EMERGING CONCEPTS IN THE USE OF COMBINATION THERAPY FOR THE TREATMENT OF DME

The latest data on anti-VEGF agents and sustained-release steroids point to a future that goes beyond monotherapy.

EXPERT INSIGHTS ON:
- Rationale for Utilizing More than One Therapy
- DRCR.net Protocol T Trial Results
- Weighing the Side Effect Profiles of Treatment Options
- Imaging and Other Innovations in DME Care
A different perspective can have the power to change your approach

**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.

**Glucoma:** 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
The pathophysiology — An inflammatory cascade plays a key role

The therapeutic targets — Suppress multiple inflammatory cytokines

The clinical results — Achieve clinically significant 3-line gains in BCVA

The #1 steroid in U.S. market share for DME

IMPORTANT SAFETY INFORMATION (continued)

Adverse Reactions (continued):

• Detachment (4%), vitreous opacities (3%), retinal aneurysm (3%), foreign body sensation (2%), corneal erosion (2%), keratitis (2%), anterior chamber inflammation (2%), retinal tear (2%), eyelid ptosis (2%). Non-ocular adverse reactions reported by greater than or equal to 5% of patients include: hypertension (13%) and bronchitis (5%).

Increased Intraocular Pressure: IOP elevation greater than or equal to 10 mm Hg from baseline at any visit was seen in 28% of OZURDEX® (dexamethasone intravitreal implant) patients versus 4% of sham patients. 42% of the patients who received 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 intravitreal steroids: December 2014.
Brief Summary—Please see the OZURDEX® package insert for full Prescribing Information.

INDICATIONS AND USAGE
Retina 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 Periorificial Infections: OZURDEX® (dexamethasone intravitreal implant) is contraindicated in patients with active or suspected ocular or periorificial 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 [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=324 (%)</th>
<th>Sham N=328 (%)</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:

Ocular Adverse Reactions Reported by ≥ 1% of Patients and Non-ocular Adverse Reactions Reported by ≥ 5% of Patients

<table>
<thead>
<tr>
<th>Ocular</th>
<th>OZURDEX® N=324 (%)</th>
<th>Sham N=328 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cataract</td>
<td>166/243 (68%)</td>
<td>49/230 (21%)</td>
</tr>
<tr>
<td>Conjunctival hemorrhage</td>
<td>73 (23%)</td>
<td>44 (13%)</td>
</tr>
<tr>
<td>Visual acuity reduced</td>
<td>28 (9%)</td>
<td>13 (4%)</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>19 (6%)</td>
<td>8 (2%)</td>
</tr>
<tr>
<td>Vitreous floats</td>
<td>16 (5%)</td>
<td>6 (2%)</td>
</tr>
<tr>
<td>Conjunctival edema</td>
<td>15 (5%)</td>
<td>4 (1%)</td>
</tr>
<tr>
<td>Dry eye</td>
<td>15 (5%)</td>
<td>7 (2%)</td>
</tr>
<tr>
<td>Vitreous detachment</td>
<td>14 (4%)</td>
<td>8 (2%)</td>
</tr>
<tr>
<td>Vitreous opacities</td>
<td>11 (3%)</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>Retinal aneurysm</td>
<td>10 (3%)</td>
<td>5 (2%)</td>
</tr>
<tr>
<td>Foreign body sensation</td>
<td>7 (2%)</td>
<td>4 (1%)</td>
</tr>
<tr>
<td>Corneal erosion</td>
<td>7 (2%)</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>Keratitis</td>
<td>6 (2%)</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>Anterior Chamber Inflammation</td>
<td>6 (2%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Retinal tear</td>
<td>5 (2%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Eyelid ptosis</td>
<td>5 (2%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Non-ocular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>41 (13%)</td>
<td>21 (6%)</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>15 (5%)</td>
<td>8 (2%)</td>
</tr>
</tbody>
</table>

*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.

