Pretreatment with Intravitreal Triamcinolone before Laser for Diabetic Macular Edema: 6-Month Results of a Randomized, Placebo-Controlled Trial

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PURPOSE. To determine whether pretreatment with intravitreal triamcinolone acetone (IVTA) before laser photocoagulation is effective in eyes with diabetic macular edema (DME).

METHODS. The study was a prospective, double-masked, placebo-controlled, clinical trial of eyes with DME and impaired vision (≤20/40) randomized to IVTA 4 mg versus placebo 6 weeks before laser treatment. The main outcome measure was the proportion of eyes with improvement of best-corrected logarithm of minimum angle of resolution (logMAR) visual acuity of ≥5 letters after 6 months. Secondary outcomes were necessity of further treatment, change in central macular thickness, and incidence of adverse events.

RESULTS. Eighty-four eyes of 54 participants were entered into the study, with 6-month data available for 81 (96%) of 84 eyes. Improvement of ≥5 logMAR letters was similar in eyes treated with IVTA before laser as placebo (18/42 [43%] IVTA vs. 16/34 [47%] laser alone; P = 0.807), as were retreatment rates at 6 months (22 [56%] IVTA vs. 21 [53%] laser alone; P = 0.727). Mean central macular thickness decreased by 50 μm (95% confidence interval, 10–96 μm) more in the IVTA treatment group than in the laser-alone group after 6 months (P = 0.016). Glaucoma therapy was necessary more frequently in IVTA-treated eyes than in those treated with laser alone (19/42 [45%] vs. 7/42 [17%]; P = 0.005).

CONCLUSIONS. Visual results and the need for further laser treatment at 6 months were no better in the IVTA group than in the laser-alone group, despite a better anatomic outcome reflected by reduction in mean central macular thickness. This study found no evidence of a synergistic effect of IVTA and laser photocoagulation for DME. (ClinicalTrials.gov number, NCT00148265.) (Invest Ophthalmol Vis Sci. 2010;51:2322–2328) DOI:10.1167/iovs.09-4400

Recent clinical research has shown that diabetic macular edema (DME) is responsive to intravitreal treatment with both steroids and antivascular endothelial growth factor agents, with favorable results reported, at least in the short term.1–5 Although laser photocoagulation remains the gold standard treatment for most eyes with DME,6 intravitreal steroids may be considered for recalcitrant DME in which laser treatment is no longer effective and feasible.7–8 However, multiple applications of both intravitreal steroid and laser are often necessary.

A key question to be addressed by randomized clinical trials is whether steroids that reduce DME can be combined with laser treatment to produce better, more efficient (i.e., less retreatment), and safer outcomes in the clinic. It is well known that the more swollen the macula, the more laser energy is needed to achieve a reaction at the level of the retinal pigment epithelium. Thus, reducing the edema before laser treatment may allow more precise laser photocoagulation with lower energy, which may be expected to result in a better outcome. Concurrently, laser treatment after application of steroids may also reduce the risk of the edema recurring as the injected steroid dissipates and thus reduce the need for further steroid injections. However, there are few prospective trials that have investigated the combined effects of intravitreal triamcinolone (IVTA) and laser on DME outcomes. One report suggested that laser treatment after IVTA for DME reduces risk of recurrence;3 however, subsequent data from another study did not support this effect.10

We conducted a randomized, double-masked, placebo-controlled clinical trial to test the hypothesis that IVTA applied before laser treatment of eyes with DME results in better clinical outcomes. In this report we focus on the short-term outcomes from this study, specifically on whether there is a synergistic effect of pretreatment of IVTA and laser on visual acuity, central macular thickness, and requirement for retreatment at 6 months.

