Evolving Strategies in the Use of Corticosteroids for the Treatment of DME

Sustained-release drug delivery options have renewed the value of steroids in the treatment paradigm.

INSIDE:
- Clinical Trials Meet Real-world Practice
- Monitoring Eyes With DME
- Considering the Cost of Treatments
- Case Studies
Indication and Usage
Diabetic Macular Edema
OZURDEX® (dexamethasone intravitreal implant) is a corticosteroid indicated for the treatment of diabetic macular edema.

Dosage and Administration
FOR OPHTHALMIC INTRAVITREAL INJECTION.
The intravitreal injection procedure should be carried out under controlled aseptic conditions. Following the intravitreal injection, patients should be monitored for elevation in intraocular pressure and for endophthalmitis. Patients should be instructed to report any symptoms suggestive of endophthalmitis without delay.

IMPORTANT SAFETY INFORMATION
Contraindications
Ocular or Periocular Infections: OZURDEX® (dexamethasone intravitreal implant) is contraindicated in patients with active or suspected ocular or periocular infections including most viral diseases of the cornea and conjunctiva, including active epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, mycobacterial infections, and fungal diseases.

Glaucoma: OZURDEX® is contraindicated in patients with glaucoma, who have cup to disc ratios of greater than 0.8.

Torn or Ruptured Posterior Lens Capsule: OZURDEX® is contraindicated in patients whose posterior lens capsule is torn or ruptured because of the risk of migration into the anterior chamber. Laser posterior capsulotomy in pseudophakic patients is not a contraindication for OZURDEX® use.

Hypersensitivity: OZURDEX® is contraindicated in patients with known hypersensitivity to any components of this product.

Warnings and Precautions
Intravitreal Injection-related Effects: Intravitreal injections, including those with OZURDEX®, have been associated with endophthalmitis, eye inflammation, increased intraocular pressure, and retinal detachments. Patients should be monitored regularly following the injection.

Steroid-related Effects: Use of corticosteroids including OZURDEX® may produce posterior subcapsular cataracts, increased intraocular pressure, glaucoma, and may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses. Corticosteroids should be used cautiously in patients with a history of ocular herpes simplex because of the potential for reactivation of the viral infection.

Adverse Reactions
Ocular adverse reactions reported by greater than or equal to 1% of patients in the two combined 3-year clinical trials following injection of OZURDEX® for diabetic macular edema include: cataract (68%), conjunctival hemorrhage (23%), visual acuity reduced (9%), conjunctivitis (6%), vitreous floaters (5%), conjunctival edema (5%), dry eye (5%), vitreous...
Glaucoma: mycobacterial infections, and fungal diseases. simplex keratitis (dendritic keratitis), vaccinia, varicella, and conjunctiva, including active epithelial herpes infections including most viral diseases of the cornea in patients with active or suspected ocular or periocular (dexamethasone intravitreal implant) is contraindicated OZURDEX® is contraindicated in patients with cup to disc ratios of greater than 0.8. OZURDEX® Contraindications IMPORTANT SAFETY INFORMATION FOR OPHTHALMIC INTRAVITREAL INJECTION.

For intravitreal injection. OZURDEX® (dexamethasone intravitreal implant) is a corticosteroid indicated for the treatment of diabetic macular edema.

Warnings and Precautions OZURDEX® (dexamethasone intravitreal implant) were subsequently treated with IOP-lowering medications during the study versus 10% of sham patients. 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).

Cataracts and Cataract Surgery: The incidence of cataract development in patients who had a phakic study eye was higher in the OZURDEX® group (68%) compared with Sham (21%). The median time of cataract being reported as an adverse event was approximately 15 months in the OZURDEX® (dexamethasone intravitreal implant) group and 12 months in the Sham group. Among these patients, 61% of OZURDEX® subjects versus 8% of sham-controlled subjects underwent cataract surgery, generally between Month 18 and Month 39 (Median Month 21 for OZURDEX® group and 20 for Sham) of the studies.

Please see Brief Summary of full Prescribing Information on next page.

*Best-corrected visual acuity.
†Based on U.S. market share of DME patients treated with steroids: December 2014.
OZURDEX® (OZURDEX® OZURDEX® (OZURDEX® (dexamethasone intravitreal implant) 0.7 mg

Brief Summary—Please see the OZURDEX® package insert for full Prescribing Information.

INDICATIONS AND USAGE
Retinal Vein Occlusion: OZURDEX® (dexamethasone intravitreal implant) is a corticosteroid indicated for the treatment of macular edema following branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO).

Posterior Segment Uveitis: OZURDEX® is indicated for the treatment of non-infectious uveitis affecting the posterior segment of the eye.

Diabetic Macular Edema
OZURDEX® is indicated for the treatment of diabetic macular edema.

CONTRAINDICATIONS
Ocular or Periocular Infections: OZURDEX® (dexamethasone intravitreal implant) is contraindicated in patients with active or suspected ocular or periocular infections including most viral diseases of the cornea and conjunctiva, including active epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, mycobacterial infections, and fungal diseases.

Glaucoma: OZURDEX® is contraindicated in patients with glaucoma, who have cup to disc ratios of greater than 0.8.

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Hypersensitivity: OZURDEX® is contraindicated in patients with known hypersensitivity to any components of this product [see Adverse Reactions].

WARNINGS AND PRECAUTIONS
Intravitreal Injection-related Effects: Intravitreal injections, including those with OZURDEX®, have been associated with endophthalmitis, eye inflammation, increased intraocular pressure, and retinal detachments.

Patients should be monitored regularly following the injection [see Patient Counseling Information].

Steroid-related Effects: Use of corticosteroids including OZURDEX® may produce posterior subcapsular cataracts, increased intraocular pressure, glaucoma, and may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses [see Adverse Reactions]. Corticosteroids should be used cautiously in patients with a history of ocular herpes simplex because of the potential for reactivation of the viral infection.