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>
<th>IOP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OZURDEX® N=324</td>
</tr>
<tr>
<td>IOP elevation ≥10 mm Hg from Baseline at any visit</td>
<td>91 (28%)</td>
</tr>
<tr>
<td>≥30 mm Hg IOP at any visit</td>
<td>50 (15%)</td>
</tr>
<tr>
<td>Any IOP lowering medication</td>
<td>136 (42%)</td>
</tr>
<tr>
<td>Any surgical intervention for elevated IOP*</td>
<td>4 (1.2%)</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.
Steroid-related Effects:
Patients should be monitored regularly following the injection of OZURDEX® to detect any changes in intraocular pressure, and retinal detachments.

Torn or Ruptured Posterior Lens Capsule:
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, gastrochisis 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.

OZURDEX® (dexamethasone intravitreal implant) 0.7 mg
For additional information, please see the full OZURDEX® package insert.

Increased Intraocular Pressure
At baseline, 243 of the 324 OZURDEX® patients had an IOP of greater than 20 mm Hg at baseline, which was decreased to 125 (25%) 10 (2%) at 1 year, and 63 (15%) 0 (0%) at 3 years.

Adverse reactions associated with ophthalmic steroids including OZURDEX® cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.
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. Dugel: Speaker and consultant for Alcon, Acucela, Alimera Sciences, Allergan, Novartis, Ophthotech, Genentech and Thrombogenics. Research funding from Alcon, Allergan, Santen, Avalanche and Genentech. Funding for travel to meetings from Alcon, Alimera Sciences, Allergan, Novartis, Ophthotech, Genentech and Thrombogenics.

Dr. Kiernan: Minor shareholder and consultant and speaker for Allergan and Alimera Sciences. Major shareholder in Clearside Biomedical.

Dr. Kurup: Advisory board for Abbott Abbvie, Allergan, Clearside, Regeneron and XOMA.

Dr. Maturi: Research support from Alcon, Alimera Sciences, Allergan, Bayer, Eli Lilly, Eyegate, GlaxoSmithKline, Quark and Santen. Consultant for Allergan and Eli Lilly.

Dr. Shah: Research support/grants from Allergan. Consulting/advisory committee for Alcon, Allergan, QLT, Regeneron. Speakers bureau/honorary with Regeneron, Alcon, QLT.

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.

Moving Beyond Monotherapy

As in other complex diseases, combination treatment is likely to become an important approach for DME.

BY SHREE K. KURUP, MD

Perhaps even more so than other retinal vascular diseases, diabetic eye disease is multifactorial. Its pathogenesis involves many mediators, including vascular endothelial growth factor (VEGF) and inflammatory cytokines. Thanks to several recent FDA approvals and indication expansions, we have more options than ever for targeting the causes of diabetic macular edema (DME). Clinical trials have shown anti-VEGF agents and steroids to be effective for improving retinal anatomy and vision in patients who have DME.

Given the results they’re capable of producing, anti-VEGF agents are first-line therapy in most cases of DME. However, achieving favorable outcomes requires frequent injections, with monthly injections leading to the best results. This level of treatment can be difficult to sustain for patients with diabetes. Often, they’re seeing several other doctors who monitor the systemic aspects of the disease; many develop DME at a relatively young age, and the disease is often bilateral. Furthermore, anti-VEGF agents don’t produce the desired result in every patient. For example, in a study by the Diabetic Retinopathy Clinical Research Network (DRCR.net Protocol I, pre-re-treatment criteria, average number of injections was 8 to 9 in year 1, 2 to 3 in year 2 and 2 in year 3), 27% of the patients who received ranibizumab (Lucentis, Genentech) treatment had macular thickness >300 µm at 1 year, and 40% had residual fluid at 2 years. At the 3-year visit, the percentage of Lucentis-treated eyes with central subfield thickness ≥250 µm was 36%. Similarly, in DRCR.net Protocol T study, after receiving an average of 10 injections in a year, 34% of aflibercept (Eylea, Regeneron) patients, 42% of Lucentis patients and 64% of bevacizumab (Avastin, Genentech) patients had >250-µm macular thickness. (For more on Protocol T, see page 9.)

