

Update on Pharmacologic Treatment of Diabetic Macular Edema

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BY GLENN J. JAFFE, MD

STATEMENT OF NEED

Diabetic macular edema (DME) is a complication of diabetes that affects an estimated 95,000 individuals each year in the United States alone.¹ DME has a significant impact on vision and quality of life; thus, new treatments offer the promise of great benefit to a growing patient population.² Beginning in 2003, the National Eye Institute of the US National Institutes of Health instituted a special program within the Diabetes Research Working Group aimed specifically at DME.³ In order to adequately respond to patient requests for information and evaluate potentially useful treatments progressing through clinical trials, eye care providers specializing in retinal care should be familiar with the current status of research into pharmacologic treatments of DME.

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2. Sharma S, Oliver-Fernandez A, Liu W, Buchholz P, Walt J. The impact of diabetic retinopathy on health-related quality of life. *Curr Opin Ophthalmol*. 2005 Jun;16(3):155-9.
3. National Eye Institute. Congressional Justification for FY 2003. Available at: www.nei.nih.gov/news/congressjust/cj2003.asp. Accessed February 12, 2006.

TARGET AUDIENCE

Medical and surgical retinologists.

LEARNING OBJECTIVES

Upon successful completion of this learning program, the participant should be able to:

- List and describe pharmacologic treatments for DME that are currently in use or undergoing human clinical trials;
- Describe the indications, prognosis and results of pharmacologic DME treatments; and
- Summarize the most recent studies in the peer-review literature on currently available pharmacologic treatments for DME and new treatments undergoing clinical trials.

METHOD OF INSTRUCTION

Participants should read the learning objectives and CME program in their entirety. After reviewing the material, they must complete the self-assessment test, which consists of a series of multiple-choice questions.

Participants have a choice of completing this activity online by visiting www.RetinaToday.com; getting real-time results at www.CMEToday.net; or by using the print forms following this activity.

Upon completion of the activity and achieving a

passing score of $\geq 70\%$ on the self-assessment test, participants will receive a CME credit letter awarding AMA PRA Category 1 Credit™ 4 weeks after the registration and evaluation materials are received. The estimated time to complete this activity is 1 hour.

ACCREDITATION

This activity has been planned and implemented in accordance with the essentials and standards of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of The Dulaney Foundation and *RETINA TODAY*. The Dulaney Foundation designates this educational activity for a maximum of AMA PRA Category 1 Credit.™ Physicians should only claim credit commensurate with the extent of their participation in the activity.

DISCLOSURE

In accordance with the disclosure policies of The Dulaney Foundation and to conform with ACCME and Food and Drug Administration (FDA) guidelines, all program faculty are required to disclose to the activity participants: 1) the existence of any financial interest or other relationships with the manufacturers of any commercial products/devices, or providers of commercial services that relate to the content of their presentation/material or the commercial contributors of this activity; and 2) identification of a commercial product/device that is unlabeled for use or an investigational use of a product/device not yet approved.

FACULTY DISCLOSURE.

Glenn J. Jaffe, MD, has received research support from Bausch & Lomb and Control Delivery systems and has a financial interest in pSividia.

FACULTY CREDENTIALS

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INTRODUCTION

Based on projections of data from the National Health and Nutrition Examination surveys, the American Diabetes Association estimates that there were 20.8 million cases of diagnosed and undiagnosed diabetes in the United States in 2005, representing 7% of the total population.¹

DME has long been recognized as an important cause of vision loss.^{2,3} Clinically significant macular edema (CSME) was defined in the Early Treatment

Diabetic Retinopathy Study (ETDRS) as any case in which there is retinal thickening within 500 μm of the center of the fovea; hard yellow exudates within 500 μm of the center of the fovea along with retinal thickening; or >1 disc area of retinal thickening, of which any part lies within 1 disc diameter of the center of the fovea.⁴

Studies have shown that poor glycemic control and higher levels of HbA1c are among the risk factors for the onset of DME.^{5,6} The Wisconsin Epidemiologic Study of Diabetic Retinopathy found rates of progression to DME of 26% in patients with diabetes for 14 years and 29% at 20 years or longer after diagnosis.^{7,8}

Based on the results of the ETDRS and subsequent clinical studies, laser photocoagulation has become the standard therapy for DME.⁹ The ETDRS found that laser photocoagulation reduced the rate of moderate visual acuity loss by 50% in eyes with CSME. The study also revealed some limitations of the treatment. Treated eyes rarely improved to 20/40 or better; only 3% of patients achieved an improvement of >3 lines of visual acuity 36 months after treatment; eyes with advanced retinopathy or diffuse macular edema responded less well; and no benefit was demonstrated in patients with non-CSME.