ADVERSE REACTIONS
Clinical Studies Experience: Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

Adverse reactions associated with ophthalmic steroids including OZURDEX® include elevated intraocular pressure, which may be associated with optic nerve damage, visual acuity and field defects, posterior subcapsular cataract formation, secondary ocular infection from pathogens including herpes simplex, and perforation of the globe where there is thinning of the cornea or sclera.

Retinal Vein Occlusion and Posterior Segment Uveitis
The following information is based on the combined clinical trial results from 3 initial, randomized, 6-month, sham-controlled studies (2 for retinal vein occlusion and 1 for posterior segment uveitis):

Adverse Reactions Reported by Greater than 2% of Patients

<table>
<thead>
<tr>
<th>MedDRA Term</th>
<th>OZURDEX® N=497 (%)</th>
<th>Sham N=498 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intraocular pressure increased</td>
<td>125 (25%)</td>
<td>10 (2%)</td>
</tr>
<tr>
<td>Conjunctival hemorrhage</td>
<td>108 (22%)</td>
<td>79 (16%)</td>
</tr>
<tr>
<td>Eye pain</td>
<td>40 (8%)</td>
<td>26 (5%)</td>
</tr>
<tr>
<td>Conjunctival hyperemia</td>
<td>33 (7%)</td>
<td>27 (5%)</td>
</tr>
<tr>
<td>Ocular hypertension</td>
<td>23 (5%)</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>Cataract</td>
<td>24 (5%)</td>
<td>10 (2%)</td>
</tr>
<tr>
<td>Vitreous detachment</td>
<td>12 (2%)</td>
<td>8 (2%)</td>
</tr>
<tr>
<td>Headache</td>
<td>19 (4%)</td>
<td>12 (2%)</td>
</tr>
</tbody>
</table>

Increased IOP with OZURDEX® peaked at approximately week 8. During the initial treatment period, 1% (3/421) of the patients who received OZURDEX® required surgical procedures for management of elevated IOP.

Following a second injection of OZURDEX® (dexamethasone intravitreal implant) in cases where a second injection was indicated, the overall incidence of cataracts was higher after 1 year.

Diabetic Macular Edema
The following information is based on the combined clinical trial results from 2 randomized, 3-year, sham-controlled studies in patients with diabetic macular edema. Discontinuation rates due to the adverse reactions listed in the table below were 3% in the OZURDEX® group and 1% in the Sham group. The most common ocular (study eye) and non-ocular adverse reactions are as follows:

<table>
<thead>
<tr>
<th>Ocular Adverse Reactions Reported by ≥ 1% of Patients and Non-ocular Adverse Reactions Reported by ≥ 5% of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>MedDRA Term</td>
</tr>
<tr>
<td>------------</td>
</tr>
<tr>
<td>Ocular</td>
</tr>
<tr>
<td>Cataract</td>
</tr>
<tr>
<td>Conjunctival hemorrhage</td>
</tr>
<tr>
<td>Visual acuity reduced</td>
</tr>
<tr>
<td>Conjunctivitis</td>
</tr>
<tr>
<td>Vitreous floaters</td>
</tr>
<tr>
<td>Conjunctival edema</td>
</tr>
<tr>
<td>Dry eye</td>
</tr>
<tr>
<td>Vitreous detachment</td>
</tr>
<tr>
<td>Vitreous opacities</td>
</tr>
<tr>
<td>Retinal aneurysm</td>
</tr>
<tr>
<td>Foreign body sensation</td>
</tr>
<tr>
<td>Corneal erosion</td>
</tr>
<tr>
<td>Keratitis</td>
</tr>
<tr>
<td>Anterior Chamber Inflammation</td>
</tr>
<tr>
<td>Retinal tear</td>
</tr>
<tr>
<td>Eyelid ptosis</td>
</tr>
<tr>
<td>Non-ocular</td>
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<tr>
<td>Hypertension</td>
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<tr>
<td>Bronchitis</td>
</tr>
<tr>
<td>Non-ocular</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Bronchitis</td>
</tr>
</tbody>
</table>

1 Includes cataract, cataract nuclear, cataract subcapsular, lenticular opacities in patients who were phakic at baseline. Among these patients, 61% of OZURDEX® subjects vs. 8% of sham-controlled subjects underwent cataract surgery.

2 243 of the 324 OZURDEX® subjects were phakic at baseline; 230 of 328 sham-controlled subjects were phakic at baseline.

Increased Intraocular Pressure

Summary of Elevated IOP Related Adverse Reactions

<table>
<thead>
<tr>
<th>Treatment: N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IOP</td>
</tr>
<tr>
<td>OZURDEX® N=324</td>
</tr>
<tr>
<td>IOP elevation ≥10 mm Hg at any visit</td>
</tr>
<tr>
<td>≥30 mm Hg IOP at any visit</td>
</tr>
<tr>
<td>Any IOP lowering medication</td>
</tr>
<tr>
<td>Any surgical intervention for elevated IOP*</td>
</tr>
</tbody>
</table>

* OZURDEX®: 1 surgical trabeculectomy for steroid-induced IOP increase, 1 surgical trabeculotomy for iris neovascularization, 1 laser iridotomy, 1 surgical iridectomy Sham: 1 laser iridotomy

Cataracts and Cataract Surgery
At baseline, 243 of the 324 OZURDEX® subjects were phakic; 230 of 328 sham-controlled subjects were phakic. The incidence of cataract development in patients who had a phakic study eye was higher in the OZURDEX® group (68%) compared with Sham (21%). The median time of cataract being reported as an adverse event was approximately 15 months in the OZURDEX® group and 12 months in the Sham group. Among these patients, 61% of OZURDEX® subjects vs. 8% of sham-controlled subjects underwent cataract surgery, generally between Month 18 and Month 39 (Median Month 21 for OZURDEX® group and 20 for Sham) of the studies.
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.
CONTRIBUTING FACULTY

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DISCLOSURES
Dr. Hariprasad: speakers bureau member or consultant for Alcon, Alimera Sciences, Allergan, Bayer, Clearside Biomedical, Genentech, Ocular Therapeutix, OD-OS, Optos, Takeda, Regeneron.

