

Intravitreal Triamcinolone for Refractory Diabetic Macular Edema

Two-Year Results of a Double-Masked, Placebo-Controlled, Randomized Clinical Trial

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Objective: To report 2-year safety and efficacy outcomes from a trial of intravitreal triamcinolone acetonide (TA) injections (4 mg) in eyes with diabetic macular edema and impaired vision that persisted or recurred after laser treatment.

Design: Prospective, double-masked, placebo-controlled, randomized clinical trial.

Participants and Controls: Sixty-nine eyes of 43 patients were entered into the study, with 34 eyes randomized to receive active treatment and 35 placebo. Two-year data were available for 60 of 69 (87%) eyes of 35 of 41 (85%) patients; 9 eyes of 6 patients were lost to follow-up, of which 6 received a placebo and 3 received intravitreal TA.

Intervention: Triamcinolone acetonide (0.1 ml) was injected through the pars plana using a 27-gauge needle. Eyes randomized to placebo received a subconjunctival injection of saline.

Main Outcome Measures: Improvement of best-corrected logarithm of the minimum angle of resolution visual acuity (VA) by ≥ 5 letters after 2 years and incidence of moderate or severe adverse events.

Results: Improvement of ≥ 5 letters' best-corrected VA was found in 19 of 34 (56%) eyes treated with intravitreal TA, compared with 9 of 35 (26%) eyes treated with the placebo ($Z_{\text{generalized estimating equation}} = 2.73$, $P = 0.006$). The mean improvement in VA was 5.7 letters (95% confidence interval, 1.4–9.9) more in the intravitreal TA-treated eyes than in those treated with the placebo. An increase of intraocular pressure (IOP) of ≥ 5 mmHg was observed in 23 of 34 (68%) treated versus 3 of 30 (10%) untreated eyes ($P < 0.0001$). Glaucoma medication was required in 15 of 34 (44%) treated versus 1 of 30 (3%) untreated eyes ($P = 0.0002$). Cataract surgery was performed in 15 of 28 (54%) treated versus 0 of 21 (0%) untreated eyes ($P < 0.0001$). Two eyes in the intravitreal TA-treated group required trabeculectomy. There was one case of infectious endophthalmitis in the treatment group.

Conclusion: Intravitreal TA improves vision and reduces macular thickness in eyes with refractory diabetic macular edema. This beneficial effect persists for up to 2 years with repeated treatment. Progression of cataract and elevation of IOP commonly occur but appear manageable. Spontaneous improvement over years can still occur in eyes that are apparently severely affected by diabetic macular edema. *Ophthalmology* 2006;113:1533–1538 © 2006 by the American Academy of Ophthalmology.

As the prevalence of diabetes steadily rises throughout the world, improving the treatment of macular edema, the most common cause of loss of vision from diabetic retinopathy,^{1,2} is a major goal of ophthalmic research. Laser treatment has been proven to reduce the risk of loss of vision in patients with

clinically significant macular edema, but it is less effective in restoring vision after it already has deteriorated.³ Moreover, laser treatment is an intrinsically destructive procedure that itself can lead to loss of vision through progressive enlargement of laser scars with time.⁴ In the Early Treatment

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Dr Gillies is included as an inventor on patents relating to the formulation of triamcinolone for ocular use and its use for the treatment of retinal neovascularization but not macular edema. Drs Sutter, Simpson, and Larsson; Ms Ali; and Dr Zhu have no conflicting or proprietary interests.

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Diabetic Retinopathy Study (ETDRS), 26% of eyes with diabetic macular edema suffered progressive loss of vision despite laser treatment.³

Recent studies have highlighted a previously unsuspected role of inflammation in the pathogenesis of diabetic retinopathy. Leukocyte adhesion to the vascular endothelium and migration into the retinal tissue is an early feature in diabetic rat retinae, possibly stimulated by elevated levels of vascular endothelial growth factor. Although aspirin did not affect progression of diabetic retinopathy in the ETDRS,³ in higher doses it inhibited the development of retinopathy in both canine⁵ and rodent⁶ models.

Anecdotal reports of the use of intravitreally injected steroids for the treatment of diabetic retinopathy in humans have claimed unprecedented efficacy in eyes with impairment of central vision caused by diabetic macular edema.⁷⁻⁹ Because the retina is ontogenically part of the central nervous system, it is of interest that systemic steroid therapy can be highly efficacious in the treatment of some forms of brain edema. Although short-term data from anecdotal reports are encouraging, there are no reports yet published from adequately powered randomized clinical trials on the longer-term effects of high-dose locally delivered steroids for the treatment of macular edema. We recently reported the 3-month results from a double-masked, placebo-controlled, randomized clinical trial that showed that, at least in the short term, intravitreal triamcinolone acetonide (TA) injections reduce macular thickness and improve vision in eyes with macular edema that persists or recurs despite previous laser treatment.¹⁰ We now report the 2-year results from this study.