My Approach to Treating DME

Most DME cases in my practice are severe, so it’s rare that a patient needs only a few anti-VEGF injections over a year’s time. More often, I recommend combination therapy as a means to potentially increase efficacy by taking advantage of more than one mechanism of action and simultaneously limiting the treatment burden by achieving a more lasting therapeutic effect.

“More often, I recommend combination therapy as a means to potentially increase efficacy by taking advantage of more than one mechanism of action and simultaneously limiting the treatment burden by achieving a more lasting therapeutic effect.”

SHREE K. KURUP, MD
When I examine a diabetic eye, I evaluate the global picture of the therapeutic need.  

SHREE K. KURUP, MD

Combination therapy makes solid theoretical sense, only a small number of prospective studies of this approach have been conducted. (See “Recent Evaluations of Combination Therapy” on page 14.) More research is needed to determine the precise effects of combination therapy and to compare options. In the meantime, we must rely on our clinical acumen to provide each patient with the best possible care.

When I examine a diabetic eye, I evaluate the global picture of the therapeutic need based on the severity of the retinal disease as indicated by clinical exam and imaging, history of treatment, pattern of recurrence, pattern of chronicity and underlying control of glucose. If the therapeutic need is significant, I know intense and prolonged treatment will be required. This also presents a high likelihood of noncompliance. Therefore, when I see this scenario, I immediately consider combination therapy, and most of my patients prefer it. I also consider combination therapy for patients with less substantial disease who are high functioning and want to have as few office visits as possible.

For patients with mild disease, anti-VEGF treatment alone could be enough to improve and sustain visual acuity and restore the macular anatomy. Based on the results of the Protocol T trial, and if conditions permit, I start with Eylea. However, if the response isn’t as predictable as I’d like, I quickly shift to combination therapy. In my opinion, there is no rationale for giving a certain number of injections before considering additional therapy. My additional therapy of choice is the dexamethasone intravitreal implant (Ozurdex, Allergan). In my experience, this implant is longer lasting and doesn’t carry the risk of intractable glaucoma or pseudoendophthalmitis that I’ve seen with triamcinolone. None of my Ozurdex patients has required any treatment beyond drops for IOP, and a vitrectomy would enable removal, if needed. Now that the fluocinolone acetonide intravitreal implant (Iluvien, Alimera Sciences) has been approved for DME, it is an option as well, although its side-effect profile appears to be a challenge.

Understanding the Limits of Monotherapy

As our scientific knowledge grows, we see that diseases have myriad reasons for coming to exist and we need to combat them on that playing field. For example, the more we understand about oncogenesis, the more we understand the way retinal diseases manifest. As in cancer, anti-VEGF represents only one branch of therapy for DME. At this point, it is inconceivable that monotherapy will be all we need for successful treatment of the ocular effects of diabetes.

References

One-year results were recently published from “Afibercept, Bevacizumab, or Ranibizumab for Diabetic Macular Edema” (Protocol T), a clinical trial conducted by the Diabetic Retinopathy Clinical Research Network. Protocol T is an excellent trial that has broken new ground — it is the only study on this scale to directly compare three anti-VEGF medications for the treatment of patients with decreased visual acuity due to center-involved DME.

What Have We Learned?
We can pull several important points from the study report.

- All three medications led to excellent vision benefits in the patient population (Table 1) as a whole. The benefits were achieved with averages of 9 or 10 injections during the year. It’s worth noting that this is more injections than patients in this population typically receive in 1 year on average in clinical practice.

In addition, the re-treatment criteria used in the trial don’t precisely parallel how most patients are managed in clinical practice. In the first 6 months of the trial, patients received an injection each month unless protocol-defined stability was achieved, visual acuity was 20/20 and OCT showed no significant central DME, which was rare. After 6 months, the modified prn dosing strategy dictated that patients did not receive a treatment if visual acuity and OCT status hadn’t changed substantially over two consecutive injections, even if the macula continued to have substantial DME. In contrast, in clinical practice, if a patient’s progress hits a “plateau,” the treating physician would likely shift to a different strategy, perhaps treating more frequently, switching to a different anti-VEGF agent or adding a steroid, rather than simply not treating.