To prevent the development of DME as well as to treat eyes that are not suitable for laser photocoagulation or have derived the maximum benefit of laser treatment, other modalities have been examined in clinical trials. Results have been reported for pharmacologic treatment of DME with corticosteroids (injected and delivered by implants), protein kinase-C (PKC) inhibitors, and vascular endothelial growth factor (VEGF) inhibitors.

CORTICOSTEROID INJECTIONS

Because they effectively inhibit inflammation, stabilize cell membranes and enhance blood retinal barrier integrity, corticosteroids have been investigated as a potential treatment for DME.^{10,11} Oral and topical routes of administration inefficiently deliver corticosteroids to the posterior segment, and there are potentially serious systemic side effects with oral administration. These drawbacks are minimized with intravitreal or sub-Tenon's injection.

The Intravitreal Steroid Injection Studies—Diabetic Macular Edema (ISIS-DME) trial is a prospective study where patients were randomized to receive intravitreal injection of either a 2- or 4-mg dose of triamcinolone acetonide (Kenalog). The study enrolled 33 patients with CSME who failed to respond to laser photocoagulation and had visual acuity of $<20/40$. Six-month

results were recently reported.¹²

In the overall group of 24 patients in both the 2- and 4-mg dose groups with 6 months of follow-up, 38% had achieved 3 lines of visual acuity improvement for at least some of the follow-up period. Fluorescein angiography (FA) was used to categorize eyes as having either cystoid or noncystoid foveal edema based on the degree of vessel leakage. There was a statistically significant difference ($P=.01$) between the subgroups, with 62% (8 of 13) of those with cystoid foveal edema having a >3-line improvement in visual acuity and only 9% (1 of 11) patients with noncystoid foveal edema having a similar improvement. Although DME had completely resolved in 39% of patients 3 months after treatment, by 6 months only 18% of patients were without edema. The need for repeat injections to sustain therapeutic effect, especially in diffuse DME, was noted in the ISIS-DME study and as well as others.¹³

A retrospective study of 1- or 4-mg intravitreal injection of triamcinolone acetonide in 210 eyes of 174 patients with diffuse CSME found a statistically significant improvement from median visual acuity, from 20/200 to only 20/80 posttreatment.¹⁴ Optical coherence tomography (OCT) imaging showed that, in a group of 23 eyes with diffuse DME (including eyes with and without previous laser treatment), visual acuity improved quickly 2 weeks after a 4-mg triamcinolone acetonide injection, remained stable until 3 months posttreatment, then decreased by the 6-month follow-up.¹⁵ A prospective study of 53 eyes with diffuse DME receiving a 20-mg dose of intravitreal triamcinolone acetonide found a significant correlation between improvement in BCVA and higher degrees of edema.¹⁶ The presence of pronounced macular ischemia or higher levels of preoperative BCVA, however, had a negative correlation to patient outcome.

IOP rise was a common adverse effect in the ISIS-DME study (31% of patients had >10 mm/Hg increase) but was managed without surgery in all cases. Another review of studies in which approximately 20 mg of triamcinolone acetonide was injected intravitreally to treat a variety of posterior segment disorders — including DME — found postinjection IOP >20 mm/Hg in 68.1% of patients.¹⁷ Most of those cases were treated with medical therapy, and only three (1%) were managed with filtration surgery. Another study examining IOP after intravitreal injection of 4 mg (0.1 mL total volume) of triamcinolone found only a moderate and transient pressure rise that did not require paracentesis or other surgical intervention.¹⁸ As with any invasive procedure, infection is a serious potential complication and occurs in 0.1% to 0.87% of eyes that have received an



Photo courtesy of p5wida

Figure 1. Retisert (fluocinolone acetonide intravitreal implant 0.59 mg; Bausch & Lomb) is composed of an inactive non-biodegradable polymer substrate designed to release active drug over approximately 30 months.

intravitreal triamcinolone acetonide injection.^{19,20} The potential for steroid-induced cataract with higher doses of triamcinolone has also been recognized in other studies, and other complications including vitreous hemorrhage and retinal detachment have been reported.²¹ The optimal dose for intravitreal injection is still unclear.