Materials and Methods

Patient Enrollment

This study was conducted in accordance with the Declaration of Helsinki and was approved by the South Eastern Sydney Area Health Service and University of Sydney research ethics committees. Safety data were reviewed by an independent safety-monitoring committee.* Patients were recruited from the retina clinics of Sydney Eye Hospital, a major public tertiary referral center, from March 2002 to April 2003. Patients with severe (involving the central fovea¹¹) diabetic macular edema, diffuse or focal, ≥ 3 months after at least one session of laser treatment and best-corrected visual acuity (BCVA) in the affected eye(s) of 20/30 or worse were included. Exclusion criteria were uncontrolled glaucoma, loss of vision due to other causes, systemic treatment with >5 -mg prednisolone (or equivalent) daily, intercurrent severe systemic disease, or any condition affecting follow-up or documentation.

Sample Size Calculation

Taking into account the results of the ETDRS,³ previous noncomparative series, and our own uncontrolled experience with intravitreal TA for diabetic macular edema, we estimated underlying event rates (gain of ≥ 5 letters on an ETDRS chart) of 10% in the

placebo group and 40% in the treatment group. A minimum of 32 eyes per group was required for 80% power of detecting this difference as significant at the 2-sided 5% level if all eyes were from different subjects. Adjusting for an estimated loss to follow up of 10% of eyes, we aimed to recruit 35 eyes per group.

Treatment Assignment

After signing the informed consent form, each patient was allocated randomly using sequentially numbered, sealed, opaque envelopes prepared from a list of computer-generated pseudo-random numbers of variable block size. Patients were randomized to receive either intravitreal TA or a placebo subconjunctival injection of saline. For patients with both eyes eligible on entry, the allocated treatment was applied to the right eye, whereas the left eye received the other treatment. For 2 patients in whom the second eye later became eligible, that eye was randomized separately.

Data Collection and Masking

Measurement of best-corrected logarithm of the minimum angle of resolution (logMAR) visual acuity (VA), the main outcome measure, was performed with ETDRS charts using standardized procedures by certified masked research officers. Intraocular pressures (IOPs) were measured using Goldman applanation tonometry. A masked clinical observer graded cataracts using Age-Related Eye Disease Study photographic standards.¹² The degree of macular edema at the fovea was graded at baseline with contact lens biomicroscopy using a subjective semiquantitative system (absent, mild, moderate, severe). When it became available, an objective measure of macular thickness, optical coherence tomography, supplanted semiquantitative grading to measure macular thickness. The average thickness of the central macula (1-mm diameter), as determined by a Fast Macular scan, was measured because this represents the most significant area for central VA. Patients were seen 1 and 4 weeks after treatment for determination of IOP and Snellen VA. They then underwent measurement of IOP, lens grading, measurement of BCVA, and measurement of central macular thickness every 3 months for the 2 years of the study. Source data verification was performed by an independent study monitor on all patients for eligibility, demographic, and all outcome data.

Grading of steroid-related adverse events was defined prospectively. Significant elevation of IOP was defined as an increase of >5 mmHg compared with the baseline level. Significant progression of cataract was defined as an increase of ≥ 2 Age-Related Eye Disease Study grades. The decision to institute glaucoma therapy was made along conventional lines in discussion with the patient, based on the degree of IOP elevation and extent of glaucomatous optic neuropathy, if present. The decision to perform cataract surgery also was made in discussion with the patient, taking into account the level of VA in both affected and fellow eyes. All eyes received a repeated injection of their assigned study medication at the time of surgery.

Treatment

Intravitreal TA (0.1 ml of 40-mg/ml TA [Kenacort 40, Bristol-Myers Squibb Pharmaceuticals, Noble Park, Australia]) was injected into the vitreous on the day of the baseline VA measurement under sterile conditions in a minor procedures area as an outpatient procedure, as previously described.¹⁰ Retreatment was considered at each visit as long as treatments were at least 6 months apart. Eyes with a reduction of VA of at least 5 letters from previous peak value and persistent central macular thickness $> 250 \mu\text{m}$ received retreatment with study medication. If VA had not im-

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proved by ≥ 5 letters when measured 4 weeks later and macular thickening persisted, then fluorescein angiography was performed and further laser treatment was applied, if the investigator thought it would be beneficial. Thus, eyes treated with a placebo or in which intravitreal TA was ineffective received standard laser treatment where appropriate.