- Based on a pre-specified subgroup analysis, eyes with initial visual acuity worse than 20/40 achieved more substantial visual acuity improvement on average with Eylea than with Avastin or Lucentis, 18.9, 11.8 and 14.2 letters respectively.

- The anatomic effect of Avastin on retinal thickening was inferior to the effect of Lucentis or Eylea regardless of initial visual acuity, an important distinction because we know chronic edema limits the visual outcomes patients can ultimately achieve. On average, central subfield thickness decreased by 169±138 µm with Eylea, 147±134 µm with Lucentis and 101±121 µm with

Table 1. Protocol T Patient Population
- 660 participants with vision loss from center-involved DME randomly assigned to receive Eylea (224), Avastin (218) or Lucentis (218)
- mean age: 61±10 years
- women: 47%
- white: 65%
- type 2 diabetes: 90% of participants
- mean duration of diabetes: 17±11 years
- mean baseline visual acuity letter score: 64.8±11.3 (Snellen equivalent = 20/50)
- mean baseline central subfield thickness: 412±130 µm
- rate of completion of the 1-year visit: 96% (deaths excluded)
Avastin (P < .001 for both Eylea vs. Avastin and Lucentis vs. Avastin; P = .036 for Eylea vs Lucentis). The greater reduction in retinal thickness produced by Eylea was associated with a lower rate of supplemental laser treatment. The percentage of patients who received focal macular laser treatment was 37% with Eylea, 46% with Lucentis and 56% with Avastin.

Cost considerations are important. Ideally, patients would receive the medication that would work best for them, and according to the Protocol T results, the more expensive agents produced the best anatomical results in all subgroups, and Eylea treatment led to significantly better visual outcomes in patients with worse initial vision. The cost issue is a nearly insurmountable challenge for an individual physician. Many would argue this issue should be addressed on a national level as has been done in many developed countries. The United States is a rarity in the developed world in not considering pricing when approving new pharmaceuticals.

For example, in British Columbia, Canada, the government endorses splitting of Lucentis and Eylea vials, allowing for more than one treatment per vial.

A concern that one or more of the anti-VEGF agents causes more intraocular inflammation than the others was not borne out in this trial. Rates among the three agents were similar.

Both Eylea and Avastin contain an Fc domain, which theoretically leads to a longer systemic half-life. Lucentis does not contain an Fc domain. Differences in systemic exposure to anti-VEGF activity between the medications based on this difference is often debated and is a potentially clinically relevant issue. While the Protocol T trial wasn’t powered to detect small differences in safety, no differences were observed among the three agents in the rates of serious systemic adverse events, Anti-Platelet Trialists’ Collaboration events or deaths.

The Avastin used in the trial was repackaged by a single compounding pharmacy and stored in glass vials. It also was independently tested for purity and potency. Because these conditions aren’t met in many clinical practices, it’s unclear how real-world results with Avastin might differ.

The 0.3-mg dose of Lucentis, used only in the United States, was used in the trial. Therefore, the results may not be applicable in other countries, where the 0.5-mg dose is used in the management of DME. However, the 0.5-mg dose of Lucentis was found to have a worse side effect profile, especially when looking at rates of death.

All patients in the trial had visual acuity of 20/32 or worse. Therefore, the results may not directly apply to patients who have center-involved DME but visual acuity of better than 20/32.

Study Year 2 in Progress
The Protocol T trial has provided us with very good 1-year data regarding the treatment of DME, a chronic and complex disease. Longer-term data is needed, and the trial will continue for an additional year. We look forward to learning about the results achieved and further guidance that will emerge in year 2.