Dr. Boyer: consultant, scientific advisory board or speakers bureau member for Alcon and Allergan, a consultant for Aeprio, Allegro, Bausch + Lomb, Bayer, Genentech, GSK, KalVista, Neuretech, Niox, Novartis Ophthalmics, Ohr, Regeneron Pharmaceuticals, Santen, ThromboGenics, Santaris Pharma, a scientific advisory board for Genentech, Novartis, Neuretech, Pfizer, Data safety monitoring board for Stem Cells Inc.; Stock in Allegro, Ohr, Neuretech.

Dr. Fine: investigator, consultant and speaker for Allergan, Genentech, Regeneron. Investigator for Alcon, Bausch + Lomb, Santen, Thrombogenics. Patent and equity interest in Avis Surgical Robotics.

Dr. Khurana: consultant, investigator for Allergan. Consultant, speaker for Genentech.

Consultant, speaker and investigator for Regeneron.

Dr. Ober: speaker and/or consultant for Allergan, OD/OS, Bayer.

Dr. Sheth: consultant for Allergan, Alimera Sciences.

Dr. Singer: medical advisory board for NeoVista; consultant, lecturer, and/or research support from Genentech, Allergan, Regeneron, Eyegate, Acucela, Thrombogenics, Optos, Bausch + Lomb, Santen, Quintiles.
The idea that intravitreal steroids could be an effective treatment for diabetic macular edema (DME) emerged more than a decade ago. Triamcinolone acetonide in particular was considered for this purpose and demonstrated the ability to reduce macular edema and improve visual acuity.\textsuperscript{1,2} Its use in clinical practice increased, but other developments called into question whether the side effects and need for repeat injections were worth the achievable outcomes. Chief among these developments were the effectiveness of anti-VEGF agents against other retinal vascular diseases and the results of the Diabetic Retinopathy Clinical Research Network’s (DRCR) trial comparing focal/grid photocoagulation and intravitreal triamcinolone (IVT) for DME (Protocol B). The latter showed laser to be superior to IVT monotherapy in the long-term.\textsuperscript{3}

Now that the FDA has approved two anti-VEGF agents for the treatment of DME as well as two sustained-release steroid implants, retina specialists have more to consider when choosing the best treatment strategy for this group of patients.

**ANTI-VEGF THERAPY: SAFETY AND EFFICACY VS. TREATMENT BURDEN**

The RISE/RIDE\textsuperscript{4} and VIVID/VISTA\textsuperscript{5} Phase III clinical trials produced Level I evidence of the effectiveness of the anti-VEGF drugs ranibizumab (Lucentis 0.3 mg, Genentech) and afibbercept (Eylea 2 mg, Regeneron) for treating DME. In RISE and RIDE, the proportions of patients who gained ≥15 letters of visual acuity from baseline at month 36 were 51.2% and 36.8%, respectively. In VIVID, 33.3% of Eylea-treated patients gained at least 15 letters from baseline to 52 weeks as did 31.1% in VISTA. The trials established the safety of both medications in DME as well. While the potential systemic exposure to VEGF inhibitors delivered intraocularly poses a theoretical risk of adverse effects such as thromboembolic events, such events did not materialize in the trials with any significance.

Given their safety and effectiveness profile, anti-VEGF agents quickly earned a place as the first-line treatment for all but a small percentage of patients with DME. “However, there is a high injection burden, especially during the first year of treatment,” says Rahul N. Khurana, MD, Northern California Retina Vitreous Associates. “Regimented treatment produces better results, although the treatment burden does decrease over time. RISE and RIDE used a monthly dosing schedule, but in the open-label extension study with prn dosing, the average number of injections needed to maintain vision gains was 3.8, and a quarter of patients needed no injections in years 4 and 5.\textsuperscript{6} The average number of Lucentis injections in RESTORE was 7 in year 1, 4 in year 2 and 3 in year 3.\textsuperscript{7} And in the DRCR Protocol I trial, with prn treatment, the Lucentis injection average was 8 to 9 in year 1, 2 to 3 in year 2 and 2 in year 3.\textsuperscript{7} Three-year data are not yet available for Eylea in DME, but in year 1 of VIVID/VISTA, a treatment was provided every 8 weeks following 5 initial monthly injections. No additional efficacy was demonstrated when it was dosed every 4 weeks.

Also very relevant to clinical practice is that anti-VEGF therapy doesn’t have the desired effect in every patient. According to Dr. Khurana, in the DRCR Protocol I study, 27% of Lucentis patients had macular thickness >300 μm at year 1, and 40% had residual fluid at 2 years. Furthermore, he says, the recently released results from the DRCR Protocol T trial show 34% of Eylea patients, 42% of Lucentis patients and 64% of Avastin patients having macular thickness >250 μm at 1 year despite receiving 10 injections during that time.\textsuperscript{9}
INTRAVITREAL STEROIDS: EXTENDING TIME BETWEEN TREATMENTS

Intravitreal steroids are another option for achieving vision gains in eyes with DME, as evidenced by the pivotal trials that led to the recent FDA approval of two sustained-release implants, dexamethasone 0.7 mg (Ozurdex, Allergan) and fluocinolone acetonide 0.19 mg (Iluvien, Alimera Sciences). In the MEAD trial of Ozurdex,20 22.2% of patients experienced a ≥15-letter improvement in vision from baseline to 3 years. In the FAME trial of Iluvien,21 28.7% of patients experienced a ≥15-letter improvement in vision from baseline to 3 years. “Although the vision gains overall weren’t as robust as with the anti-VEGF agents, we saw in MEAD and FAME that the outcomes were good and achieved with far fewer treatments, an average of one implant over 3 years in FAME and 4.1 implants over 3 years in MEAD,” Dr. Khurana notes. Interestingly, in a FAME subgroup analysis, the vision outcomes were even better, with 34% of patients who reported DME duration of greater than 3 years at baseline gaining ≥15 letters of vision.12

