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Retina Today

PART XII

DME RESOURCE CENTER: BEYOND THE CLINICAL TRIALS

An educational series on managing the ocular manifestations of diabetes in real-world settings.

Diabetic retinopathy is one of the leading causes of visual impairment in adults of working age.[1] One of the sources of visual impairment in diabetic retinopathy is diabetic macular edema (DME), a thickening of the macula that can occur at any stage of severity of diabetic retinopathy.[2] The pathogenesis of DME is multifactorial. Laser photocoagulation was long the mainstay of treatment for DME, and it is still the preferred treatment for non–center-involving DME.[1]

Recently, however, pharmacologic approaches to treatment of DME have increasingly gained acceptance and popularity. Intravitreal injection of an anti-VEGF agent has been found to be an effective treatment for center-involving DME, as well as an alternative therapy for proliferative diabetic retinopathy.[1,3] A recent meta-analysis of clinical trials found that the anti-VEGF agent ranibizumab (Lucentis, Genentech) alone, or ranibizumab plus laser, had better visual and anatomic outcomes than laser alone in the treatment of DME.

Anti-inflammatory drugs, specifically corticosteroids, have also been used in the treatment of DME. Intravitreal injection of triamcinolone acetonide has been used, but disappointing results in large-scale clinical trials, including frequent need for intraocular pressure–lowering therapies, dampened enthusiasm for this approach.[4,5] Long-acting, sustained-release steroid formulations have been developed in efforts to avoid the negative effects of bolus steroid injections. In the 3-year MEAD studies, the dexamethasone intravitreal implant 0.7 mg met its primary endpoint of improving visual acuity in patients with DME.[6]

In this installment of the DME Resource Center, Part 12, Jeremy D. Wolfe, MD, describes his experience in a small, short-term clinical trial directly comparing anti-VEGF and corticosteroid therapies in the two eyes of a series of patients with DME. He explores the possible reasons for the differences in outcomes observed in the trial.

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Case Prompts Comparison Trial of Two DME Management Modalities

BY JEREMY D. WOLFE, MD

This installment of the DME Resource Center is different from previous installments. Rather than start with background information on diabetic macular edema (DME) and then proceed to describe illustrative clinical cases, this time I will lead with a case presentation. Then I will describe the rationale, design, and results of a small investigator-initiated trial that my colleagues and I undertook based on our results with this particular patient.

CASE PRESENTATION

A 62-year-old man with type 2 diabetes mellitus presented in August 2013 with the chief complaint of decreased vision in both eyes. Visual acuity was 20/40 in the right eye (OD) and 20/30 in the left (OS). Optical coherence tomography (OCT) revealed center-involving DME in both eyes (Figure 1). Treatment was initiated with intravitreal ranibizumab (Lucentis, Genentech) injections in both eyes.

Two months later, the edema persisted in both eyes, although lessened, and visual acuity OD had improved somewhat to 20/30 (Figure 2). Treatment with ranibizumab was continued.

At 1 year later, in December 2014, DME was still present in both eyes, although it had improved from baseline (Figure 3), and visual acuity was still suboptimal, at 20/40 OD and 20/30 OS. At this visit the patient received his 12th injection OD and 14th injection OS.

