

Intravitreal Triamcinolone for the Treatment of Diabetic Macular Edema

Jointly sponsored by The Dulaney Foundation and *RETINA TODAY*.

Release Date: September 1, 2007. Expiration Date: October 31, 2008.

This continuing medical education activity is supported by
an educational grant from Genentech.

BY MICHAEL S. IP, MD

STATEMENT OF NEED

Diabetic macular edema (DME) is a common manifestation of diabetic retinopathy (DR) that can have a serious impact on vision, including loss of central vision with related functional impairment. The prevalence of DME increases with the duration of both type 1 and type 2 diabetes. It is estimated that, over 15 years of diagnosed diabetes, approximately 20% of people with type 1 diabetes, 25% of people with type 2 diabetes taking insulin, and 15% of people with type 2 diabetes not taking insulin, will develop DME. The prevalence reaches approximately 30% in those who have had either type of the disease for 20 years.

The incidence of type 2 diabetes has increased in the United States in recent years, in conjunction with an increase in the incidence of obesity.⁴ This increase, in conjunction with the high incidence of DME in the diabetic population, makes DME a significant public health concern.

TARGET AUDIENCE

This activity is designed for retinal specialists and other ophthalmologists.

LEARNING OBJECTIVES

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

- Discuss the prevalence and natural history of DME.
- Cite the results of the DCCT trial and the ETDRS in terms of DME treatments and prevention.
- Explain the rationale, background, and results for laser treatment in DME.
- Discuss the current pharmacological options for the treatment of DME.
- Identify the rationale for the use of steroids in DME treatment and results from published data.

METHOD OF INSTRUCTION

Participants should read the learning objectives and

continuing medical education (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. This test is available exclusively online, at www.CMEToday.net. Once you register and log in, you can take the test, get real-time results, and print out your certificate. E-mail ckoury@bmctoday.com or call 484-581-1821 if you have any questions or technical problems with the Web site.

Upon completing the activity and achieving a passing score of $\geq 70\%$ on the self-assessment test, participants can print out a CME credit letter awarding *AMA/PRA Category 1 Credit*.™ 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 1 *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 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 CREDENTIALS

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FACULTY DISCLOSURE DECLARATIONS

Dr. Ip disclosed that he is a consultant for Sirion Therapeutics, Pfizer, Bausch and Lomb, Genentech, and QLT. He is on the speaker's list for Eli Lilly and Company.

INTRODUCTION

DME, a common manifestation of DR, can have a serious impact on vision, including loss of central vision with related functional impairment. The prevalence of DME increases with the duration of both type 1 and type 2 diabetes.¹⁻³ It is estimated that, during 15 years of diagnosed diabetes, approximately 20% of people with type 1 diabetes, 25% of people with type 2 diabetes on insulin therapy, and 15% of people with type 2 diabetes not on insulin therapy, will develop DME.³ The prevalence reaches approximately 30% in those who have had either type of the disease for 20 years.¹

The incidence of type 2 diabetes has increased in the United States in recent years, in conjunction with an increase in the incidence of obesity.⁴ This increase, in conjunction with the high incidence of DME in the diabetic population, makes DME a significant public health concern.

PROVEN THERAPIES

The only therapies that have been shown in large, long-term, prospective randomized studies to reduce the risk of vision loss from DME are tight control of glucose levels⁵ and laser photocoagulation⁶ (Figure 1).

In the Diabetes Control and Complications Trial (DCCT), tight glycemic control resulted in a reduction in risk of onset of DME by almost 25% compared with conventional care over a mean 6.5-year follow-up. In a 4-year extension of that study, risk of development of DME was reduced by 58% with the same regimen of intensive glucose control.⁷

Focal laser photocoagulation was shown to lower the risk of moderate visual loss in patients with DME by approximately 50% in the Early Treatment Diabetic Retinopathy Study.

