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RETINA TODAY

PART V

DME RESOURCE CENTER:
BEYOND THE CLINICAL TRIALS

A comprehensive series on the implications of managing the ocular manifestations of diabetes in real-world settings.

Retina specialists are quite familiar with the diabetic patient population, as related eye conditions are frequently encountered. The most common of these conditions is diabetic retinopathy, which is a leading cause of blindness in American adults, thanks in part to diabetic macular edema (DME). Because the incidence and prevalence of this systemic disease are on the rise, retinal physicians will be treating a growing number of patients with DME.

Of course, treatment of DME is anything but straightforward. Ask three retina specialists and you may well get three different answers. Furthermore, new treatments and techniques that promise to improve patient outcomes are emerging. Data from clinical trials offer some insights but do not necessarily reflect real-world practice. For that reason, learning about what works for other physicians may be the best way to develop one's own approach to treating and managing patients with DME.

Over the course of this ongoing series, experts will explore the developing landscape of managing patients with DME. Here in part 5, Sanket U. Shah, MD, a third-year resident at Indiana University School of Medicine in Indianapolis, Ind., and Raj K. Maturi, MD, of the Midwest Eye Institute in Indianapolis, Ind., share a comparison of the results of two different treatments for DME in several patient cases.

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Dexamethasone Implant vs. Bevacizumab Injection for Treatment of DME

BY SANKET U. SHAH, MD, AND RAJ K. MATURI, MD

One in every 25 diabetic patients of age 40 or older experiences diabetic macular edema (DME).[1] Although there has been a paradigm shift in their management with the advent of anti-VEGF agents, a sizeable number of patients with DME are resistant to these agents despite frequent (monthly) intravitreal injections. Several recent studies have shown incomplete response to such agents despite rigorous study protocols, illustrating the problem of persistent DME.[2,3] The management of these patients is challenging and frustrating. We recently completed a study comparing the intravitreal dexamethasone implant (Ozurdex, Allergan) with bevacizumab (Avastin, Genentech) for such recalcitrant cases. The following three cases highlight some nuances in management of persistent DME.

CASE NO. 1

In this case, we treated a 69-year-old woman with a 6-year history of DME. She has had diabetes for a much longer duration, and it has remained poorly controlled. The patient's right eye received previous treatment with 36 intravitreal injections of bevacizumab, one intravitreal injection of compounded triamcinolone acetonide, and focal macular laser. In her left eye, she received 33 intravitreal injections of bevacizumab and two dexamethasone intravitreal implants. She presented with significant macular edema in both eyes (Figure 1).

As part of our study, we randomized each eye to a different treatment arm. We injected a dexamethasone intravitreal implant in her right eye, and her visual acuity improved significantly within the first month. At 2 months after implant, her visual acuity in the right eye had returned to baseline, and her optical coherence tomography (OCT) showed resolution of macular edema (Figure 1). The patient's contralateral (left) eye started off with a similar amount of edema but did not change much despite receiving three intravitreal injections of bevacizumab on a monthly basis. In fact, her OCT actually showed worsening of macular edema (Figure 1).

The patient returned for continued treatment, and, as per our study protocol, she received two additional

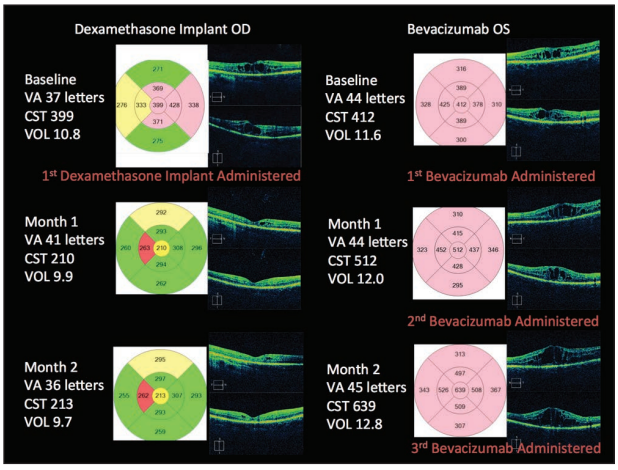

Figure 1. Case No. 1: OCT images of patient receiving treatment for DME.