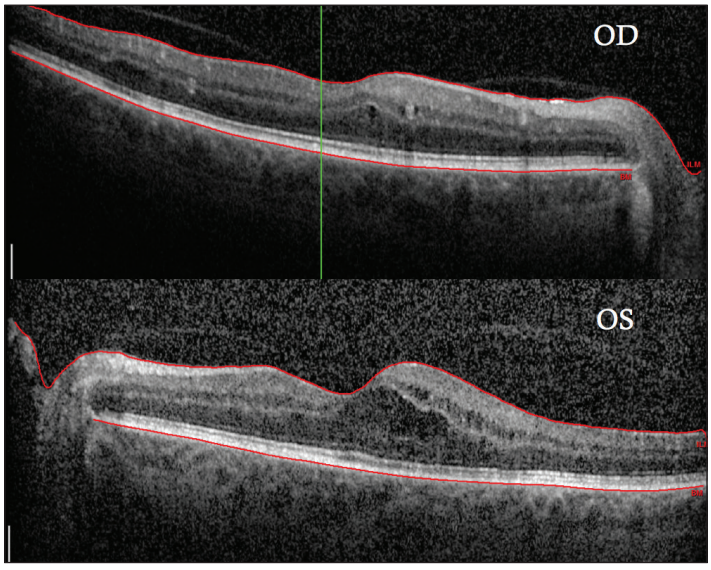


Figure 2. Two months later, the edema persisted in both eyes, although lessened, and visual acuity had improved somewhat OD.

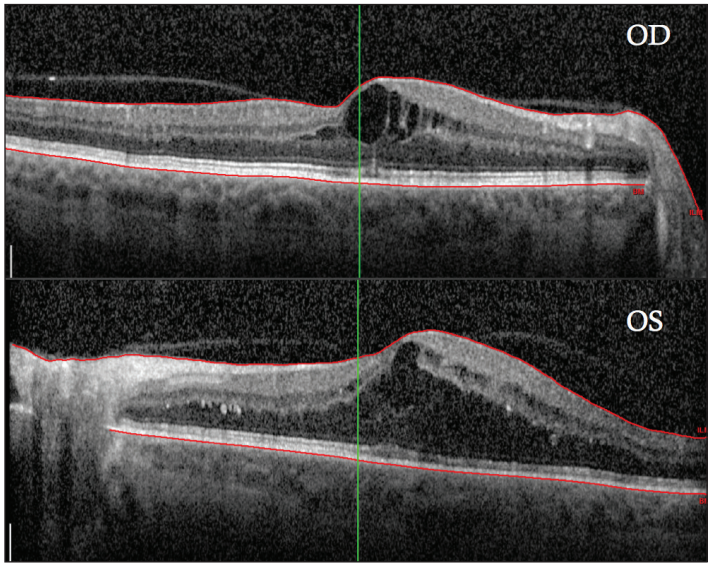


Figure 1. Center-involving DME in both eyes of a patient with diabetes mellitus. The patient was started on ranibizumab intravitreal injections.

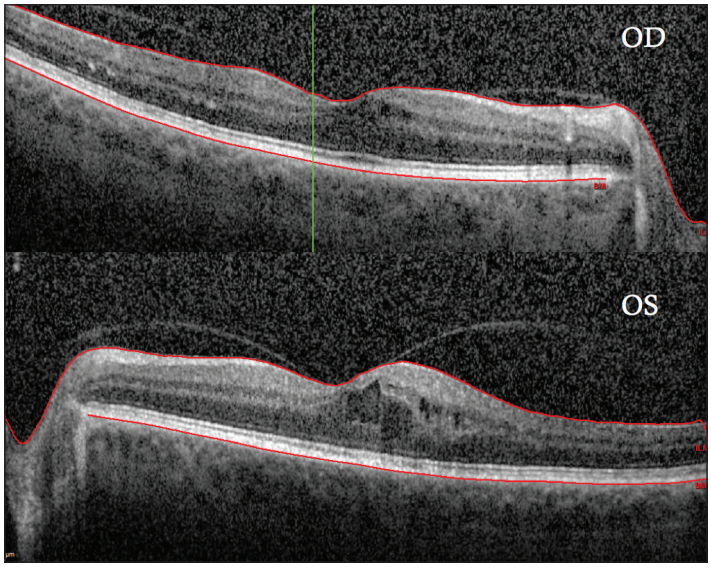


Figure 3. One year later, there was still DME in both eyes, although it had improved from baseline.

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.