Focal laser photocoagulation was shown to lower the risk of moderate visual loss in patients with DME by approximately 50% (from 24% to 12%) in the Early Treatment of Diabetic Retinopathy Study (ETDRS).⁶ Although laser photocoagulation was effective for some patients in this trial, 12% of treated patients developed visual loss by 3 years after initiation of treatment. In addition, in approximately 40% of treated eyes that had central macular edema at baseline, the central edema persisted at 1 year, and in 25% of

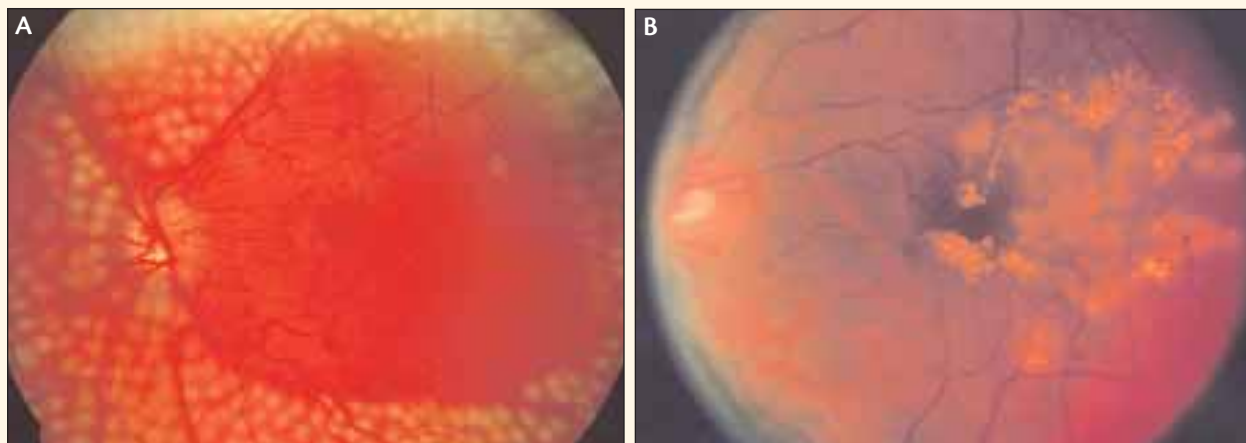


Figure 1. Fundus photos showing scatter laser surgery for DR (A), and focal laser surgery (B).

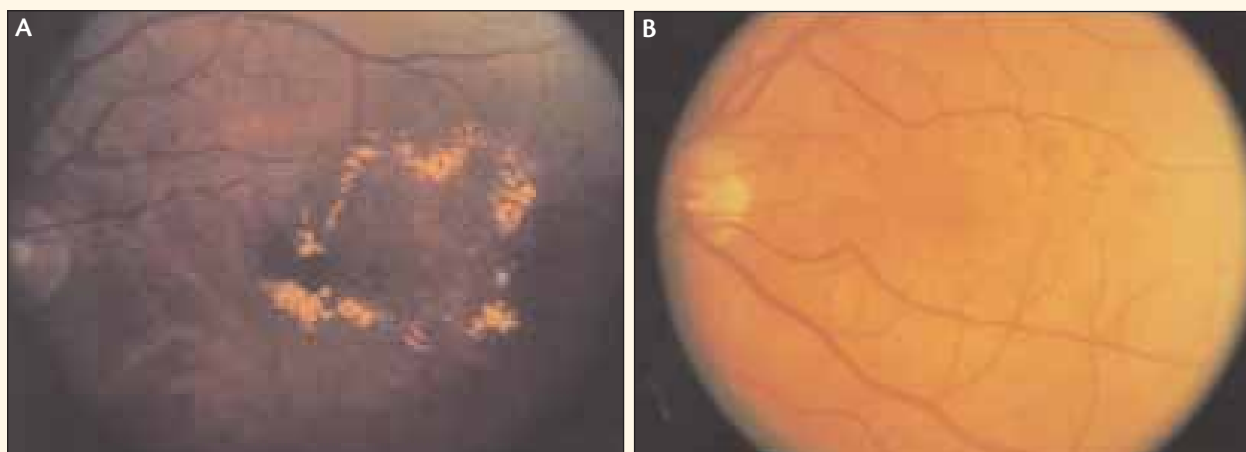


Figure 2. Fundus photo showing DME (A) and background retinopathy (B). Background DR is a slight deterioration in the small blood vessels of the retina, portions of the vessels may swell and leak fluid into the surrounding retinal tissue.

treated eyes it persisted at 3 years.