Reference
The recently completed round of clinical trials evaluating treatments for DME has led to FDA approval of several new options. While retina specialists can look to these trials for guidance on how to use the options in practice, we must also use our clinical acumen to determine what treatment strategy is best for each patient. Educating patients on the potential side effects of anti-VEGF agents and sustained-release steroid implants, and how we can manage them, so they’re active participants in their care, is a cornerstone of the approach employed in my practice.

**Anti-VEGF Agents**

The RISE/RIDE\(^1\) and VIVID/VISTA\(^2\) Phase III clinical trials confirmed the safety and efficacy of the anti-VEGF drugs Lucentis 0.3 mg and Eylea for the treatment of DME. With regard to safety, in RISE/RIDE there was a trend, which did not reach statistical significance, for a higher incidence of serious adverse events potentially related to systemic VEGF inhibition with the 0.5-mg dose of Lucentis compared with the 0.3-mg dose (the dose ultimately approved by the FDA). Also, when Lucentis and Avastin were compared for the treatment of age-related macular degeneration in the CATT trial,\(^3\) there was a signal, not statistically significant, for more serious systemic adverse events with the use of Avastin 1.25 mg.

I’ve found that when my patients weigh the potential yet largely theoretical systemic side effects of the anti-VEGF agents with the ability of these medications to save their vision, more often than not, they choose to proceed with anti-VEGF therapy as first-line. I discuss this option even with patients who have had a stroke. However, because vision doesn’t worsen in DME as quickly as it does in AMD, initial treatment with a steroid implant is a reasonable alternative for patients who suffered a stroke as recently as a few weeks ago if they are averse to any systemic risk. If necessary, we can supplement with anti-VEGF treatment in a few months.

**Sustained-Release Steroid Implants**

Two sustained-release steroid implants have also been cleared by the FDA for use in patients with DME. The MEAD\(^4\) and FAME\(^5\) clinical trials confirmed the safety and efficacy of Ozurdex and Iluvien for this indication. Cataract and glaucoma are the side effects of greatest concern with these treatment options. Cataracts, which are easily treated, tend to be less of a concern for me and my patients than the development of glaucoma. While an increase in IOP may occur with Ozurdex, it tends to be very predictable and the effect peaks in about 60 days. It’s reasonable to use Ozurdex in patients whether or not they have ocular hypertension if it is the only treatment that will save vision. For patients with ocular hypertension, I test their level of response to steroids with topical difluprednate ophthalmic emulsion 0.05% (Durezol, Alcon) prior to implanting Ozurdex. An increase of 1-2 mmHg does not concern me, while an increase of 4-5 mmHg may. I also consult with a glaucoma specialist to determine what IOP the patient can tolerate and I’m certain to measure IOP consistently at the same time of day.

It is not yet clear to me what role Iluvien will play in my practice, although I suspect I will recommend it for a very small minority of patients, perhaps those who have failed all other therapies and have a post-vitrectomized eye. The implant’s predicted 3-year duration of action is good, but we want to avoid the need for incisional glaucoma surgery that was noted in the clinical trial. This is especially true for young patients, in whom glaucoma surgery would alter
“Educating patients on the potential side effects of anti-VEGF agents and sustained-release steroid implants, and how we can manage them, so they’re active participants in their care, is a cornerstone of the approach employed in my practice.”

GAURAV K. SHAH, MD

the dynamics of the eye and potentially quality of life going forward. Also, it is difficult to predict which patients would actually require steroid treatment of a long duration such as 3 years. Finally, it remains to be seen whether commercial insurance carriers may be hesitant to cover a long-term steroid device in younger patients, which may lead to policies that curtail access to Iluvien.

Can Combination Therapy Enhance Safety?

We do have a strong rationale for utilizing combination therapy in patients with DME (See “Moving Beyond Monotherapy,” on page 7), although at this point, we don’t have supporting evidence from prospective clinical trials. That said, it’s not unreasonable to expect that if adding a drug to a treatment regimen allows us to use less of another drug that it would be beneficial with regard to safety.