Sub-Tenon's injection/infusion of corticosteroids has been investigated as a way to avoid potential complications of intravitreal injection. However, two recent prospective studies comparing sub-Tenon's to intravitreal injection of triamcinolone treatment for refractory DME found that both macular thickness (measured by OCT) and visual acuity were significantly better after intravitreal injection.^{22,23} The treatments were equivalent in terms of IOP rise and other adverse events in both studies. Thus, there seems to be no advantage to the sub-Tenon's route of corticosteroid injection. The need for repeat injections of steroids, however, could potentially be avoided if a sustained-release drug-delivery device were available. Several such devices are now being investigated.

CORTICOSTEROID IMPLANTS

Retisert

Implantable devices to deliver drugs to the posterior segment have been in clinical trials for more than a decade.²⁴ Retisert (fluocinolone acetonide intravitreal implant 0.59 mg; Bausch & Lomb, Rochester, NY) was granted an orphan drug approval by the FDA in April

TABLE 1. RESULTS OF PHASE 2 STUDY OF POSURDEX DEXAMETHASONE IMPLANT

| | 350- μ g group (n=100) | 700- μ g group (n=101) | Observation only (n=105) | P-value* |
|---|----------------------------------|----------------------------------|--------------------------------|----------|
| ETDRS visual acuity improvement > 2 lines | | | | |
| Day 90 | 26.1% | 36.7% | 19.0% | 0.005 |
| Day 180 | 27.2% | 35.7% | 19.0% | 0.008 |
| ETDRS visual acuity improvement > 3 lines | | | | |
| Day 90 | 13.0% | 16.3% | 9.0% | 0.115 |
| Day 180 | 13.0% | 19.4% | 8.0% | 0.020 |

* For 700- μ g dosage group versus observation-only group.

Results of the study are for macular edema associated with diabetes, retinal vein occlusion, noninfectious uveitis, or cataract surgery. Comparison of 350 μ g and 700 μ g implant dosages with patients receiving observation only.

Source: Allergan news release of data presented at American Academy of Ophthalmology, Nov. 20, 2003.

2005 for the treatment of chronic noninfectious uveitis affecting the posterior segment of the eye. The implant is composed of an inactive nonbiodegradable polymer substrate designed to release active drug over approximately 30 months (Figure 1).²⁵

Patients usually have a loss of visual acuity immediately after surgical implantation of the device, but this is a temporary phenomenon that resolves from 1 to 4 weeks after surgery. Medical therapy to control IOP was necessary in approximately 60% of patients enrolled in the uveitis study, and 32% of patients were expected to require filtering surgery within 2 years postimplantation. Almost all patients were expected to require cataract surgery by 2 years.²⁶ The implant was effective in controlling inflammation and improving visual acuity in patient with noninfectious uveitis that did not respond to other treatments.^{27,28}

The multicenter clinical trial of Retisert for the treatment of DME completed phase 3 in September 2005.²⁹ A group of 197 patients randomized to receive either the Retisert implant or repeat laser photocoagulation found that 58% of the eyes in the Retisert group had no evidence of DME at the 3-year follow-up point, whereas only 30% of the laser-treated eyes had a resolution of edema. These results were statistically significant

($P < .001$).³⁰ Visual acuity improvement of >3 lines was attained by 28% of eyes in the Retisert group versus 15% in the laser group ($P < .05$). Loss of >3 lines visual acuity was equivalent in both groups (19% with Retisert vs 16% with laser).

Adverse events included cataract in 95% of implanted phakic eyes over the 3-year study period. Of all implanted eyes, IOP rise was noted in 35%, the rate of filtration surgery was 28%, and in 5% of eyes the device was explanted to manage IOP. An analysis of prognostic factors revealed that patients with higher levels of BCVA; shorter duration of diabetes; and less severe DME derived significantly better results from the Retisert implant.³¹ Less benefit was noted in patients with cardiovascular disease and preoperative vitreomacular attachment. Resolution of DME was associated with better postoperative BCVA, but also with higher levels of postoperative IOP.

Posurdex

A biodegradable anterior-chamber intraocular implant (originally Surodex, later changed to Posurdex after the manufacturer was acquired by Allergan, Irvine, Calif) was developed by Oculex Pharmaceuticals to deliver dexamethasone at constant therapeutic levels.³²



Figure 2. The Medidur implant (fluocinolone intravitreal implant device) is a small device designed to be injected in an office setting.