The lack of success in some DME patients (Figure 2) treated with laser photocoagulation has led to the investigation of other therapies. Vitrectomy, with resulting relief of vitreomacular traction, has been shown to resolve macular edema and partially restore visual function in some patients with DME.^{8,9,10} The surgery is complex and invasive, however, and it may benefit only a subset of patients with DME.

PHARMACOLOGIC APPROACHES

A number of pharmacologic therapies have been investigated for treatment of DME. Some of the most promising approaches involve the inhibition of vascular endothelial growth factor (VEGF), a potent vascular permeability factor.¹¹ VEGF inhibition has been investigated through intravitreal delivery of both corticosteroids and antibodies to VEGF. The two VEGF

inhibitors that have been approved in the United States for treatment of AMD, pegaptanib (Macugen; OSI/Eyetech and Pfizer, New York, NY) and ranibizumab (Lucentis; Genentech, San Francisco, CA.), are being investigated in clinical trials for their efficacy and safety in treating DME.^{12,13}

Much attention has been paid lately to these VEGF antibodies for the treatment of retinal diseases, but it should not be forgotten that corticosteroids have also been shown in the laboratory to inhibit the expression of VEGF.^{14,15} Because of this VEGF-blocking ability, corticosteroids including dexamethasone and triamcinolone acetonide have been investigated as possible treatments for DME.

INTRAVITREAL STEROIDS

Intravitreal delivery of corticosteroids can be accomplished by intravitreal injection or by implantation of a

sustained-delivery device. This activity concentrates on the intravitreal injection of the steroid triamcinolone acetonide (Kenalog; Bristol-Myers Squibb, New York, NY) for the treatment of DME.

The rationale for the use of triamcinolone in the treatment of DME is the steroid's ability to attenuate VEGF-mediated vascular permeability. Intravitreal injection places the drug in the posterior segment in close proximity to the target macular tissue. The treatment is easy to perform and inexpensive, and while data from large-scale prospective studies have been lacking, its popularity as a therapeutic option has been driven by promising initial anecdotal reports.

Machemer and colleagues first proposed the intravitreal use of triamcinolone to prevent the formation of proliferative vitreoretinopathy after retinal detachment surgery.¹⁶ Following animal studies to establish the safety of commercial triamcinolone acetonide for intravitreal use,^{17,18} the compound has been used to treat a number of retinal diseases, including AMD.¹⁹⁻²¹

The use of intravitreal triamcinolone for treating DME was first proposed in 1999 and reported in 2001.²² It was initially used only in patients whose DME was refractory to laser treatment,²³ but with promising early results and growing familiarity it is now used by many as a first-line treatment for DME.

A SAMPLING OF RECENTLY PUBLISHED EXPERIENCE WITH INTRAVITREAL TRIAMCINOLONE ACETONIDE IN DME:

Bonini-Filho MA, Jorge R, Barbosa JC, et al. Intravitreal injection versus sub-Tenon's infusion of triamcinolone acetonide for refractory diabetic macular edema: a randomized clinical trial. *Invest Ophthalmol Vis Sci.* 2005;46:3845-3849.

The authors compared the effectiveness of intravitreal injection with posterior sub-Tenon's infusion of triamcinolone acetonide in a prospective, randomized trial. In 28 eyes with diabetic macular edema (DME) that completed 24-week follow-up, macular thickness was reduced and visual acuity was improved more in the intravitreal group than in the sub-Tenon's group.

