naïve and previously treated patients.

BY ANAT LOEWENSTEIN, MD

Diabetic retinopathy (DR) affects one-third of people with diabetes mellitus. Of the many manifestations and complications of this disease entity, diabetic macular edema (DME) is the leading cause of vision loss among patients with DR. It is also a leading cause of visual loss in working-age populations.1

The pathogenesis of DME is multifactorial. Retinal capillary permeability increases significantly with breakdown of the blood-retina barrier, which leads to retinal edema.2,4 VEGF plays a major role in breakdown of the blood-retina barrier.5 It has also been shown that inflammation is an important factor in the process of DME development.6

TREATMENT OPTIONS

In recent decades, the treatment paradigm for DME has shifted, from focal/grid laser photocoagulation as the mainstay of treatment7 to newer treatment modalities, including anti-VEGF and corticosteroid therapies.8,9 Despite these advances in therapy, no single algorithm for the selection of patients and choice of therapeutic modality or regimen has been established. This article reviews evidence-based recommendations for the selection of treatment modality according to patient and disease characteristics and presents several cases from real-world encounters with diabetic patients.

Laser Surgery

Before the introduction of intravitreal corticosteroids and anti-VEGF drugs, macular laser photocoagulation was the mainstay of treatment for patients with DME.7 In focal/grid macular laser treatment, small laser burns are applied to leaking blood vessels in areas of edema near the center of the macula to slow the leakage of fluid and reduce swelling in the retina.

Anti-VEGF Therapy

Anti-VEGF drugs are injected to block VEGF, a growth factor that can encourage abnormal blood vessels to grow and leak fluid. Ranibizumab (Lucentis, Genentech), bevacizumab (Avastin, Genentech), and aflibercept (Eylea, Regeneron) are anti-VEGF drugs used in the treatment of DME.

Corticosteroids

Corticosteroids inhibit the expression of VEGF by the VEGF gene.6,9 This class of drug also has antiinflammatory properties related to its ability to interfere with regulatory components of gene expression and to inhibit the factors expressed by proinflammatory genes, such as tumor necrosis factor-alpha and other cytokines.10 Additionally, corticosteroids induce the expression of antiinflammatory factors.

For posterior segment applications, corticosteroids may be injected or implanted into the eye. They may be used as monotherapy or in combination with other drugs or laser surgery to treat DME. The dexamethasone intravitreal implant 0.7 mg (Ozurdex, Allergan) and the fluocinolone acetonide intravitreal implant 0.19 mg (Iluvien, Alimera Sciences) are biodegradable implants that release sustained doses of corticosteroid to suppress DME.

It is important to note that injections into the vitreous carry the risk of endophthalmitis, retinal detachment, eye inflammation, and increased intraocular pressure (IOP). In particular, injection of corticosteroids may lead to the development of posterior subcapsular cataracts and glaucoma and may increase the risk of secondary eye infections. It should also be remembered, however, that in most cases IOP elevation is easily controllable with pressure-lowering medications. Cataract surgery, too, can be performed with excellent visual outcomes.

PATIENT CASE NO. 1

A 65-year-old woman with significant DME presented with BCVA of 20/80 and central macular thickness (CMT) of 840 µm (Figure 1A). Because she did not want monthly injections, a dexamethasone intravitreal implant was administered as first-line treatment. For 4 months she responded very nicely with sustained reduction of CMT (Figures 1B and C), but the edema recurred (Figure 1D). A second dexamethasone implant was administered, and the patient responded just as she did to the first implant. This process was repeated two more times, and it was noted that, in this case of severe DME, each dexamethasone intravitreal implant lasted about 4 months. Nine weeks after the patient received her third dexamethasone implant she developed a nuclear and posterior subcapsular cataract. She underwent phacoemulsification with intraocular lens (IOL) implantation. Four weeks after the cataract procedure she received her fourth dexamethasone intravitreal implant. Five weeks after the patient received her seventh dexamethasone intravitreal implant, her BCVA was 20/100 and CMT was 179 µm (Figure 2).

In this case, with each implant the patient’s edema resolved and visual acuity improved. This case illustrates...
DME: Beyond the Clinical Trials

that there is potential to treat patients with severe DME using this corticosteroid implant.