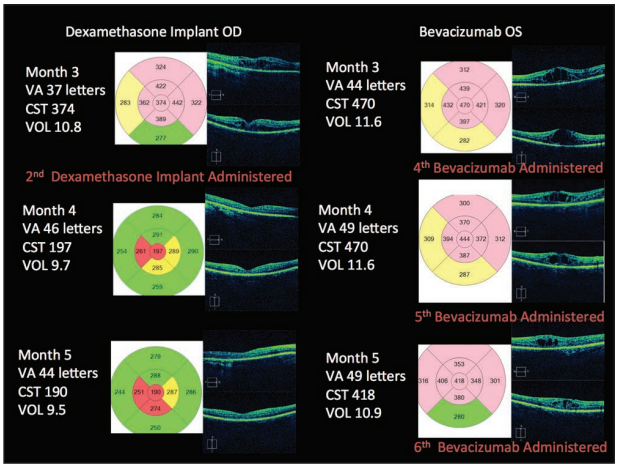

Figure 2. Case No. 1: Improvement seen with treatment in the patient's right eye, but her left eye remains unresponsive to treatment.

dexamethasone injections (one every 3 months) in her right eye and six additional bevacizumab injections (one every month) in her left eye. The macular edema in her right eye showed sustained improvement after the second dexamethasone implant administered at month 3 (Figure 2). By month 5, it was completely flat, and the

TABLE 1. CASE NO. 1: TREATMENT EFFECT ON VA AND DME

OD	VA (Snellen lines)	OCT CST (µm)	Treatment
Baseline	37	399	Dexamethasone implant
Month 1	41	210	
Month 2	36	213	
Month 3	37	374	Dexamethasone implant
Month 4	46	197	
Month 5	44	190	
Month 6	40	182	Dexamethasone implant
Month 7	52	195	
OS	**VA (Snellen lines)**	**OCT CST (µm)**	**Treatment**
Baseline	44	412	Bevacizumab injection
Month 1	44	512	Bevacizumab injection
Month 2	45	639	Bevacizumab injection
Month 3	44	470	Bevacizumab injection
Month 4	49	444	Bevacizumab injection
Month 5	49	418	Bevacizumab injection
Month 6	47	370	Bevacizumab injection
Month 7	48	446	

Abbreviations: CST, central subfield thickness; DME, diabetic macular edema; OCT, optical coherence tomography; OD, right eye; OS, left eye; VA, visual acuity

TABLE 2. CASE NO. 2: TREATMENT EFFECT ON VA AND DME

OD	VA (Snellen lines)	OCT CST (µm)	Treatment
Baseline	37	399	Bevacizumab injection
Month 1	41	210	Bevacizumab injection
Month 2	36	213	Bevacizumab injection
Month 3	37	374	Bevacizumab injection
Month 4	46	197	Bevacizumab injection
Month 5	44	190	Bevacizumab injection
Month 6	40	182	Bevacizumab injection, CEIOL
Month 7	52	195	Post-study dexamethasone implant
OS	**VA (Snellen lines)**	**OCT CST (µm)**	**Treatment**
Baseline	44	412	Dexamethasone implant
Month 1	44	512	
Month 2	45	639	
Month 3	44	470	Dexamethasone implant
Month 4	49	444	
Month 5	49	418	
Month 6	47	370	Dexamethasone implant
Month 7	48	446	

Abbreviations: CEIOL, cataract extraction with intraocular lens implantation; CST, central subfield thickness; DME, diabetic macular edema; OCT, optical coherence tomography; OD, right eye; OS, left eye; VA, visual acuity

macular volume was reduced. By month 7, her visual acuity had improved by 3 Snellen lines and her OCT results showed sustained resolution of edema (Table 1). On the other hand, despite six successive monthly injections of bevacizumab, the left eye had only 1 Snellen line of improvement in visual acuity and persistent macular edema on OCT (Figure 2).