“Triamcinolone, dexamethasone and fluocinolone all exhibit efficacy against DME, but in the absence of head-to-head comparisons, we don’t know whether one gives a far better effect than another,” says David S. Boyer, MD, Retina-Vitreous Associates Medical Group in Southern California. “All eventually cause cataract if given frequently. Studied individually, each affected IOP differently. Increases in IOP associated with Ozurdex, for instance, tended to be self-limiting and require surgery less often than with Iluvien.” Over 3 years in the MEAD study of Ozurdex, 0.6% of patients who received the implant required trabeculectomy. In the FAME trial in the same timeframe, 4.8% of patients who received Iluvien required incisional glaucoma surgery.

Howard F. Fine, MD, MHSc, NJ Retina, elaborates: “All corticosteroid molecules are 4-member rings, and their anti-inflammatory potency is typically compared with cortisol. As we see in basic pharmacology textbooks, triamcinolone is approximately 5 times as potent as cortisol, and both dexamethasone and fluocinolone are approximately 25 times as potent as cortisol. While there are overlapping biologic pathways common to all corticosteroids, there are uniquely expressed genes regulated by each.13 For instance, in a study by Nehme,14 the number of uniquely expressed genes regulated by each steroid was 555 for triamcinolone, 745 for dexamethasone and 2,294 for fluocinolone. Therefore, it does not follow logically that toxicity such as cataract and glaucoma correlates precisely with potency. We would need head-to-head trials to answer this question.”

Although IVT plus laser demonstrated similar efficacy to ranibizumab plus laser among pseudophakic patients in DRCR Protocol I (Figure 1), use of IVT will likely decrease with the approval of the extended-release steroid options for the DME indication. Prior to the approval of Ozurdex, Michael D. Ober, MD, Retina Consultants of Michigan, found that centrifuge-concentrated IVT, which he prepares in-office using Triense (triamcinolone acetonide injectable suspension 4 mg, Alcon) can maintain effectiveness in the eye for an average of 9 months and often longer.15 That said, he expects to use Ozurdex in its place more often. “The pharmacodynamics of Ozurdex are much more reliable, and the side effects are more predictable,” he explains. “It behaves in a very reproducible fashion, and we know the peak efficacy is 60 days. In comparison, IVT can have a highly variable effect, and to a certain extent, no two injections are the same even in the same eye.” Adds Michael A. Singer, MD, Medical Center Ophthalmology Associates in San Antonio, Texas, “Several different preparations of triamcinolone have been used in clinical studies, and the formulation used in any given study isn’t necessarily the one you get in clinical practice. The formulations all have different inactive ingredients, pH levels, particle sizes and preservatives. Also, the triamcinolone branded as Kenalog carries a warning in the label that states it’s not for intraocular use.”

In light of all the new DME data, Dr. Khurana notes several scenarios in which the dexamethasone implant is needed:
  - for the approximately one-third of patients who don’t have an adequate response to anti-VEGF therapy
  - when a patient has an increased risk of thromboembolic events, which is common among diabetic patients, and an anti-VEGF agent would, therefore be best avoided
  - for treating pregnant women with DME rather than potentially exposing the fetus to an anti-VEGF agent
  - in vitrectomized eyes, also common among diabetes patients, in which anti-VEGF agents have been speculated to have decreased durability but the implant has been shown to work well.16

In addition, Dr. Khurana conducted a pilot study of Ozurdex in patients who have diabetes and pseudophakic cystoid macular edema and was very pleased with the results.17 (See “Dexamethasone Implant for Pseudophakic CME in a Patient with Diabetes” on page 14.)

While its expected 3-year duration of effect makes Iluvien an attractive treatment option, most physicians anticipate using it cautiously at first. Dr. Singer expects his initial cases with Iluvien to be patients who have had mul-
tiple Ozurdex treatments and are becoming burdened by it and patients who have already had glaucoma surgery. Veeral S. Sheth, MD, MBA, FACS, director of Scientific Affairs with University Retina and Macula Associates in Chicago, lists his criteria as “previous Ozurdex, no IOP issues and pseudophakic.” Dr. Fine explains the caution: “Early in the clinical experience with Iluvien, I’ll be extremely conservative. I suspect if I determine a patient requires a sustained-release steroid implant, I’ll choose Ozurdex in the vast majority of cases. If a concerning IOP spike occurs with Ozurdex, we have the option of not re-implanting it for the balance of 3 years, but that’s not an option with Iluvien.” Dr. Khurana adds that in order to recommend Iluvien for a patient, he’ll need to be confident he or she is willing and able to keep follow-up appointments for monitoring.

Unlike Ozurdex, Iluvien isn’t biodegradable; therefore, doctors will be cognizant of the potential for the empty device to cause visual symptoms. It could possibly migrate into the anterior chamber as well, which can also occur with an active dexamethasone implant, however, the dexamethasone implant will dissolve with time.

MORE OPTIONS FACILITATE CASE-SPECIFIC TREATMENT

Dr. Sheth points out that access to two FDA-approved steroid implants and two FDA-approved anti-VEGF agents for DME improves his ability to individualize treatment. “Now we can change or supplement treatments to achieve the best possible results while adding more durability,” he says.