Outcomes

Primary outcome measures were the percentage of eyes in which best-corrected logMAR VA improved by ≥ 5 letters at 2 years and percentage of eyes with moderate or severe adverse events. Secondary outcome measures were any change in VA relative to preinjection level and change in macular thickness as determined by optical coherence tomography. The number of macular laser treatments performed was recorded, but this was not a prospectively defined outcome. The decision to perform laser treatment was made by masked observers according to prospectively identified criteria as set out above.

Statistical Analysis

Efficacy data at 2-year follow-up were analyzed by intention to treat. For patients lost to follow-up before 2 years, the last observation was carried forward.¹³ A sensitivity analysis was performed

for the primary outcome, improvement of ≥ 5 letters, to investigate the potential effect of the missing data, by alternately assuming that all missing eyes had actually improved by ≥ 5 letters or that all missing eyes had not improved.¹³

Data were analyzed in SAS (SAS Institute, Cary, NC). Possible correlation between eyes of the same patient was taken into account using generalized estimating equation (GEE) methods.¹⁴ The primary outcome was analyzed using logistic regression with GEE, whereas continuous outcomes were analyzed using linear regression with GEE, with the baseline value as a covariate. Category of change in VA, number of treatments given, and cataract grade were compared between groups using the Mantel-Haenszel test for trend in proportions.

Adverse events were analyzed by treatment received for patients completing at least 12 months' follow-up. Proportions were compared between groups using the chi-square or Fisher exact test, as appropriate.

Results

A total of 69 eyes from 41 patients were included in the trial, of which 34 eyes were randomized to receive intravitreal TA and 35 to a placebo. **Figure 1** shows the flow of patients through the study. Two-year data were available for 60 of 69 (87%) eyes of 35 of 41

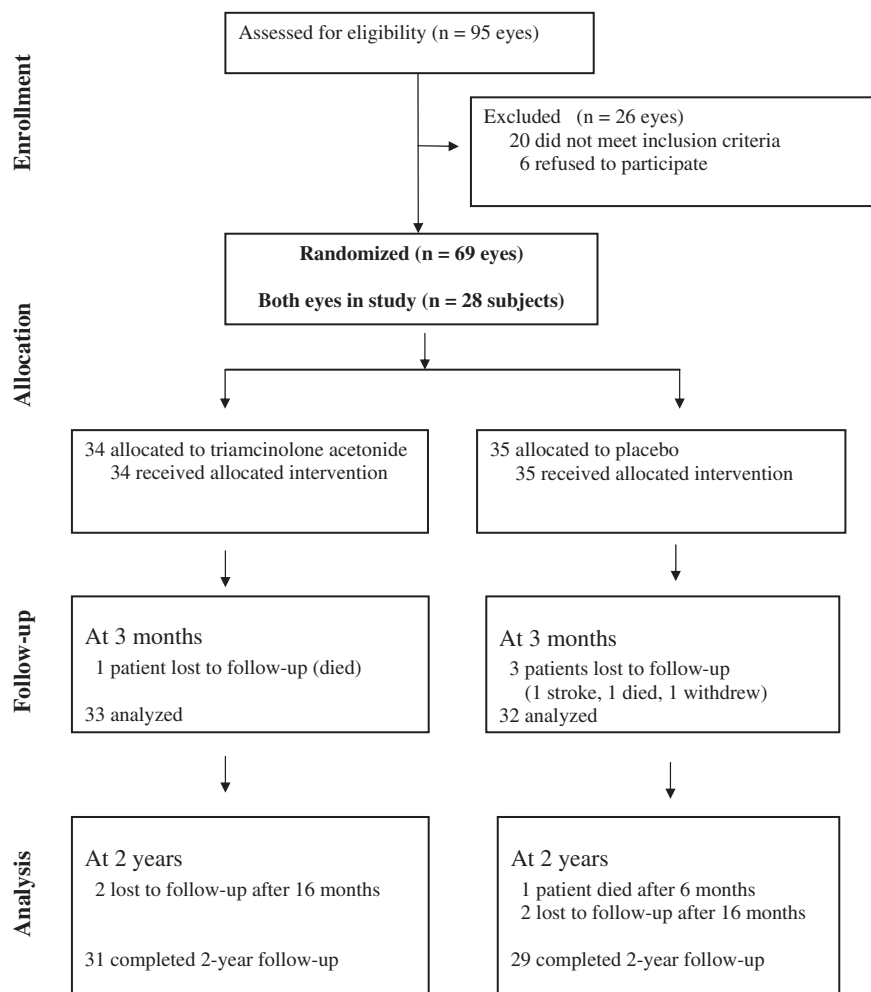


Figure 1. Flow of patients through the study.