METHODS

Patient Enrollment

This study was conducted in accordance with the tenets of the Declaration of Helsinki and was approved by the Research Ethics Committees of the four participating clinical centers. Safety data were reviewed by an independent Safety Monitoring Committee. Patients were recruited from the Retina Clinics of the Sydney Eye Hospital; the Royal Victorian Eye and Ear Hospital, Melbourne; the Lions Eye Institute, Perth; and Marsden Eye Specialists, Sydney from April 2005 to April 2007. Consecutive patients with diffuse or focal DME involving...
the central fovea with central macular thickness (CMT) of greater than 250 μm as measured by optical coherence tomography (Stratus; Carl Zeiss Meditec, North Ryde, NSW, Australia) and best-corrected logarithm of the minimum angle of resolution (LogMAR) visual acuity (VA) in the affected eye(s) of 17 to 70 letters (~20/40–20/400) were invited to enter the study. In contrast to our previous randomized clinical trial of triamcinolone for advanced DME,7 the investigator had to consider it likely that laser treatment would be beneficial and also that it could be delayed for 6 weeks without significant adverse effects. Exclusion criteria were uncontrolled glaucoma or controlled but with a glaucomatous visual field defect; loss of vision due to other causes; systemic treatment with >5 mg prednisolone (or equivalent) daily; retinal laser treatment within 4 months; intraocular surgery within 6 months; and concurrent severe systemic disease or any condition affecting follow-up or documentation.

Sample Size Calculation

Taking into account the results of the Early Treatment of Diabetic Retinopathy Study (ETDRS) and our own experience with IVTA for DME,7 we estimated an underlying event rate (gain of ≥5 letters on a logMAR chart) of 15% in the placebo group and 45% in the treatment group. A minimum of 36 eyes per group was required for an 80% power of detecting this difference as significant at the two-sided 5% level, if all eyes were from different subjects. Adjusting for an estimated loss to follow-up of 15% of the eyes, we sought to recruit 42 eyes per group.

Treatment Assignment

After providing informed consent, each patient was randomly allocated to receive either IVTA or a placebo by means of sequentially numbered, sealed, opaque envelopes, each containing a number from a list of computer-generated pseudorandom numbers of variable block size. For patients with both eyes eligible on entry, the allocated treatment was applied to the right eye, and the left eye received the other treatment. A master code was kept in a sealed envelope in the locked filing cabinet of another clinical coordinator in the department who was not otherwise involved in the study. Eyes randomized to receive placebo were prepared the same way as those receiving IVTA, but an empty syringe without a needle was used to mimic the feeling of pressure on the eye.

Patients were seen 1 and 3 weeks after study treatment for determination of IOP and logMAR VA. They underwent laser treatment 6 weeks after injection of the study medication according to prospectively defined guidelines that took into account the nature, distribution, and extent of leakage exhibited on the angiogram that was performed before the study injection. For four patients in whom the second eye later became eligible, that eye was allocated the same study number as the first enrolled eye but received the reverse treatment from that of the first enrolled eye.

Data Collection and Masking

The measurement of best-corrected logMAR VA, the main outcome measure, was performed according to standardized procedures by certified research officers who were masked to treatment allocation. IOPs were measured by Goldmann applanation tonometry. A masked clinical observer graded cataracts according to Age-Related Eye Diseases Study (AREDS) photographic standards.11 Optical coherence tomography (OCT) was performed (Stratus; Carl Zeiss Meditec) to measure the average thickness of the central macula (1 mm diameter) as determined by a Fast Macular scan, which was selected because it represents the most significant area in central VA. Patients were also masked to whether they received IVTA or placebo before laser treatment.

After the initial treatment cycle of the study injection followed by laser, participants underwent measurement of IOP, lens grading, best-corrected VA, and CMT every 3 months for 12 months.

The grading of steroid-related adverse events was defined prospectively. Significant elevation of the IOP was defined as an increase of more than 5 mm Hg compared with the baseline level. Significant progression of cataract was defined as an increase of two or more AREDS 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 the extent of glaucomatous optic neuropathy, if present. The decision to perform cataract surgery was also made in discussion with the patient, taking into account the level of VA in both the affected and fellow eyes. All eyes received a repeated injection of their assigned study medication within 1 month before surgery or at the time of surgery.

Treatment

Eyes assigned to IVTA received an intravitreal injection of 0.1 mL of 40 mg/mL triamcinolone acetonide (Kenacort 40; Bristol-Myers Squibb Pharmaceuticals, Noble Park North, Victoria, Australia) on the day of the baseline VA measurement under sterile conditions in an outpatient minor-procedures area, as previously described.1 Eyes assigned to laser alone were prepared in the same way but had the barrel of the syringe without a needle pushed firmly against the eye to simulate an injection.