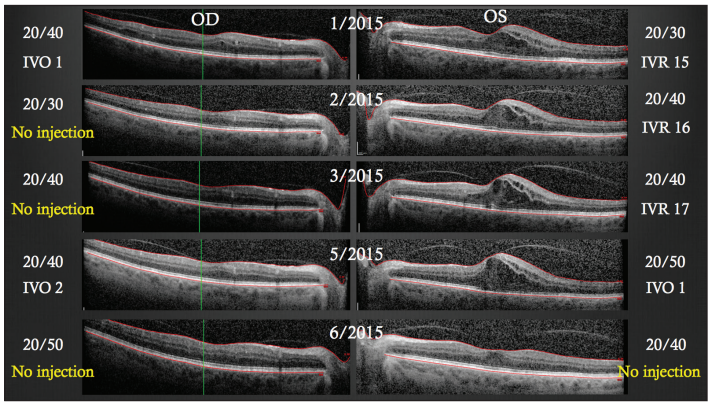


Figure 4. At the following visit, the patient was switched to the dexamethasone intravitreal implant (IVO) OD and continued on monthly ranibizumab (IVR) OS. The course of treatment over the next few visits is shown.

In January 2015, the patient was switched to the dexamethasone intravitreal implant 0.7 mg (Ozurdex, Allergan) OD and continued on monthly ranibizumab OS (Figure 4). There was improvement in the DME on OCT without subsequent injection OD for 3 months. The edema persisted OS, however, and visual acuity worsened in that eye. In May 2015, the patient received his second dexamethasone implant OD and was switched to the dexamethasone implant OS. The following month, OCT showed that the DME had resolved in both eyes (Figure 4).

In summary, this was a patient with persistent DME who reached a plateau in treatment with anti-VEGF therapy. He was switched to the dexamethasone implant in one eye, which showed improvement, and he was therefore subsequently switched to the dexamethasone implant in the other eye, which thereafter also improved.

CLINICAL TRIAL

Our experience with this patient led us to design a clinical trial comparing the dexamethasone intravitreal implant 0.7 mg with anti-VEGF therapy in matched eyes of the same patient. We enrolled 11 consecutive patients, none of whom had pre-

TABLE 1. CLINICAL TRIAL DEMOGRAPHICS

Sex	4 men, 7 women
Mean age	62 (range, 51-84) years
Diabetes type	All type 2
Lens status	8 pseudophakic, 3 phakic
Mean duration of DME before entering trial	19 (range, 5-50) months
Mean A1C (for 8 of 11 patients)	6.5 (range, 5.9-7.0) mg/dL
Mean No. anti-VEGF injections prior to entering trial	9

Abbreviations: DME, diabetic macular edema; A1C, glycosylated hemoglobin

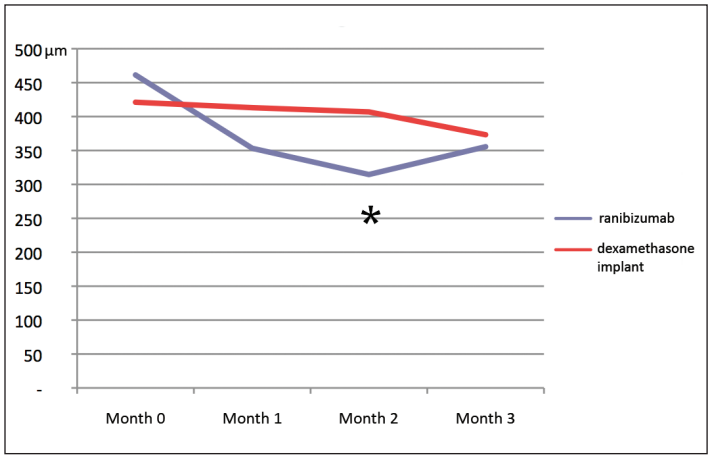


Figure 5. Mean improvement in CMT over time in 11 patients treated with ranibizumab in one eye (red) and the dexamethasone intravitreal implant in the other (blue). The area between the curves shows that greater anatomic response was seen in eyes receiving the dexamethasone implant.

viously received a dexamethasone intravitreal implant. All patients enrolled had previously received multiple injections of an anti-VEGF agent at regular intervals (every 4 to 6 weeks). All patients had had moderately successful response to treatment, with stable visual acuity but persistent DME. In other words, their response to anti-VEGF treatment had plateaued, as was observed in the patient described above.