(85%) patients; 9 eyes of 6 patients were lost to follow-up, of which 6 received the placebo and 3 received intravitreal TA. For the 27 patients with both eyes receiving different treatments, the average age was 64 years, and 13 (48%) were male. One 69-year-old man received intravitreal TA in both eyes, 6 months apart. Of the other 13 patients, 5 (mean age, 60 years; 3 male) received intravitreal TA and 8 (mean age, 67 years; 5 male) received the placebo. Baseline characteristics of intravitreal TA- and placebo-treated eyes were very similar (Table 1). The mean number of letters read by both groups at baseline was 61 (20/60).

For patients who completed the 2-year visit, intravitreal TA-treated eyes received significantly more treatments with study medication (mean, 2.6) than placebo-treated eyes (mean 1.8) (Table 2). By contrast, only 1 intravitreal TA-treated eyes, compared with 16 placebo-treated eyes, required further macular laser treatment ($P = 0.0001$).

Improvement of ≥ 5 letters' BCVA was found in 19 of 34 (56%) eyes treated with intravitreal TA, compared with 9 of 35 (26%) eyes treated with the placebo ($z_{GEE} = 2.73, P = 0.006$). The correlation between paired eyes was 0.27. Of the 9 placebo-treated eyes that gained ≥ 5 letters, 8 were from patients with both eyes in the study. Only 6 of 34 (18%) treated eyes lost ≥ 5 letters, compared with 13 of 35 (37%) untreated eyes (Table 3). The mean improvement in VA was 5.7 letters (95% confidence interval [CI], 1.4–9.9) more in the intravitreal TA-treated eyes than in those treated with placebo, allowing for correlation of 0.46 between paired eyes.

The sensitivity analysis showed that the analysis of the primary outcome was robust to the treatment of the missing data. If all missing eyes actually had improved by ≥ 5 letters, an improvement would have been found in 22 of 34 (65%) intravitreal TA-treated eyes, compared with 14 of 35 (40%) placebo-treated eyes ($z_{GEE} = 2.70, P = 0.007$). On the other hand, if all missing eyes had not improved, 19 of 34 (56%) intravitreal TA-treated eyes would have improved, compared with 8 of 35 (23%) placebo-treated eyes ($z_{GEE} = 3.18, P = 0.002$).

Macular Thickness

Optical coherence tomography became available after the 25th eye had been enrolled. Baseline data were available for all but 2 of the 44 eyes enrolled thereafter (Table 3). Foveal thickness had decreased by 59 μm (95% CI, 15–104) more in the treatment group than in the placebo group at 2 years ($z_{GEE} = 2.62, P = 0.009$).

Table 1. Baseline Characteristics of Eyes in Intravitreal Triamcinolone Acetonide (TA) and Placebo Groups

Characteristic	Intravitreal TA (n = 34)	Placebo (n = 35)
Visual acuity (letters) [mean (SD)]	60.5 (11.9)	61.3 (13.2)
Central macular thickness* (μm) [mean (SD)]	444 (125)	439 (101)
Intraocular pressure (mmHg) [mean (SD)]	16.6 (2.5)	16.3 (2.9)
Foveal edema [n (%)]		
Mild	10 (29)	11 (31)
Moderate	17 (50)	16 (46)
Severe	7 (21)	8 (23)
Cataract grade (% grade 0:1:2:3)		
Nuclear	54:43:3:0	47:50:3:0
Cortical	49:29:20:3	47:41:9:3
Posterior subcapsular	91:6:3:0	97:3:0:0

SD = standard deviation.
*n = 21 for each group.

Table 2. Distribution of Number of Treatments Given by Treatment Group for Patients Completing 2-Year Follow-up

No. of Treatments	Intravitreal TA (n = 31)	Placebo (n = 29)
1	6 (19%)	11 (38%)
2	9 (29%)	13 (45%)
3	10 (32%)	4 (14%)
4	4 (13%)	1 (3%)
5	2 (6%)	0
Mean	2.6	1.8
Median	3	2

TA = triamcinolone acetonide.
Mantel-Haenszel trend test $\chi^2_1 = 7.57, P = 0.006$.