Dr. Singer summarizes his treatment algorithm as follows: “We all agree that DME, more so than AMD, is a multifactorial disease, so steroids definitely have a role. But unless there’s an absolute contraindication or I have concerns about a patient’s systemic comorbidities, an anti-VEGF agent is my first-line choice. Initially I see patients monthly. At 3 months, if I don’t see consistent improvement in visual acuity or on OCT, I give another injection and bring the patient back in 2 weeks, which allows me to determine whether there is significant resistance to anti-VEGF treatment or whether there’s a response but the effect is not lasting. If there is an effect but it’s not optimal, I may switch to a different anti-VEGF agent, especially if the patient has a history of glaucoma. In other cases, I may add a steroid, usually Ozurdex rather than triamcinolone, because it’s likely something other than VEGF is driving the disease. The other time I add a steroid is when treatment burden is an issue, i.e., a patient who needs monthly anti-VEGF injections to stay fluid-free but can’t keep the appointments.”

Like Dr. Singer, many retina specialists consider a treatment after evaluating the eye’s response to 3 or 4 anti-VEGF injections. That includes Dr. Ober, who chooses his next move based on the patient’s age, disease status, tolerance for side effects and phakic status. “I may switch within the anti-VEGF category or supplement with steroids,” he says. “I ‘move up the ladder’ faster in someone who has a great disease burden and a greater tolerance for side effects. For pseudophakic patients without glaucoma, I’m much quicker to combine anti-VEGF and steroid therapy or move to steroids alone.”

Dr. Khurana takes a slightly different approach to when he considers a therapy change. “I give six anti-VEGF injections first,” he explains. “I don’t think a loading dose of three, as is common for AMD, is sufficient for DME. In the DRCR Protocol I study, patients got two additional injections if needed after the first four. And in
RISE/RIDE, OCT measurements continued to improve after the third injection. I have tried a different anti-VEGF agent when a patient isn’t responding adequately to the first, but haven’t been too impressed with the result. I lean more toward laser or steroid and usually choose Ozurdex. Focal laser treatment remains a sensible option for non-center-involved DME, and I typically apply it after the anti-VEGF agent is on board.”

Both Dr. Singer and Dr. Fine are taking a closer look at subthreshold laser therapy (MicroPulse, Iridex) for treating DME. According to Dr. Fine, “Larger studies with long-term follow-up are needed, but I do think there’s an increasing role for MicroPulse (MP) laser in DME. First, for focal leakage outside the fovea that I previously would have treated with traditional modified ETDRS (mETDRS) focal laser. Second, for cases with more diffuse center-involved edema that may require combination therapy with anti-VEGF, steroid and laser. In one study, for example, MP was as effective as mETDRS in terms of visual acuity and reduction in OCT thickness, but MP improved retinal sensitivity on microperimetry while the mETDRS approach worsened it.” This suggests MP may offer a safety advantage over traditional laser. Another randomized prospective study showed a greater improvement in visual acuity with high-density MP laser compared with traditional mETDRS focal laser, suggesting that visual acuity results may be superior with MP in certain cases.”

**STEROIDS REMAIN AN INTEGRAL PART OF TODAY’S STANDARD OF CARE**

In the absence of a single therapy that is 100% effective for all patients with DME, the best approach to safeguarding vision is working to understand what role each option can play. And, as Dr. Fine affirms, “Corticosteroids remain an important class of agents for DME, in addition to the anti-VEGF drugs. Triesence has become more reproducible to dose, which in turn makes the safety profile more predictable. Also, implant technology has allowed for the sustained release of medication with a longer durability of action. Many patients with DME are young, working-age individuals and lessening their treatment burden in this manner can be a major advantage.”

**REFERENCES**


6. Data not yet published.


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Fluorescein angiography (FA) and spectral domain optical coherence tomography (SD-OCT) are the primary imaging modalities utilized by vitreoretinal specialists for managing patients with DME. Typically, both FA and OCT are used initially and OCT is used at each subsequent visit.

“I use the initial FA because I want to know whether the leakage is focal or diffuse and whether there is non-central edema I could treat with laser to potentially decrease the injection burden,” says Dr. Sheth. Dr. Ober uses widefield FA in particular “because in some cases, I see a featureless retina on clinical exam and widefield FA reveals severe capillary dropout in the periphery.” In select circumstances, it may be helpful to perform FA again after the baseline test. As Dr. Singer explains, “I rarely do another FA, but I may if I can’t explain why a patient’s retina is not getting dry with treatment.”

Once patients receive treatment for DME, “SD-OCT tells me more about when I need to see them again than anything else I can do,” Dr. Ober says. He obtains six radial scans for DME patients at every visit. “If I want to see more detail in a certain area, I follow the individual line scans,” he continues. “I use a treat-and-extend approach to minimize the treatment burden for patients, so SD-OCT shows me for how long treatment is effective.”

**MONITORING IOP IN THE PRESENCE OF SUSTAINED-RELEASE STEROID IMPLANTS**

When steroids are part of a patient’s treatment for DME, IOP must also be monitored. Last year, the FDA approved the sustained-release dexamethasone intravitreal implant (Ozurdex, Allergan) for the treatment of DME. The unofficial consensus that has emerged among doctors who use Ozurdex for this new indication is to check IOP approximately 6 weeks (but no longer than 2 months) after a patient’s first implantation. This decision is based on the MEAD study, during which IOP peaked at week 6 following Ozurdex implantation.1 Dr. Ober adds, “Most of my Ozurdex patients receive an implant every 3 months; therefore, 6 weeks is not only the right time for an IOP check but it’s also halfway through that 3-month time period, which is a good point to determine whether I need to supplement treatment.” Dr. Boyer also checks IOP at 6 weeks after patients receive the first Ozurdex implant. “If I have any concerns with that first check, I see them back in another 6 weeks, which is when I’m usually considering whether to repeat Ozurdex and/or add an anti-VEGF agent,” he explains. “In my experience, if IOP is less than 16 mmHg prior to implantation, the patient tends not to have a significant increase, but if IOP is 17-20 mmHg at the outset, the pressure seems to go higher, so I watch that latter group a little more closely.”