The goal of the trial was to assess the short-term response to simultaneously treating one eye of each patient with ranibizumab and the other with the dexamethasone implant, with the treatment for each eye chosen at random for each patient. Patients enrolled had the same stage of diabetic retinopathy and equal degree of DME in each eye. They had a symmetric treatment history, with consistent dosing of anti-VEGF therapy, despite which they had similar persistence of DME in each eye.

Patient demographics are shown in Table 1. It is noteworthy that these patients had been diagnosed with DME a mean 19 months before enrollment in the trial and that they had received an average of nine anti-VEGF injections. Their type 2 diabetes was in general well controlled, with an average A1C of 6.5 mg/dL.

The baseline characteristics (Table 2) show that visual acuity was similar in both eyes of each patient, the central macular thickness (CMT) was slightly greater in the dexamethasone-treated eyes, and intraocular pressures (IOPs) were similar between the two eyes.

After random eye assignment, one eye of each patient continued monthly ranibizumab for 3 months, and one eye received the dexamethasone intravitreal implant. Monthly assessment at each visit included visual acuity, CMT, and IOP.

RESULTS

At 3 months, there was improvement in visual acuity and reduction in CMT in both the ranibizumab- and dexamethasone-

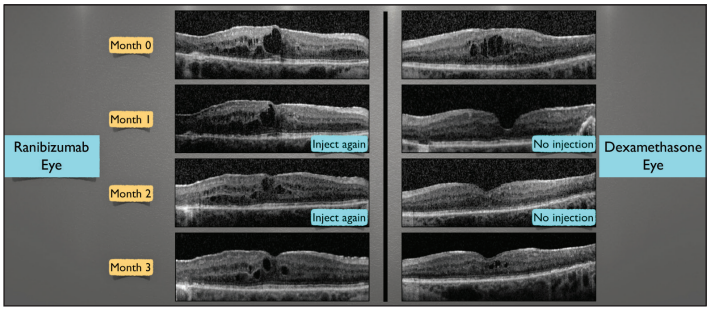


Figure 6. Serial OCTs illustrate the course of treatment of one patient in the study.

treated eyes (Table 2). The reduction in CMT was greater in the dexamethasone-treated eyes.

The graph in Figure 5 shows the improvement in CMT over time. The difference between eyes was statistically significant at 2 months. The area between the curves shows that there was better anatomic response in the eyes treated with the dexamethasone intravitreal implant.

At the conclusion of the study, patients were given the option to receive whatever treatment they wanted. Interestingly, eight of the 11 patients elected to have the dexamethasone implant in both eyes. Two patients chose to continue the study regimen, and one asked to have the treatments switched between the two eyes.

No serious complications were seen. There was a moderate increase in IOP (> 30 mm Hg) in the dexamethasone eye in two patients, which normalized by the 3-month study endpoint. No complications were seen in the ranibizumab eyes.

STUDY CASE EXAMPLE

The serial OCTs in Figure 6 illustrate the course of treatment of one patient in the study. It shows a reaction similar to that of the patient described above, with improvement in DME in both eyes,

TABLE 2. BASELINE CHARACTERISTICS AND RESULTS

	Ranibizumab Eye	Dexamethasone Eye
Mean VA, baseline	20/52	20/50
Mean VA, month 3	20/37	20/36
Mean CMT, baseline	421 µm	461 µm
Mean CMT, month 3 (difference from baseline)	373 (-48) µm	356 (-105) µm
Mean IOP (mm Hg), baseline	16.9	17.2
Mean IOP (mm Hg), month 3	16.1	19.0

Abbreviations: VA, visual acuity; CMT, central macular thickness; IOP, intraocular pressure