A phase 2 randomized, multicenter controlled clinical study of the device to control persistent refractory macular edema by implantation into the posterior segment of the eye followed 306 patients, 165 of whom were affected by DME (Table 1). At the 6-month follow-up point, visual acuity was statistically significantly better in the subgroup receiving the 700- μ g implant, and a trend toward better visual acuity outcomes was noted in the 350- μ g group as well. Retinal thickness measured by OCT and vessel leakage measured by FA in eyes treated with both implant dosages were significantly better than observation-only eyes.

Adverse effects were usually related to the implantation procedure, in which the device was placed into the vitreous base region through a small pars plana sclerotomy. These included self-limited subconjunctival and vitreous hemorrhage.

Another study evaluated the 700- μ g Posurdex device inserted into the pars plana via a preloaded 22-gauge applicator (n=20) compared with incisional placement (n=10).³³ Sutures were not required for patients in the applicator group but were needed to close the wound in all patients in the incisional group. The incidence of adverse ocular events was reported to be lower and the implantation procedure was completed more quickly in the applicator group versus the incisional group.

Medidur

The Medidur implant, also a nonbiodegradable fluci-

nolone delivery device, was developed by the same manufacturer that created the Retisert implant (Control Delivery Systems, recently acquired by pSivida, Perth, Australia). The current phase 3 US and European clinical trials are underwritten by Alimera Sciences (Atlanta). Medidur is a smaller implant (Figure 2) designed to be injected in an office setting. No clinical study data on results with Medidur were available at press time.

PKC AND VEGF INHIBITORS

Increased levels of VEGF are associated with angiogenesis and increased vascular permeability that cause significant vision loss not only in DME but also in age-related macular edema (AMD). Blocking the action of VEGF has been found to be effective in inhibiting these processes.³⁴ PKC mediates the effects of VEGF, and when activated it will increase VEGF expression. Several agents to inhibit the activity of PKC and VEGF in diabetic vasculopathy are currently in clinical trials for systemic as well as ophthalmic applications.

Ruboxistaurin (Eli Lilly and Company, Indianapolis, Ind), is a selective PKC-beta inhibitor being investigated for treatment of diabetic peripheral neuropathy symptoms and diabetic macular edema. A clinical study found that, compared with placebo, orally administered ruboxistaurin significantly reduced retinal vascular leakage in patients with DME.³⁵ The effect was greater in eyes that had more leakage prior to treatment.

In the Protein Kinase-C Beta Inhibitor Diabetic Retinopathy Study (PKC-DRS), 252 patients with moderately severe to very severe nonproliferative diabetic retinopathy were randomized to receive placebo or 8-, 16-, or 32-mg doses of oral ruboxistaurin per day.³⁶ Patients receiving the 32-mg dosage had a delayed onset of moderate and severe visual acuity loss compared with the placebo group, and this effect was found to be associated with higher levels of DME prior to treatment. Rates of progression to proliferative diabetic retinopathy were equivalent among all groups. There were small but statistically significant differences in the rates of various adverse events among the subgroups, but these did not correlate with drug dosage.

Pegaptanib (Macugen; OSI Eyetech, Melville, NY/Pfizer, New York, NY) has been approved by the FDA for the treatment of AMD. Pegaptanib, administered by repeat intravitreal injection every 6 weeks, selectively binds to the VEGF₁₆₅ isoform. Results of a phase 2 study of 0.3-, 1-, and 3-mg doses the drug versus placebo injections in 172 patients were recently reported.³⁷

At the 36-week follow-up, patients receiving the 0.3-mg dose of pegaptanib had significantly higher median

visual acuity (20/50) compared with the sham-treatment group (20/63). A gain of approximately 2 lines of visual acuity was seen in 34% of the 0.3-mg treatment group versus 10% of the placebo group, which was also statistically significant. Mean central retinal thickness as measured by OCT was found to decrease in the treatment group (by 68 μm) but increase in the sham-treatment group (by 4 μm). Fewer patients who received pegaptanib went on to require laser photocoagulation. Adverse events were associated with the injection rather than the drug (one case of endophthalmitis, retinal detachment and vitreous hemorrhage) and did not have a significant effect on final visual acuity.

CONCLUSION

Laser photocoagulation has been a powerful tool in the treatment of diabetic eye disease. The growing variety of pharmacologic treatments and preventive agents for DME promise to preserve vision for even more patients at risk from this increasingly prevalent condition. ■

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This activity may also be completed online at www.cmetoday.net.

CME QUESTIONS

Circle the most appropriate answer in the "ANSWER SECTION" on the following page.