Jonas JB, Martus P, Degenring RF, et al. Predictive factors for visual acuity after intravitreal triamcinolone treatment for diabetic macular edema. *Arch Ophthalmol.* 2005;123:1338-1343.

In a prospective interventional study that included 53 eyes, the authors evaluated factors that contributed to maximum visual acuity improvement after intravitreal injection of triamcinolone acetonide for diffuse DME. Using multiple linear regression analysis, with a mean follow-up of 10.6 months, pronounced macular edema at baseline was significantly positively correlated with improvement in visual acuity. Marked macular ischemia was negatively correlated with visual acuity improvement. Previous macula grid laser treatment was not correlated with visual acuity improvement.

Ramezani A, Tabatabaie H, Ahmadi H. Diabetic macular edema before and after intravitreal triamcinolone injection.

Korean J Ophthalmol. 2007;21:95-99.

In this prospective interventional case series, the authors compared intravitreal triamcinolone acetonide to the natural course of refractory DME. Twenty-five eyes that had been assigned to the observation group in a previous trial were compared to 20 treated eyes. The authors found that treatment had a beneficial effect on macular thickness at 4 months but no significant effect on visual acuity compared to the natural course of DME.

Dehghan MH, Ahmadi H, Ramezani A, et al. A randomized, placebo-controlled clinical trial of intravitreal triamcinolone for refractory diabetic macular edema. *Int Ophthalmol.* 2007 Jun 23; [Epub ahead of print].

In this placebo-controlled prospective trial, 88 eyes with refractory DME were randomly assigned to receive intravitreal triamcinolone or placebo subconjunctival injection. Improvement in visual acuity and decrease in central macular thickness on OCT were significantly greater in the treated group at 2 months than in the sham group, but the difference disappeared by 4 months. Significantly greater reduction in hard exudates persisted in the treated group to 4 months.

Lam DS, Chan CK, Mohamed S, et al. Intravitreal triamcinolone plus sequential grid laser versus triamcinolone or laser alone for treating diabetic macular edema six-month outcomes. *Ophthalmology.* 2007; [Epub ahead of print]

This prospective, randomized, three-armed clinical trial evaluated sequential intravitreal triamcinolone acetonide

The dose generally used by ophthalmologists to treat DME is 4 mg in 0.1 mL.¹⁷ With the patient under topical anesthesia in the outpatient setting, the medication is delivered into the vitreous via the pars plana through a 27- to 30-gauge needle.

PUBLISHED DATA

Until recently there have been few published data on the efficacy and safety of triamcinolone for treatment of DME, but now data have begun to emerge from larger case series and from single-center prospective, controlled clinical trials (see *A Sampling of Recently Published Experience With Intravitreal Triamcinolone Acetonide in DME*).

followed by grid laser treatment versus either treatment alone in 111 eyes with DME. After treatment, significant reductions in central foveal thickness were seen in the intravitreal triamcinolone and combined groups, but not in the laser group. Differences in mean central foveal thickness between the groups were not significant at 6 months. Visual acuity improved significantly in the intravitreal triamcinolone group at 4 and 9 weeks, but not in the other two groups. The combination treatment did not yield better results than intravitreal triamcinolone alone. Laser alone was significantly worse than the other two treatments.

Sutter FK, Simpson JM, Gillies MC. Intravitreal triamcinolone for diabetic macular edema that persists after laser treatment: three-month efficacy and safety results of a prospective, randomized, double-masked, placebo-controlled clinical trial. *Ophthalmology*. 2004;111:2044-2049.

This prospective, double-masked, placebo-controlled, randomized, single-center study investigated whether intravitreal triamcinolone acetonide improves visual acuity in DME after laser treatment. Sixty-five eyes completed the 3-month study. Visual acuity improved by five or more letters in 55% of treated eyes and 16% of eyes receiving placebo injection. Macular edema was reduced by one or more grades on subjective assessment in 75% of treated eyes and 16% of placebo eyes. One eye developed endophthalmitis, which was treated without loss of visual acuity.