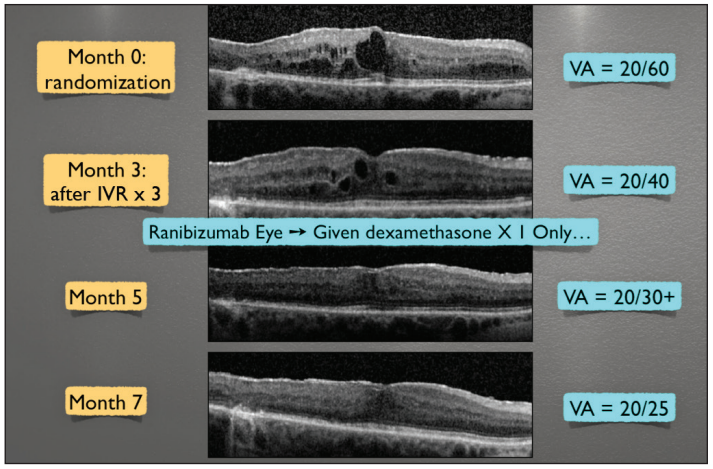


Figure 7. At the conclusion of the study, this patient elected to receive the dexamethasone implant in the eye that had received ranibizumab during the study, and edema subsequently improved.

but with the dexamethasone eye improving more quickly and with greater reduction in edema.

At the conclusion of the study, this patient elected to receive the dexamethasone implant in the eye that had received ranibizumab during the study. Figure 7 shows that after injection of the implant at month 4 the edema greatly improved.

CONCLUSION

There are many cytokines that contribute to DME. Cell-signaling molecules such as tumor necrosis factor-alpha (TNF-α), interleukin 1-beta (IL-1β), intercellular adhesion molecule 1 (ICAM-1), and others can contribute to capillary degeneration, pericyte loss, and vascular permeability.

Steroids attack many of the soluble cytokines responsible for multiple pathophysiologic changes seen in DME. By contrast, anti-VEGF therapies target only VEGF, which is an important molecule but only one among many that are affected in DME.[1-6]

Our experience in this small study suggests that there can be a difference in response to intravitreal injections based on the mechanisms involved in DME. In some cases, the steroid approach will have a greater effect.

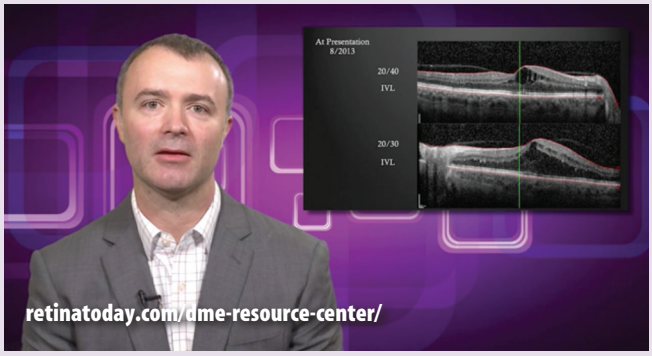
In this study in matched eyes of the same patients, both agents showed clinical improvement. The antiinflammatory activity of the dexamethasone and the anti-VEGF activity of ranibizumab both improved visual acuity and reduced DME. Recurrence of DME also occurred after both agents had cleared the eye; however, recurrence occurred at 4 to 5 weeks after ranibizumab injection compared with 3 to 4 months after dexamethasone implant.

In addition, we saw improvement in the eyes receiving anti-VEGF therapy even though the patients' response had plateaued before study initiation. This was likely due to the fact that the patients were treated more vigilantly with regular monthly anti-VEGF injections under the study protocol. However, in these patients with persistent DME despite chronic anti-VEGF treatment, there was further, greater reduction in DME in the eyes treated with the dexamethasone implant compared with those who continued to receive ranibizumab.

I would like to acknowledge my colleagues and collaborators in this study at Associated Retinal Consultants and Oakland University William Beaumont School of Medicine: Tarek S. Hassan, MD; Benjamin J. Thomas, MD; and Yoshihiro Yonekawa, MD. ■

Watch the Video

Dr. Wolfe describes this DME case report and the design and execution of the study described.



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