CASE NO. 2

A 60-year-old man with a 3-year history of DME presented to our practice. He had previously received 25 intravitreal injections of bevacizumab, 11 intravitreal injections of triamcinolone, and focal macular laser in his right eye and, in his left eye, 26 intravitreal injections of bevacizumab, 13 intravitreal injections of triamcinolone, and focal laser.

As part of the study protocol, the patient's eyes were randomized to two study arms identical to the first case: the right eye to the bevacizumab arm and the left eye to dexamethasone implant arm. The patient was followed for 7 months. Despite seven injections of bevacizumab in the right eye, there was a significant amount of persistent DME at the end of the study. By comparison, the left eye, which received three dexamethasone implants over the 7 months, showed significant improvement of DME, although some edema persisted (Table 2).

CASE NO. 3

A 68-year-old woman with a 7-year history of DME received the following prior treatment: intravitreal bevacizumab (45 injections in the right eye, 44 in the left eye); intravitreal triamcinolone (multiple in each eye); and focal macular laser in each eye. She presented with significant edema, noted on both OCT (Figure 3) and fluorescein angiography.

The patient received a dexamethasone implant in her right eye at baseline, at which time her retinal central subfield thickness was 413 µm. At the end of 2 months, the edema had resolved (Figure 3). The left eye received three monthly injections of bevacizumab yet continued to have significant edema.

At month 3 (and after a second dexamethasone implant), the patient's

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 3 times an OZURDEX® injection in humans (0.7 mg dexamethasone) 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.

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 treatment with OZURDEX® is low. It is not known whether intravitreal treatment with OZURDEX® could result in sufficient systemic absorption to produce detectable quantities in human milk. Exercise caution when OZURDEX® is administered to a nursing woman.

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.

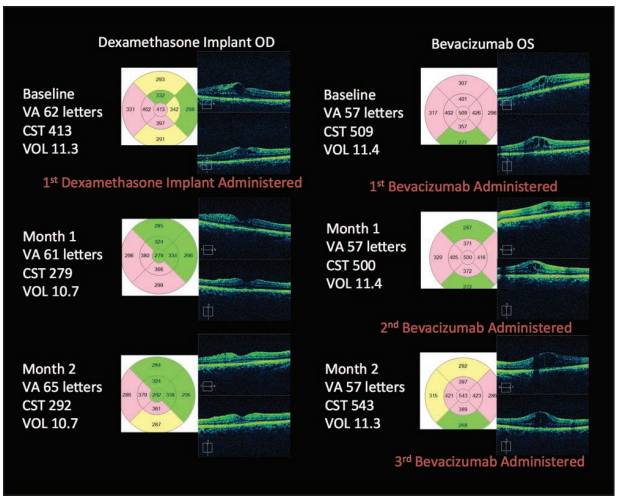

Figure 3. Case No. 3: Effectiveness of treatment with a dexamethasone implant (right eye) and bevacizumab injections (left eye) from baseline to month 2.

right eye showed continued flattening. Her left eye showed persistent edema despite monthly bevacizumab injections (Figure 4). At months 6 and 7, both eyes continued in the same pattern (Table 3). After three dexamethasone implants given 3 months apart, a 2.5-line improvement on the Snellen chart was noted for the patient's right eye. Conversely, visual acuity in the left eye improved by 1 line with the use of bevacizumab. Edema, however, persisted in this eye. Therefore, after the study, the patient's left eye was switched to receive dexamethasone implant, resulting in improvement of edema with a minimal improvement of acuity.

DISCUSSION

DME is a result of endothelial dysfunction, increased vascular permeability, and release of several cytokines. Currently, anti-VEGF agents are the first-line therapy—and the gold standard—for managing DME. Although these agents are effective in several cases, patients can be resistant to treatment, as illustrated in the three cases detailed in this article. It is thought that inhibition of VEGF alone is insufficient, and that other proinflammatory cytokines and pathways may play more important roles in such resistant cases. Corticosteroids have multiple mechanisms of action, including inhibition of VEGF synthesis and leukocyte migration, down-regulation of intercellular adhesion molecule-1 expression, antagonism of prostaglandins and other cytokines, and an antipermeability effect, thereby enhancing the barrier function of vascular tight junctions.[4]