In my practice, I combine anti-VEGF agents with a steroid implant or intravitreal triamcinolone (Triesence, Alcon) and/or laser when it’s necessary to achieve the desired treatment effect. I also may switch back and forth between different treatments, such as starting with an anti-VEGF agent, switching to Ozurdex, which may “break the cycle” of the disease, and then returning to anti-VEGF injections. In recalcitrant cases, I check for mechanical traction on the retina as well as consider systemic fluid overload and impaired kidney function as sources of macular edema. It is paramount to treat those issues before considering treatment for macular edema because not addressing them would only lead to treatment failure. It is helpful to work with internists and endocrinologists to aggressively manage systemic issues.

Focus on the Individual

From any perspective, having additional treatment options for our patients with DME has been a welcome development. As far as using them in the most effective and safe manner, I’ve found it works best to avoid fixed treatment protocols and see each patient as an individual, to follow the patient’s lead with regard to tolerance of side effects, and to take a direct role in helping patients to maintain solid control of the many systemic problems that accompany diabetes.

References


Iluvien, approved by the FDA last year, is the first DME treatment designed to have a therapeutic effect for 36 months. In a subgroup analysis from the pivotal Phase III FAME clinical trial, 34% of patients who had chronic DME (duration of ≥3 years) at baseline gained ≥15 letters of vision with Iluvien at 36 months compared with 22.3% of those with nonchronic DME. This may lend credence to the hypothesis that there are pathologic differences between chronic and nonchronic DME. “DME may progress through stages,” explains Pravin U. Dugel, MD. “For instance, it likely begins as a permeability-driven disease but over time becomes primarily an inflammation-driven disease. That means different treatments may be more or less effective at various stages, a concept we may someday be able to apply to clinical practice.”

For similar reasons, “As we gain more experience with Iluvien, we may find it to be useful as part of combination therapy,” notes Michael A. Singer, MD. “I’m currently following the first several patients in whom I’m using Iluvien.” (Figure 1)

Combination therapy for macular edema secondary to retinal vein occlusion (RVO) is being evaluated in a Phase II clinical trial, which will likely have eventual implications for DME as well. The trial is comparing the safety and efficacy of a suprachoroidal injection of a proprietary formulation of triamcinolone (CLS-TA, Clearside Biomedical) continued on page 15.

Figure 1. Prior to implantation of Iluvien, central foveal thickness (CFT) as measured by OCT in this eye with DME was 485 µm (a) and visual acuity was 20/150. One month after implantation, CFT had improved to 198 µm (b) and visual acuity was 20/70. Peripheral ischemia is also being monitored, and the implant had begun to have an effect on the ischemic index at 1 month. The index (area of ischemia defined as a percentage of the total visible retina) decreased from 71.4% prior to implantation (c and d) to 69.4% 1 month after implantation (e and f).
Recent Evaluations of Combination Therapy

Studies suggest that combining anti-VEGF and sustained-release steroid therapy may be beneficial in treating retinal vascular disease.

BY DESIREE IFFT, CONTRIBUTING EDITOR

The results of two recent prospective studies support the idea that combining anti-VEGF and sustained-release steroid therapy can be beneficial for patients with retinal vascular disease.

According to Michael A. Singer, MD, “In our study, we looked at the effectiveness of the combination of Avastin and Ozurdex in patients with retinal vein occlusion, primarily in terms of duration. We wanted to see whether the combination could add predictability to the equation, which it did.” The therapeutic effect of combination therapy, i.e., an edema-free macula on OCT, lasted for an average of 4 months in the study patients. The study also demonstrated the anatomic benefits of combined therapy. For example, at the second study visit, 38% of the patients treated with Avastin had central field thickness less than 300 µm. When Ozurdex was added, the percentage increased to 68%. “We expect these types of results to translate to patients with DME as well,” Dr. Singer says. “A number of studies are looking at this now, including REINFORCE.”