In the MEAD study, 36.0% of patients treated with Ozurdex 0.7 mg had an IOP adverse event, and 41.5% of patients in the 0.7-mg group used medication to control IOP. “Most IOP increases in the trial occurred with the first or second implant,” Dr. Singer says.2 “Seventy-five percent was the approximate likelihood of a spike in IOP associated with the first two implantations; 85% was the likelihood associated with the first three implantations. If a patient’s IOP didn’t increase significantly during the first three cycles, it was unlikely to increase significantly following subsequent implantations.” Dr. Singer also notes that patients who experienced an increase in IOP of at least 10 mmHg during the MEAD study (0.7 mg) had similar mean visual acuity outcomes to patients who did not have that level of increase. Based on the MEAD data, Dr. Sheth and others generally see patients for a pressure check at 6 weeks and 12 weeks (3 months) after their first and second Ozurdex implantations but not until the 3-month mark following subsequent implantations.

**FLUCINOLONE IMPLANT MAY REQUIRE DIFFERENT IOP MONITORING SCHEDULE**

In addition to Ozurdex, the FDA has approved the sustained-release flucinolone acetonide intravitreal
implant (Iluvien, Alimera Sciences) for the treatment of DME. “Predicting IOP issues related to Iluvien hasn’t been elucidated yet,” Dr. Singer says.

“Because the medication lasts in the eye for years rather than months, I expect to monitor IOP in Iluvien patients more closely,” says Dr. Khurana. Dr. Fine cites a recent study that may offer some guidance: “The FAMOUS Study Group found that following Iluvien injection in patients with DME, the levels of fluocinolone in the aqueous reached a steady state by roughly 6 months and were quite stable out to 3 years. Aqueous fluocinolone levels were 2.17 ng/mL at month 1, 1.76 ng/mL at month 3, 1.18 ng/mL at month 6, 0.70 ng/mL at month 12 and 0.55 ng/mL at month 36. Therefore, I suspect regular monitoring would be required for the first several months, and after that time, an IOP spike would be much less likely.”

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2. Singer M. Intraocular pressure in patients with diabetic macular edema treated with dexamethasone intravitreal implant: MEAD study findings. Paper presented during the 2014 American Society of Retina Specialists meeting; August 9-13, 2014; San Diego, CA.

CASE STUDY #1  Howard F. Fine, MD, MHSc

BILATERAL DEXAMETHASONE IMPLANTS FOLLOWING INCOMPLETE RESPONSE TO ANTI-VEGF THERAPY

This patient with type 2 diabetes had non-proliferative diabetic retinopathy and diabetic macular edema in both eyes. By Sept. 10, 2014, the right eye had received 10 monthly anti-VEGF injections. Visual acuity on that day, which was 4 weeks after the previous injection, was 20/70. Also on that day, a dexamethasone intravitreal implant (Ozurdex) was given in that eye. Eight weeks later, SD-OCT showed complete resolution of the macular edema with a 387-μm improvement in central retinal thickness (Figure 1). Visual acuity had improved to 20/30.

Five weeks after a fifth monthly anti-VEGF injection in the left eye, the patient’s visual acuity in that eye was 20/100. On Sept. 16, 2014, Ozurdex was implanted. Seven weeks later, OCT showed resolution of the macular edema and a 208-μm improvement in central retinal thickness (Figure 2). Visual acuity had improved to 20/70.

Figure 1. Before and after Ozurdex implantation OD.
Figure 2. Before and after Ozurdex implantation OS.
A 70-year-old Asian female with moderate non-proliferative diabetic retinopathy presented with vision loss in the left eye 7 weeks after uncomplicated cataract extraction and IOL insertion. Her ocular history in the left eye included episodes of clinically significant macular edema and two treatments with focal laser photocoagulation. Her medical history included hypertension and insulin-controlled diabetes mellitus of 16 years’ duration. Her ocular medications included topical ketorolac and prednisolone acetate four times per day. Best-corrected visual acuity at presentation was 20/80. Dilated funduscopic examination showed macular edema, scattered intraretinal hemorrhages and prior focal laser scars. Fluorescein angiography showed disk leakage in addition to petalloid leakage in the macular region. Diffuse macular edema with a central retinal thickness of 457 μm was detected on OCT (Figure 1).

Treatment with topical ketorolac and prednisolone acetate was continued for another 20 days with no improvement in visual acuity or macular edema. At this point, the patient was enrolled in a pilot study evaluating the dexamethasone implant (Ozurdex 0.7 mg) for pseudophakic cystoid macular edema in patients with diabetes.1 She received the implant 68 days after her cataract surgery. Her visual acuity improved from 20/80 at baseline to 20/40 at day 30 and day 60, 20/32 at day 90, and 20/25 at day 180. Macular edema improved as well, with central retinal thickness decreasing from 430 μm prior to implantation to 330 μm at day 30 (Figure 2), 321 μm at day 60, 318 μm at day 90 (Figure 3) and 359 μm at day 180 (Figure 4). Intraocular pressure was 16 mmHg at baseline, 18 mmHg at day 30, 17 mmHg at day 60, 14 mmHg at day 90 and 12 mmHg at day 180. She experienced no adverse events.

REFERENCE
Considering the Cost of Treatments for DME

AN ACCURATE ASSESSMENT OF THE RELATIVE COST OF THERAPY OPTIONS IS ELUSIVE BUT COULD BE A USEFUL TOOL FOR IMPROVING OVERALL QUALITY OF CARE.

BY DESIREE IFFT, CONTRIBUTING EDITOR

To pose the question “What is the cost of X treatment?” for a medical condition is to prompt a long list of additional questions. Direct cost or indirect? Cost to whom – doctors, patients, the healthcare system? Cost for any patient treated or a specific group of patients? Do the outcomes associated with treatment justify additional costs associated with potential side effects? Comparing the costs of one treatment to another is even more complex. However, attempting to answer the questions is an important endeavor if the goal is to ensure patients receive the best possible care. It will be a must in the value-based system envisioned by both the government and the private sector.