Brasil OF, Smith SD, Galor A, et al. Predictive factors for short-term visual outcome after intravitreal triamcinolone acetonide injection for diabetic macular oedema: an optical coherence tomography study. *Br J Ophthalmol*. 2007;91:761-765. Epub 2006 Nov 15.

This retrospective chart review identified predictive fac-

Until recently there have been few published data on the efficacy and safety of triamcinolone for treatment of DME, but now data have begun to emerge.

Martidis and colleagues²² were among the first to report their results with this treatment in a series of 16 eyes with clinically significant DME that had been unresponsive to laser treatment. All eyes completed

tors for visual outcome in 73 eyes treated with triamcinolone acetonide for refractory DME. With mean follow-up of 324 days, 27.3% of eyes had improvement of three lines or more of visual acuity, 6.8% showed a loss of three or more lines, and 60.2% remained within one line of baseline visual acuity. Factors associated with visual improvement included presence of subretinal fluid and worse visual acuity at baseline. Baseline factors negatively affecting visual outcome included presence of cystoid macular edema and epiretinal membrane. The authors concluded that OCT and baseline visual acuity can be helpful in predicting outcomes of intravitreal triamcinolone injection in refractory DME.

Trials evaluating intravitreal triamcinolone for DME currently under way by the Diabetic Retinopathy Clinical Research Network (DRCR.net)

- A Randomized Trial Comparing Intravitreal Triamcinolone Acetonide and Laser Photocoagulation for Diabetic Macular Edema

Status: enrollment completed; follow-up (3 years) ongoing

- Intravitreal Ranibizumab or Triamcinolone Acetonide in Combination with Laser Photocoagulation for Diabetic Macular Edema

Status: currently enrolling patients

Related DRCR.net trials:

- A Pilot Study of Peribulbar Triamcinolone Acetonide for Diabetic Macular Edema

Status: enrollment completed; follow-up (3 years) ongoing

- A Phase 2 Evaluation of Anti-VEGF Therapy for Diabetic Macular Edema: [Intravitreal] Bevacizumab (Avastin)

Status: enrollment completed; follow-up (70 weeks) ongoing ■

3 months' follow-up, and eight eyes completed 6 months' follow-up. Central retinal thickness, measured by optical coherence tomography, decreased from baseline by 55% at 1 month, 57.5% at 3 months, and 38% at 6 months, and mean visual acuity improvement was 2.4 lines, 2.4 lines, and 1.3 lines at those same intervals, respectively. Anatomical improvement was seen in 11 of the 16 eyes at 3 months.

Jonas and colleagues reported a series of 26 eyes with visual loss due to DME treated with intravitreal triamcinolone.²⁴ Visual acuity improved in treated eyes from a mean of 20/165 at baseline to a mean of 20/105 at the end of a mean follow-up period of 6.6 months. In a control group of eyes treated with laser, there was no improvement in visual acuity. In 21 patients for whom both pre-injection and post-injection fluorescein angiography were available, leakage decreased after the injection.

UNRESOLVED ISSUES

While these early case series and others subsequently published have been encouraging, there remain some caveats regarding the use of intravitreal triamcinolone acetonide to treat DME.

Adverse events, related to both the injection itself and to the potential toxicity of steroids, have been reported in published cases and case series to date. Events related to injection have included endophthalmitis, retinal detachment, and vitreous hemorrhage. Potential problems related to steroid toxicity include cataractogenesis and the development of glaucoma. In addition, the treatment effect is temporary, and repeated treatments expose the patient each time to the same risks.

There are also issues regarding the use of Kenalog, the commercially available formulation of triamcinolone acetate, for this indication. The drug is formulated for intramuscular or intra-articular use, not for intraocular use.²⁵ Its use for intravitreal injection is "off-label." Sterile inflammatory reactions after intravitreal injection of triamcinolone have been reported, and these can be difficult to distinguish from bacterial infection.