In another recent study, Raj Maturi, MD, and colleagues examined whether it’s beneficial to add Ozurdex to the treatment regimen of patients whose DME had been only partially responsive to multiple Avastin injections. Patients in the study were randomized to receive Avastin plus Ozurdex or Avastin monotherapy. Monotherapy eyes received Avastin monthly if indicated. Combination therapy eyes received monthly Avastin if indicated plus Ozurdex at month 1, month 5 and month 9. An Avastin injection was indicated at every monthly visit if central subfield thickness (CST) on OCT was greater than 250 µm and visual acuity was worse than 20/25.

At 12 months, visual acuity gains were similar in both groups, but improvement in CST and retinal volume were superior in the combination therapy group. The combination therapy group received three fewer

**Figure 1.** In Maturi et al., continued repeated Avastin injections did not provide a visual benefit in the Avastin alone group of DME patients. However, patients in the combination therapy group who had received the most Avastin injections prior to study enrollment gained the most vision with the addition of Ozurdex.
supplemental Avastin injections than the monotherapy group, but also required an average of 2.1 Ozurdex implants, somewhat of a counterbalance from a treatment burden standpoint. “Interestingly, it appears that once a patient receives multiple anti-VEGF injections, additional anti-VEGF injections don’t bring about any further reduction in edema,” Dr. Maturi says (Figure 1). “On the other hand, edema decreased markedly in the group that also received Ozurdex, leaving us to wonder if perhaps the best course might be to use sustained-release steroids alone in patients who are only partially responsive to a trial of anti-VEGF therapy.”

The study also demonstrated that the therapeutic effects of Ozurdex in the DME patient population last approximately 3 months. Based on that finding and others from this study, Dr. Maturi is conducting an additional study involving patients with anti-VEGF-resistant DME in which Ozurdex will be given every 3 months while supplemental Avastin is discontinued. He expects to have results from the follow-up study by summer 2015.

References

What’s New In DME Care

**continued from page 13**

combined with a single intravitreal injection of an anti-VEGF agent vs. the anti-VEGF agent alone.

“This is definitely an exciting concept because suprachoroidal delivery of the medication may produce fewer side effects, such as IOP elevation, than intravitreal treatments or drops, and the combination of steroid and anti-VEGF may have a longer-lasting effect than either treatment alone,” says Daniel Kiernan, MD. “Suprachoroidal delivery and new drug delivery strategies like nanoparticles will probably be how we treat retinal diseases in the future.”

Clearside recently announced results from another of its clinical trials, a Phase I/II study in which noninfectious uveitis was treated with a suprachoroidal injection of triamcinolone. At 6 months, the treatment led to anatomic and visual improvements and no patient required IOP-lowering medication.

> Widefield imaging has been an essential tool for exploring concepts related to macular edema and peripheral retinal ischemia. “Widefield angiography will be a game-changer for the DME patient population,” says Dr. Singer. “We’ve shown in RVO² that the extent of peripheral ischemia (assessed with the 200Tx, Optos) varies and fluctuates over time, changes dynamically in response to treatment and correlates with severity of edema and vision loss. We’ll be able to use this knowledge to monitor and perhaps even predict response to different treatments.”

Dr. Singer and colleagues have also used widefield imaging to map peripheral ischemia in patients with rebound edema so it can be treated with guided/targeted photocoagulation (Navilas laser, OD-OS). The company recently reported its finding that in order to achieve the best results, ischemia should be measured at the time of macular edema.³ “The map to follow is what’s measured when the retina is most swollen,” he says. “Steroid or anti-VEGF treatment can then be given prior to laser treatment.”

> OCT angiography (AngioVue, Optovue and Spectralis, Heidelberg Engineering), which enables 3D visualization of the retinal vasculature without a contrast agent, is also on the cutting edge of imaging for DME. According to Dr. Dugel, “New therapies and combination therapies being explored⁴,⁵ appear able to alter or stabilize the eye’s blood vessels in ischemic retinopathies such as diabetic eye disease. What better way to assess these types of changes than with OCT angiography?”

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