Adverse Events

Moderate and severe adverse events are shown in Table 4. There were no cases of damage to the lens or retinal detachment after the intravitreal injections. The eye that developed endophthalmitis, the outcome of which was described previously,¹⁰ maintained improvement of vision throughout the study. Most eyes requiring glaucoma therapy began it within 6 months of baseline, but 2 of 15 (13%) eyes started treatment 7 to 9 months after treatment, indicating the need for continued vigilance.

Cataract surgery was performed in 15 of 28 (54%) intravitreal TA-treated eyes that were phakic at baseline, compared with 0 of 21 placebo-treated eyes (Table 4). Development of cataracts was delayed, with one third being removed each in the first, middle, and last thirds of the second year. The primary outcome (≥ 5 -letter improvement) actually was achieved in a slightly greater proportion of eyes that did not undergo cataract surgery (11/19 [59%]) versus those that did (8/15 [53%]), showing that the high rate of removal of cataract from intravitreal TA-treated eyes did not bias results in favor of the treated group. A more detailed description of the incidence and management of steroid-induced cataracts will appear elsewhere.

Table 3. Effect of Intravitreal Triamcinolone Acetonide (TA) on Change in Eye Outcomes from Baseline

Characteristic	Intravitreal TA (n = 34)	Placebo (n = 35)	P Value
Visual acuity [n (%)]			0.013*
Gain of ≥ 15 letters	4 (12)	1 (3)	
Gain of 10–14 letters	3 (9)	3 (9)	
Gain of 5–9 letters	12 (35)	5 (14)	
No change (gain or loss < 5 letters)	9 (26)	13 (37)	
Loss of 5–9 letters	3 (9)	4 (11)	
Loss of 10–14 letters	2 (6)	5 (14)	
Loss of ≥ 15 letters	1 (3)	4 (11)	
Mean gain in visual acuity (letters)	3.1	-2.9	0.01†
Reduction in central macular thickness‡ (μm)	125	71	0.009†

*From exact Mantel-Haenszel trend test, testing for overall shift across the 7 categories of change in visual acuity. This indicates a significant shift towards greater gain in the intravitreal TA group.
†Using generalized estimating equations to allow for correlations between paired eyes.
‡n = 21 for each group.

Table 4. Adverse Events by Received Treatment Group for Patients Completing at Least 12 Months' Follow-up

	Intravitreal TA (n = 34)	Placebo (n = 30)	P Value
2-yr cataract grade (% grade 0:1:2:3)			
Nuclear	68:29:3:0	33:57:7:3	0.007
Cortical	74:18:9:0	43:33:17:7	0.01
Posterior subcapsular	74:18:9:0	77:17:7:0	0.7
Moderate			
IOP increase \geq 5 mmHg	23 (68%)	3 (10%)	<0.0001
Glaucoma medication	15 (44%)	1 (3%)	0.0002
Cataract progression by \geq 2 grades	12/28 (43%)	3/21 (14%)	0.03
Cataract surgery	15/28 (54%)	0/21 (0%)	<0.0001
Trabeculectomy	2 (6%)	0	
Severe			
Infectious endophthalmitis	1 (3%)	0	
Corneal decompensation	0	1 (3%)	

IOP = intraocular pressure; TA = triamcinolone acetonide.

One patient allocated to placebo actually received intravitreal TA at 12 mos.

Discussion

This study demonstrates for the first time that treatment with intravitreal TA reduces thickening and improves vision for up to 2 years in eyes with advanced diabetic macular edema. Previous short-term uncontrolled studies could not address the possibility of spontaneous improvement that may occur in diseases such as diabetic retinopathy, nor did they take account of the effect of removal of steroid-induced cataract, which might eventually leave eyes worse off because cataract surgery is known to aggravate diabetic retinopathy.¹⁵ The high-level evidence from this double-masked placebo-controlled study that intravitreal TA not only improves vision but also reduces central macular thickening, the anatomical correlate of loss of vision in diabetic maculopathy, supports consideration of the treatment in carefully selected eyes that are losing vision despite standard treatment.