1. Approximately what percentage of patients with a diagnosis of diabetes can be expected to progress to DME within 20 years?
 - a. 5%
 - b. 15%
 - c. 30%
 - d. 50%
2. The Early Treatment Diabetic Retinopathy Study found that focal laser photocoagulation reduced the rate of moderate visual acuity loss by:
 - a. 5%
 - b. 15%
 - c. 30%
 - d. 50%
3. Potential complications of intravitreal corticosteroid injection include:
 - a. Retinal detachment
 - b. Endophthalmitis
 - c. Cataract
 - d. All of the above
4. The Retisert drug-delivery device can best be described as:
 - a. A nonbiodegradable intravitreal implant approved for the treatment of chronic noninfectious uveitis and currently in clinical trials for DME treatment
 - b. A biodegradable anterior-chamber intraocular implant currently in clinical trials for DME treatment; can be inserted using a 22-gauge applicator
 - c. An intraocular implant designed to be injected in an office setting, currently in clinical trials for DME treatment
 - d. None of the above
5. The Medidur drug-delivery device can best be described as:
 - a. A nonbiodegradable intravitreal implant approved for the treatment of chronic noninfectious uveitis and currently in clinical trials for DME treatment
 - b. A biodegradable anterior-chamber intraocular implant currently in clinical trials for DME treatment; can be inserted using a 22-gauge applicator
 - c. A nonbiodegradable intraocular implant designed to be injected in an office setting, currently in clinical trials for DME treatment
 - d. None of the above
6. The Posurdex drug-delivery device can best be described as:
 - a. A nonbiodegradable intravitreal implant approved for the treatment of chronic noninfectious uveitis and currently in clinical trials for DME treatment
 - b. A biodegradable anterior-chamber intraocular implant currently in clinical trials for DME treatment; can be inserted using a 22-gauge applicator
 - c. An intraocular implant designed to be injected in an office setting, currently in clinical trials for DME treatment
 - d. None of the above
7. Clinical studies of the protein kinase-C inhibitor ruboxistaurin found that:
 - a. The drug significantly delayed the onset of proliferative diabetic retinopathy
 - b. The 32-mg dosage significantly delayed the onset of moderate or severe visual acuity loss
 - c. Patients receiving higher dosages of the drug had more adverse events
 - d. All of the above
8. Patients who received intravitreal injection of pegaptanib versus placebo injection were found to:
 - a. Have improvement of 2 lines of visual acuity in more cases
 - b. Experience a reduction of central retinal thickness as measured on OCT
 - c. Have no greater rate of adverse events
 - d. All of the above

REGISTRATION/EVALUATION FORM: UPDATE ON PHARMACOLOGIC TREATMENT OF DIABETIC MACULAR EDEMA

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ANSWER SECTION

Circle the best answer for each question on page 40.

1. A B C D 2. A B C D 3. A B C D 4. A B C D 5. A B C D
 6. A B C D 7. A B C D 8. A B C D

REGISTRATION FORM

First name _____ Last name _____ Degree (MD, PhD) _____

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OBJECTIVES

(Please circle the number that is most accurate; 5 represents strongly agree, and 1 represents strongly disagree.)

After successful completion of this program, you should be able to:

- List and describe pharmacologic treatments for DME that are currently in use or undergoing human clinical trials 5 4 3 2 1
- Describe the indications, prognosis and results of pharmacologic DME treatments 5 4 3 2 1
- Summarize the most recent studies in the peer-reviewed literature on currently available pharmacologic treatments for DME and new treatments undergoing clinical trials 5 4 3 2 1

OVERALL EVALUATION

(Please circle the number that is most accurate; 5 represents strongly agree, and 1 represents strongly disagree.)

- The information presented increased my awareness/understanding of the subject. 5 4 3 2 1
- The information presented will influence how I practice. 5 4 3 2 1
- The information presented will help me improve patient care. 5 4 3 2 1
- The faculty demonstrated current knowledge of the subject. 5 4 3 2 1
- The program was educationally sound and scientifically balanced. 5 4 3 2 1
- The program avoided commercial bias or influence. 5 4 3 2 1
- Overall, the program met my expectations. 5 4 3 2 1
- I would recommend this program to my colleagues. 5 4 3 2 1

• If you anticipate changing one or more aspects of your practice as a result of your participation in this activity, please provide a brief description of how you plan to do so: _____

• Please provide any additional comments pertaining to this activity (positive and negative) and suggestions for improvements: _____

• Please list any topics you would like to see addressed in future educational activities: _____