The superiority of the dexamethasone implant over bevacizumab in macular edema control (noted in the previous cases) is thought to be related to its myriad mechanisms of action, as opposed to the sole action of VEGF. Few studies in the literature have compared these two agents. BEVORDEX, a randomized, controlled trial comparing dexamethasone implant and bevacizumab in

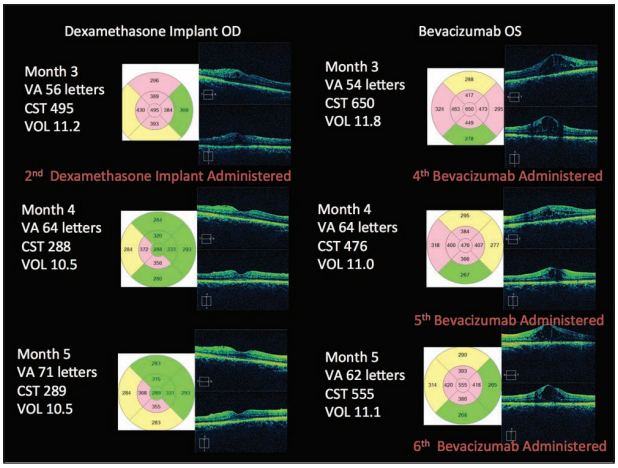

Figure 4. Case No. 3: After the administration of two dexamethasone implants, the patient's right eye shows improvement. Despite regular injections of bevacizumab, her left eye shows minimal improvement.

TABLE 3. CASE NO. 3: TREATMENT EFFECT ON VA AND DME

OD	VA (Snellen lines)	OCT CST (µm)	Treatment
Baseline	62	413	Dexamethasone implant
Month 1	61	279	
Month 2	65	292	
Month 3	56	495	Dexamethasone implant
Month 4	64	288	
Month 5	71	289	
Month 6	72	348	Dexamethasone implant
Month 7	73	289	
OS	**VA (Snellen lines)**	**OCT CST (µm)**	**Treatment**
Baseline	57	509	Bevacizumab injection
Month 1	57	500	Bevacizumab injection
Month 2	57	543	Bevacizumab injection
Month 3	54	650	Bevacizumab injection
Month 4	64	476	Bevacizumab injection
Month 5	62	555	Bevacizumab injection
Month 6	58	622	Bevacizumab injection
Month 7	62	595	Post-study aflibercept* injection

Abbreviations: CST, central subfield thickness; DME, diabetic macular edema; OCT, optical coherence tomography; OD, right eye; OS, left eye; VA, visual acuity
*Eylea, Regeneron

the treatment of DME resistant to macular laser, found similar visual acuity gains but significantly greater OCT macular thickness in dexamethasone-treated eyes.[5] The effect of a single dexamethasone implant was originally intended to last 6 months; however, several studies have shown its effect to last about 3 months, after which reinjection is required to sustain improvement.[6]

A video of Dr. Maturi presenting these cases can be found on *Retina Today's* DME Resource Center (www.retinatoday.com/dme-resource-center/) or by scanning this QR code.

Why the visual acuity improvement did not correspond to the macular edema reduction in the cases presented here remains uncertain, although it is most likely related to chronicity of macular edema. Several studies have shown that macular edema that persists for a prolonged period may result in chronic permanent damage to the retinal cells, limiting the potential for visual recovery, even if the edema were to resolve at that stage. Therefore, it seems prudent to try to flatten the macula faster, and, more importantly, as early in the disease process as possible. In our experience, when an eye fails to respond to anti-VEGF agents as expected (within the first 3-6 months), then we have a low threshold to switch to a different agent, such as the dexamethasone implant, with the goal of achieving macular deturgence at the earliest point in time. This threshold is even lower for pseudophakic eyes. An additional advantage is the need for fewer injections, and therefore fewer patient visits.

As we know, corticosteroid agents are not without attendant risks. Intraocular pressure elevation and cataract formation are the most notable side effects, for which we regularly monitor our patients started on dexamethasone implant therapy. In our experience, these side effects, although common, are effectively managed with topical glaucoma medications and cataract surgery, respectively. ■

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