PATIENT CASE NO. 2

A 71-year-old woman presented with prolonged DME and vitreomacular traction (VMT) in her right eye (OD). She had previously received focal laser treatment and multiple intravitreal injections of anti-VEGF agents (bevacizumab four times, ranibizumab six times) in the affected eye. Despite these treatments, DME persisted at presentation, with CMT of 446 µm and BCVA of 6/15 OD; in the left eye (OS), by contrast, CMT was 251 µm and BCVA was 6/6 (Figure 3).

At this visit, focal laser OD was repeated, but 5 weeks later CMT in this eye was 427 µm and BCVA was 6/18. At this time, the dexamethasone intravitreal implant was administered OD. In the contralateral eye, with BCVA of 6/12 and CMT of 293 µm, ranibizumab was administered.

At 3, 9, 14, and 18 weeks after the dexamethasone intravitreal implant OD, BCVA improved to approximately 6/8.5, and CMT was reduced to the range of 250 to 275 µm (Figure 4). The contralateral eye continued to have BCVA of approximately 6/6 after the ranibizumab injection.

By 23 weeks after the first dexamethasone intravitreal implant, DME returned OD, with CMT of 316 µm and BCVA of 6/9. A second implant was administered OD at this visit, and 5 weeks later CMT had returned to less than 250 µm. Still no action was taken in the other eye (Figure 5).

This pattern continued, with implants given every 20 to 30 weeks OD as signs of edema returned, and no intervention required OS. The lesson in this patient with bilateral DME is that different eyes—even in the same patient—can have different responses to therapy. The eye with mild VMT and severe, resistant DME showed a
The increase in mean IOP was seen with each treatment cycle, and the mean IOP generally returned to baseline between treatment cycles (at the end of the 6 month period).

**USE IN SPECIFIC POPULATIONS**

**Pregnancy Category C**

*Risk Summary*

There are no adequate and well-controlled studies with OZURDEX® in pregnant women. Animal reproduction studies using topical ocular administration of dexamethasone were conducted in mice and rabbits. Cleft palate and embryofetal death in mice and malformations of the intestines and kidneys in rabbits were observed. OZURDEX® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

*Animal Data*

Topical ocular administration of 0.15% dexamethasone (0.375 mg/kg/day) on gestational days 10 to 13 produced embryofetal lethality and a high incidence of cleft palate in mice. A dose of 0.375 mg/kg/day in the mouse is approximately 4 times an OZURDEX® dose of 0.7 mg/dexamethasone). A dose of 0.20 mg/kg/day on gestational days 7-18 produced intestinal anomalies, intestinal aplasia, gastroschisis and hypoplastic kidneys. A dose of 0.13 mg/kg/day in the rabbit is 3 times an OZURDEX® dose of 0.7 mg/dexamethasone.

*Nursing Mothers:*

Systemically administered corticosteroids are present in human milk and can suppress growth and interfere with endogenous corticosteroid production. The systemic concentration of dexamethasone following intravitreal administration of 0.7 mg dexamethasone (0.20 mg/kg/day) on a mg/m² basis. In rabbits, topical ocular administration of 0.1% dexamethasone throughout organogenesis (0.13 mg/kg/day, on gestational day 6 followed by 0.20 mg/kg/day on gestational days 7-18) produced intestinal anomalies, intestinal aplasia, gastroschisis and hypoplastic kidneys. A dose of 0.13 mg/kg/day in the rabbit is approximately 4 times an OZURDEX® injection in humans (0.7 mg dexamethasone) on a mg/m² basis.

**Pediatric Use:**

Safety and effectiveness of OZURDEX® in pediatric patients have not been established.

**Geriatric Use:**

No overall differences in safety or effectiveness have been observed between elderly and younger patients.

**NONCLINICAL TOXICOLOGY**

*Carcinogenesis, Mutagenesis, Impairment of Fertility*

No adequate studies in animals have been conducted to determine whether OZURDEX® (dexamethasone intravitreal implant) has the potential for carcinogenesis. Although no adequate studies have been conducted to determine the mutagenic potential of OZURDEX®, dexamethasone has been shown to have no mutagenic effects in bacterial and mammalian cells in vitro or in the in vivo mouse micronucleus test. Adequate fertility studies have not been conducted in animals.

**PATIENT COUNSELING INFORMATION**

**Steroid-related Effects**

Advise patients that a cataract may occur after repeated treatment with OZURDEX®. If this occurs, advise patients that their vision will decrease, and they will need an operation to remove the cataract and restore their vision.

Advise patients that they may develop increased intraocular pressure with OZURDEX® treatment, and the increased IOP will need to be managed with eye drops, and, rarely, with surgery.