The conventional requirement for improvement in VA is by \geq 10 letters because of random fluctuation in VA measurements. The use of a 5-letter improvement in this study has allowed us to include patients with less advanced disease, which is when both the patient and the doctor may want new treatments—that is, when significant macular edema persists despite standard therapy but vision is not so severely affected and irreversible damage is less likely to have occurred. These patients would be unlikely to gain 10 letters because they have not yet lost that amount. Once the trial demonstrated a significant beneficial effect of treatment with respect to this primary end point of a small improvement by 5 letters, the overall pattern of changes in VA was examined. This revealed that intravitreal TA had as significant an effect on further deterioration as it had on improvement, with actively treated eyes having roughly half the chance of getting worse and twice the chance of improving.

Intravitreal TA-treated eyes commonly developed moderate steroid-related adverse events. The use of multiple

injections in the present study resulted in a greater risk of requiring glaucoma medication (44%) and cataract surgery (54%) than that associated with a single injection given in eyes with exudative age-related macular degeneration (41% and 34%, respectively¹⁶). Surgical intervention was required in 2 intravitreal TA-treated eyes during the study; otherwise, elevated IOP was controlled adequately with topical medication where required. Because intraocular surgery may exacerbate macular edema, the potential need for glaucoma surgery and the likelihood of cataract formation in phakic eyes should be emphasized when advising patients with diabetic macular edema in whom local steroid treatment is being considered. Eyes that underwent surgery had, on average, a visual outcome similar to that of those that did not, probably because the intravitreal TA, which was given at the time of surgery, prevented the exacerbation of retinopathy. This moderate risk of adverse events, however, may be outweighed by the beneficial effect that was seen in the treatment group in eyes for which there is no other treatment likely to improve vision or prevent its further deterioration. The low but significant risk of severe adverse events that may be associated with an intraocular injection, which have been reported to occur in 0.16% to 1% of injections,^{17–20} may also be acceptable in this context.

Although the number of eyes in each group in this trial was relatively small, the magnitude of the differences between treated and control groups was similar to that predicted, resulting in highly significant differences between the two groups for the primary and secondary efficacy outcomes. The greater dropout rate from the placebo-treated group may have biased the final result, but the sensitivity analysis suggests that this is unlikely. The high rate of cataract removal may have added bias in favor of the triamcinolone-treated groups, because nuclear sclerosis and cortical cataract did progress somewhat more in placebo-treated eyes. However, eyes in the triamcinolone-treated group that underwent cataract surgery had, if anything, a slightly lower rate of vision improvement than that of eyes that did not undergo surgery, suggesting that this was not the case.

We were surprised at the rate of spontaneous improvement of both vision and macular thickness among the placebo-treated eyes in the study, which was not evident at the 3-month visit but became quite prominent by the end of the study. The main outcome of the ETDRS was moderate visual loss, but they also reported that around 25% of eyes with macular edema, mild to moderate diabetic retinopathy, and VA of 20/40 or less assigned to delayed photocoagulation gained \geq 6 letters over 2 years, compared with around 42% of eyes allocated to receive immediate treatment. In the present study, 26% of placebo-treated eyes gained \geq 5 letters over 2 years, as did 56% of intravitreal TA-treated eyes.²¹ Although the early features of diabetic retinopathy certainly can regress if blood pressure and glycemic control improve, not only did eyes enrolled in this study have reduction of central vision, which was the result of an already relatively advanced stage of diabetic maculopathy, but this had persisted or recurred after standard laser treatment. Further laser treatment was not practicable in many. Although 8 of 9 cases of vision improvement in placebo-treated eyes oc-

curred in patients who had both eyes in the study and thus had received active treatment in the fellow eye, it seems unlikely but not impossible that the small dose of intravitreal TA that was instilled in one eye would have affected the fellow eye. More likely, participation in the study stimulated patients to redouble their efforts in controlling the systemic features of their diabetes. This also may have contributed to the lower than expected requirement for retreatment, with 48% of intravitreal TA-treated eyes requiring only 1 or 2 injections over the 2 years of the study. These observations emphasize the need to continue to stress to patients with advanced diabetic retinopathy and their caregivers the importance of achieving the best possible control of their systemic risk factors.

How locally delivered steroids should best be combined with existing treatments, such as retinal laser therapy, is the subject of ongoing clinical research. The potential efficacy of anti-vascular endothelial growth factor strategies for diabetic macular edema has been confirmed by a phase II study of pegaptanib.²² These treatments currently need to be given more frequently and are more expensive, but they also have fewer associated adverse events. Further elucidation of the mechanism of action of steroids in laboratory models may identify whether there is potential for synergy of steroids and photocoagulation or anti-vascular endothelial growth factor agents, which will then need to be tested in randomized clinical trials.

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