Here, leading retina specialists share their top-of-mind thoughts and insights related to the cost of treatments for DME.

HOWARD F. FINE, MD, MHSC: If by treatment we mean only on-label, FDA-approved monotherapy, Ozurdex offers a significant cost saving over the anti-VEGF agents Lucentis and Eylea due to their dosing frequency. However, off-label treatments, such as Avastin or triamcinolone, can be cost effective because of their lower price.

MICHAEL A. SINGER, MD: Depending on which anti-VEGF agent you use, cost can vary widely. As we know, Avastin, which is used off-label, costs significantly less than the others. There are also indirect costs to patients to consider, such as getting to our practices and loss of work time. One way to decrease the number of patient visits is to combine treatments to produce a more durable effect. Patients may actually be more likely to keep their appointments if they know they don't have to come in every single month.

RAHUL N. KHURANA, MD: In DME clinical trials, Ozurdex had a lower treatment burden than the anti-VEGF agent Lucentis, although there was less improvement in visual acuity as well. Patients in the MEAD study received an average of 4.1 Ozurdex implants over 3 years, which is far fewer than the average number of Lucentis injections given in the DRCR.net Protocol I, RESTORE, RISE and RIDE trials, which ranged from 14 to 35 over 3 years. The cost is a complex question as it includes the cost of the medication, treatment visits and potential complications such as cataract surgery and elevated IOP management.

All medications are expensive, and results of separate clinical trials aren't directly comparable, but the economic effect on patients depends on their insurance status. They're less affected if their insurance pays in full than if they are responsible for a copay. Many also receive help from the pharmaceutical companies' payment assistance programs. But, no matter what the scenario, someone is paying for the treatments.

MICHAEL D. OBER, MD, FACS: Treatment burden was less in DME clinical trials with Ozurdex compared with Lucentis, but in my estimation, patients in the MEAD trial of the implant were undertreated. Patients could receive an implant no more frequently than every 6 months, but the effect peaked at 60 days. In real-world clinical practice, as well, the implant isn't a 6-month drug. Over time in the MEAD trial, patients stopped requiring an implant every 6 months, but my DME patients are requiring a repeat implant more frequently in the beginning, closer to every 3 months, making the 4.1 3-year average in MEAD an underestimate. In addition, if the side effect profile of the steroid implant is greater with more frequent use, there will be an inherent cost to that.

Treatment costs vary within drug classes, too. Avastin is a lower-cost, albeit off-label, option in the anti-VEGF category as is triamcinolone in the steroid category. Those treatments do, however, have their own drawbacks,
not the least of which is the risk of infection caused by bevacizumab prepared for intraocular use at compounding pharmacies.

VEERAL S. SHETH, MD, MBA, FACS: Any comparative analysis of the cost of treatments for DME based on currently available data must be undertaken with caution. First, as we always keep in mind, it isn’t possible to truly compare the results of clinical trials given how different they are with regard to protocols, study populations, retreatment criteria, analysis methods and dropout rates. Second, conclusions reached from a comparative cost analysis must be viewed in light of what variables are and are not included in the analysis.

One way to consider cost differences among treatments is to look at the price of the drug per letter of vision gain. This could be helpful in framing discussions such as how good is good enough for a treatment? In other words, what are we willing to spend for how much vision we expect

<table>
<thead>
<tr>
<th>Drug/Protocol</th>
<th>Average No. of injections/implants (3 years)</th>
<th>Price of drug per tx</th>
<th>Total price of drug</th>
<th>No. of non-tx visits (3 years)</th>
<th>Total cost of non-tx visits (@ $141 per visit)</th>
<th>Total cost (drug plus visits)</th>
<th>Average no. of letters gained (3 years)</th>
<th>Cost per letter of vision gained (3 years)</th>
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<tbody>
<tr>
<td>RIDE ranibizumab</td>
<td>34</td>
<td>$1,188</td>
<td>$40,392</td>
<td>n/a</td>
<td>n/a</td>
<td>$40,392</td>
<td>10.6</td>
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<td>RISE ranibizumab</td>
<td>35</td>
<td>$1,188</td>
<td>$41,580</td>
<td>n/a</td>
<td>n/a</td>
<td>$41,580</td>
<td>14.2</td>
<td>drug only $2,928</td>
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<tr>
<td>Protocol I ranibizumab + deferred laser group (non-DME 0.5-mg dose)</td>
<td>14</td>
<td>$2,028</td>
<td>$28,392</td>
<td>17</td>
<td>$2,397</td>
<td>$30,789</td>
<td>9.7</td>
<td>drug only $1,714</td>
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<tr>
<td>Protocol I ranibizumab + deferred laser group (0.3-mg dose for DME)</td>
<td>14</td>
<td>$1,188</td>
<td>$16,632</td>
<td>17</td>
<td>$2,397</td>
<td>$19,029</td>
<td>9.7</td>
<td>drug only $1,714</td>
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<tr>
<td>MEAD dex implant (all patients)</td>
<td>4.1</td>
<td>$1,347</td>
<td>$5,522</td>
<td>15</td>
<td>$2,115</td>
<td>$7,637</td>
<td>3.5</td>
<td>drug only $1,577</td>
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<tr>
<td>MEAD dex implant (pseudophakic patients)</td>
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<td>$5,522</td>
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<td></td>
<td></td>
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<td>3 year data not yet available</td>
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</table>

Table 1. Cost of treatment per letter gained.
to achieve? For example, over 3 years in the MEAD trial, patients received an average of 4.1 Ozurdex implants. At the price of $1,346.80 each, that’s a total cost of $5522 rounded to the nearest dollar. The average number of letters gained in 3 years was 3.5 (0.7-mg group), making the cost per letter $1,578. Pseudophakic patients gained an average of 6.5 letters, making their cost per letter $850.