**Intravitreal Injection-related Effects**

Advise patients that in the days following intravitreal injection of OZURDEX® patients are at risk for potential complications including in particular, but not limited to, the development of endophthalmitis or elevated intraocular pressure.

**When to Seek Physician Advice**

Advise patients that if the eye becomes red, sensitive to light, painful, or develops a change in vision, they should seek immediate care from an ophthalmologist.

**Driving and Using Machines**

Inform patients that they may experience temporary visual blurring after receiving an intravitreal injection. Advise patients not to drive or use machines until this has been resolved.

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**Figure 4. Patient Case No. 2.** After dexamethasone intravitreal implant OD, BCVA improves and CMT is reduced to the range of 250 to 275 µm for 4 months. The contralateral eye maintains good BCVA after one ranibizumab injection.

**PATIENT CASE NO. 3**

A 62-year-old diabetic man with a complex ocular history presented to our center. He had primary open-angle glaucoma in both eyes, for which he was taking multiple medications: a fixed combination of latanoprost and timolol maleate (Xalacom, Pfizer) plus brinzolamide (Azopt, Alcon). He had also experienced nonarteritic ischemic optic neuropathy in both eyes. On top of this, the patient had nonproliferative DR in both eyes. He also had DME OS, for which he had received multiple intravitreal injections of bevacizumab.

At the time of presentation, 6 months after his ninth injection of bevacizumab, the patient’s BCVA was 6/7.5, his CMT was 359 µm, and his IOP was 20 mm Hg. He was treated with three monthly doses of bevacizumab, but 5 weeks after the last dose his BCVA was 6/12, CMT was 386 µm, and IOP remained 20 mm Hg. He was then treated with three monthly doses of ranibizumab. Four weeks
After the last dose, he received three more monthly doses of ranibizumab, with little effect on BCVA or CMT.

At this point, despite the risk of elevating IOP in this patient with existing glaucoma, we decided to try the dexamethasone implant. Four weeks after administration of the implant, the patient’s CMT had decreased to 299 µm, BCVA was 6/10, and IOP was 20 mm Hg. At 10 weeks, these numbers were basically unchanged.

The lesson from this case is that every glaucoma patient is not a steroid responder. This patient with resistant DME had a good response to the dexamethasone intravitreal implant, with no additional IOP increase after the treatment.

**PATIENT CASE NO. 4**

A 67-year-old man with mild nonproliferative DR in both eyes developed moderate DME OD. The eye with DME was pseudophakic, and the contralateral eye had a cataract. In our effort to bring the DME under control, we treated with grid laser twice OD and administered eight intravitreal injections of bevacizumab. The DME persisted despite these treatments, with CMT of 577 µm and BCVA of 6/15.

At this point we elected to administer the dexamethasone intravitreal implant. The patient’s IOP was 12 mm Hg OD. Four weeks after the implant, CMT had decreased to 261 µm and BCVA improved to 6/10, but IOP had risen to 18 mm Hg. Five weeks later, the edema was still resolved, but the IOP had risen to 26 mm Hg, so treatment with timolol was initiated. Four weeks later (13 weeks after the implant), CMT was 255 µm, BCVA was 6/7.5, and IOP was 12 mm Hg. By 17 weeks after implantation, BCVA was still good, but edema was starting to return.

At 22 weeks after implantation, with CMT at 411 µm, and the edema again resolved. With continuation of the timolol, both IOP and DME remained under control for almost 5 months. The timolol was discontinued once the patient’s IOP normalized. A third dexamethasone intravitreal implant was placed 20 weeks after the second implant, and the status was maintained for another 20 weeks.

The lesson of this case is that steroid responders are often easy to treat. In this patient, resistant DME showed a good response to the dexamethasone intravitreal implant, and, even though there was a significant increase in IOP in response to the steroid, it was easily managed.

**CONCLUSION**

The pathogenesis of DME is complex, and there is no one treatment that works for every patient. The dexamethasone intravitreal implant can be a beneficial therapy for DME in both treatment-naïve and previously treated patients. The treatment effect of the implant lasts roughly 4 months, and side effects such as cataract and increased IOP can usually be managed easily.

That said, investigation of other potential treatment options is obviously warranted to optimize patient outcomes. Organizations such as the US National Eye Institute are conducting and supporting research on how to better detect, treat, and prevent vision loss in people with diabetes.

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**References:**