Over the past year, an increasing number of these sterile inflammatory reactions have been documented, and as a result many clinicians no longer use the commercial formulation of triamcinolone for intravitreal injection. Triamcinolone prepared at a compounding pharmacy is now typically used when it is believed that a corticosteroid injection is indicated. If clinical trials in progress demonstrate that triamcinolone

injections for DME are safe and effective, a sterile formulation of triamcinolone acetonide specifically for ophthalmology will be needed, containing no preservatives and no endotoxins.

Another concern related to the use of the commercial formulation of triamcinolone is that the optimal dose for intravitreal use has never been established. The current most commonly used dose, 4 mg in 0.1 mL, was arrived at more out of convenience than through empirical testing. The drug as supplied, 40 mg/mL, can easily be aliquoted into 4 mg/0.1 mL doses, and this volume is small enough to be tolerated in intravitreal injection. No data exist to support the safety or efficacy of this dose over any other, but an ongoing randomized, prospective clinical trial is investigating both a 4- and a 1-mg dose of triamcinolone for DME.²⁶

The Diabetic Retinopathy Clinical Research Network has a number of multicenter controlled clinical trials ongoing to assess the efficacy and safety of intravitreal triamcinolone.

In light of the potential benefit of intravitreal injection of triamcinolone in the treatment of DME, and the rapid adoption of this therapeutic option by the ophthalmic retina community, reliable evidence of the technique's safety and efficacy is needed. The Diabetic Retinopathy Clinical Research Network (www.drccr.net) has a number of multicenter controlled clinical trials ongoing to assess the efficacy and safety of intravitreal triamcinolone for DME in comparison to other treatments. In particular, one of the earliest trials undertaken by the DRCCR is comparing intravitreal triamcinolone injection with laser photocoagulation;²⁶ that study has completed enrollment and is in the follow-up phase. It is hoped that the results of the study will guide ophthalmologists in the proper use of this emerging treatment for DME. ■

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CME QUESTIONS

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1. What is the prevalence of diabetic macular edema (DME) in people who have had diabetes for at least 20 years?
 - a. 10%
 - b. 20%
 - c. 30%
 - d. 50%
2. The therapies that have been shown in large-scale prospective randomized trials to reduce vision loss in DME are:
 - a. intravitreal triamcinolone injection
 - b. tight glucose control
 - c. laser grid photocoagulation
 - d. (a) and (c) only
 - e. (b) and (c) only
3. Despite laser treatment, approximately what percentage of patients with DME experience vision loss by 3 years after initiation of treatment?
 - a. 5%
 - b. 12%
 - c. 20%
 - d. 25%
4. The dose of intravitreal triamcinolone that is commonly used to treat DME is:
 - a. 0.1 mg/mL
 - b. 0.4 mg/mL
 - c. 0.4 mg/0.1 mL
 - d. 0.8 mg/0.1 mL
5. Adverse ocular events that have been reported in relation to intravitreal injection of triamcinolone include:
 - a. retinal detachment
 - b. endophthalmitis
 - c. vitreous hemorrhage
 - d. all of the above
 - e. (a) and (c) only
6. Possible ocular sequelae of intravitreal triamcinolone related to steroid toxicity include:
 - a. cataract formation
 - b. secondary glaucoma
 - c. macular fold
 - d. all of the above
 - e. (a) and (b) only
7. Potential concerns regarding the use of the commercial formulation for triamcinolone acetonide for intravitreal injection include:
 - a. The drug is not formulated for intraocular use.
 - b. Use of the drug for this indication is "off-label."
 - c. Sterile inflammatory reactions have been increasingly reported with this application.
 - d. all of the above.
8. In addition to intravitreal triamcinolone injection, other options that are under investigation for treatment of DME include:
 - a. intravitreal injection of ranibizumab
 - b. intravitreal injection of pegaptanib
 - c. sub-Tenon's injection of triamcinolone
 - d. intraocular implantation of a device for sustained delivery of a steroid
 - e. all of the above