The same calculation applied to the RIDE trial of Lucentis for DME — an average of 34 injections over 3 years at the price of $1,188 per injection for a total cost of $40,392, divided by the 10.6 letters gained — results in a higher cost per letter gained of $3,810. And in the RISE trial of Lucentis for DME, where there was a 3-year average of 35 injections and 14.2 letters gained, the cost per letter gained would be $2,928.

The difference in cost per letter of vision gained between Lucentis and the Ozurdex implant is large in this simple comparison, but we must keep in mind that in clinical practice, most patients aren’t treated monthly with an anti-VEGF agent, especially not for 3 years, as they were in RISE/RIDE. Therefore, the DRCR.net Protocol I trial may represent a more real-world scenario. In Protocol I, patients received Lucentis treatment as needed according to the study guidelines (and deferred laser). On average, over 3 years, they received 14 injections (0.5 mg at $2,028 each for a total cost of $28,392) and gained an average of 9.7 lines of vision, a cost per letter gained of $2,927. However, the 0.5-mg dose used in the study wasn’t the dose approved for DME, which is 0.3 mg at the $1,188 price. In clinical practice, if 14 injections of the approved 0.3-mg dose were given over the course of 3 years, assuming the same vision outcomes as in Protocol I, the cost per letter gained would be less, $1,714.

A variable not mentioned so far is the cost of office visits for examination and imaging, which would of course increase the cost per letter gained for any treatment. In a RISE/RIDE scenario, where it’s known that an injection will be given monthly, monthly charges for the visits aren’t necessarily rendered. In contrast, when treatment is as needed, which matches Protocol I and clinical practice more closely, charges for non-treatment visits could be part of the equation. Applying that to the Protocol I data, patients had an average of 17 non-treatment visits in 3 years, which at approximately $144 per visit would amount to $2,397, increasing the overall cost of therapy to $19,029 and the cost per letter of vision gained to $1,961 (from $16,632 and $1,714 when only drug price is considered).

Adding the office visit variable to the other scenarios where it’s relevant as well as the sustained-release fluocinolone acetonide intravitreal implant (Iluvien, Alimera Sciences), a cost-per-letter-of-vision-gained analysis breaks down as seen in Table 1.

While cost per letter of vision gained based mainly on drug price is a good example of how assessing treatment costs could aid quality-of-care decision-making, as mentioned previously, we need to keep in mind the variables that are not included. The potential systemic side effects associated with anti-VEGF agents and the cataracts and glaucoma associated with steroid implants could change the results of the analysis significantly. We may achieve cost-related gains with either treatment, e.g., efficacy or time/decreased treatment burden, only to give them back when patients need treatment for side effects. Additional care can be especially problematic for DME patients because they’re already seeing doctors in so many different specialties given the nature of diabetes.

CONNECTING THE PIECES OF THE PUZZLE

Cost of treatment may become a more significant factor in our decision-making as new therapies for DME emerge, especially if they provide us with multiple ways to bring patients to the same endpoint. In the meantime, we’ll continue to follow the treatment algorithms we’ve developed, which utilize both anti-VEGF agents and intravitreal steroids, based on the data and experience we have.

In addition, work will continue toward discovering better ways of stratifying patients to determine who may be better suited for one treatment or a combination of treatments over another.

REFERENCES

Evolving Strategies in the Use of Corticosteroids for the Treatment of DME

This 77-year-old female patient had received multiple injections of Avastin and Lucentis in the right eye for diabetic macular edema since October 2011. With injections every 2 months, her vision ranged from 20/80 pre-injection to 20/60 post-injection. Upon presentation 3 months after the previous injection, visual acuity had declined to 20/150 and OCT measured central foveal thickness at 496 µm and a macular volume of 10.9 (Figure 1). At this visit, she was given an anti-VEGF injection. By follow-up 1 month later, visual acuity had improved to 20/50, central foveal thickness had improved to 294 µm and macular volume had decreased to 10.1. At this visit, the patient received an Ozurdex implant (Figure 2).

One month after Ozurdex implantation, central foveal thickness further improved to 290 µm, macular volume decreased further to 9.9 and visual acuity was maintained at 20/50. (Figure 3) Three months later, 4 months after Ozurdex implantation, macular edema remained controlled and visual acuity was 20/50-3 (Figure 4).

CASE STUDY #3  Michael A. Singer, MD

Dexamethasone implant one month after most recent anti-VEGF injection for chronic DME

Figure 1. Macular edema 3 months after the latest injection of an anti-VEGF agent.

Figure 2. At this visit, 1 month after an anti-VEGF injection, the patient received an Ozurdex implant.

Figure 3. One month after Ozurdex implantation.

Figure 4. Four months after Ozurdex implantation, macular edema remained controlled and vision gains were maintained.
ADDRESSING RESIDUAL FLUID WITH THE DEXAMETHASONE IMPLANT

This patient, a 61-year-old male with a 25-year history of type 2 diabetes, is among the 15% to 20% of my patients in whom anti-VEGF therapy doesn’t completely resolve diabetic macular edema. On initial presentation, clinical examination of the right eye demonstrated dot-blot hemorrhages with diffuse central edema, the patient’s visual acuity OD was 20/60, and OCT measured central macular thickness of 632 μm (Figure 1).

In the subsequent 6 months, the patient was treated with five injections of Lucentis or Avastin. (The dexamethasone implant, Ozurdex, was not FDA-approved for diabetic macular edema at that time.) The anti-VEGF injections resulted in an improvement in vision to 20/40 but only moderate improvement in retinal anatomy to 437 μm (Figure 2). The patient then received an Ozurdex implant, which further improved central macular thickness and visual acuity, to 359 μm and 20/25, at 6 weeks (Figure 3).

Figure 1. OCT on initial presentation. Visual acuity was 20/60.

Figure 2. Five anti-VEGF injections in 6 months led to only moderate improvement in retinal anatomy.

Figure 3. At 6 weeks after Ozurdex implantation, central macular thickness was 359 μm and visual acuity was 20/25.
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