Retreatment with injection of study medication followed by laser was considered at the discretion of the chief investigator at each site at each visit, as long as treatments were at least 6 months apart, unless any of the following was present:

- The investigator considered the macula nearly flat, and central OCT thickness was <300 μm.
- VA was 79 letters or better (20/25) or VA had improved by ≥5 letters compared with the best VA after treatment or baseline acuity.
- Laser treatment was considered by the investigator as inappropriate or the patient had no potential for improvement.

Outcomes

The primary outcome measures were the proportion of eyes in which best corrected logMAR VA improved by 5 letters after 6 months, and the proportion of eyes with adverse events. Secondary outcome measures were any change in VA compared with the preinjection level, change in CMT as determined by OCT, requirement for further treatment at 6 months, and the proportion of eyes with adverse events. Since the decision to perform laser treatment was made by masked observers according to these prospectively identified criteria, the third secondary outcome was expected to provide a measure of disease persistence or recurrence.

Statistical Analysis

Data were analyzed on the basis of original intention-to-treat 6 months after entry into the study. In the 54 patient (84 eyes) records, the last observation was carried forward for the three eyes with missing 6-month data (Stata SE, ver. 9.2; StataCorp, College Station, TX). Correlation between the eyes of the same patient was taken into account by using generalized estimating equation (GEE) methods. The continuous measurement of reduction in OCT CMT, was analyzed by using linear regression with GEE, with the baseline value as a covariate and logistic regression for binary outcomes. Category of change in VA was compared between groups, with the Mantel-Haenszel extension of χ² used to ascertain the statistical significance of a trend for proportions.

Results

A total of 84 eyes of 54 patients were enrolled in the trial, of which 42 eyes were randomized to receive IVTA plus laser treatment and 42 to laser treatment alone. Flow of patients through the study is presented in Figure 1. Three patients (three eyes) missed their 6-month visit, of which two received laser alone and one received IVTA plus laser. For these three eyes with missing 6-month data, the last observation was car-
ried forward from their 3-month records. Baseline, 3-month, and 6-month characteristics of 54 participants (84 eyes) are shown in Table 1.

Visual Acuity

Change in VA is presented in Table 2. Improvement of $\geq 5$ letters of best corrected VA was found in 18 (43%) of 42 eyes treated with IVTA before laser compared with 16 (38%) of 44 eyes treated with laser alone ($z_{\text{GEE}} = 0.24, P = 0.807$). The correlation between paired eyes was 0.32. Of the 16 laser-alone–treated eyes that gained $\geq 5$ letters, 12 were of patients with both eyes in the study. Loss of $\geq 5$ letters was found in 13 (31%) of 42 IVTA-treated eyes, compared with 11 (26%) of 42 eyes in the laser-alone group. The laser-alone group had a mean improvement in VA of 0.2 (95% confidence interval [CI], 0.2 to 3.7) letters more than the IVTA-treated eyes, allowing for correlation of 0.32 between paired eyes (Table 2). Individual VA responses over the 2 years of the study are presented in Figure 2.

Central Macular Thickness

Mean CMT decreased by 50 $\mu$m (95% CI, 10–96 $\mu$m) more in the treatment group than in the laser-alone group after 6 months ($z_{\text{GEE}} = 2.42, P = 0.016$; Table 2). The laser-alone group showed a slight gradual decrease in CMT, whereas the triamcinolone plus laser patients had a marked reduction in CMT after 6 weeks followed by slight increases at 3 and 6 months (Fig. 3).

Retreatment at 6 Months

Twenty-two (56%) eyes in the IVTA group needed retreatment at 6 months, compared with 21 (53%) for laser alone. The observed difference was not statistically significant ($P = 0.727, \chi^2$).

Safety

Elevated IOP $\geq 22$ mm Hg at any time during the 6 months after study entry was found in 25 (60%) of 42 eyes treated with IVTA compared with 15 (36%) of 42 receiving laser alone ($P = 0.029$), and increased IOP by $\geq 5$ mm Hg at any time during follow-up was found in 29 (69%) of 42 eyes treated with IVTA compared with 17 (40%) of 42 receiving laser alone ($P = 0.009$). Glaucoma therapy was commenced in 19 (45%) of 42 eyes in the IVTA group versus 7 (17%) of 42 in the laser-alone group ($P = 0.005$).

Progression of nuclear, cortical, or posterior subcapsular cataract was not found in any eye of either group.

The only severe local adverse event was one case of culture-negative endophthalmitis in an eye treated with IVTA. This eye was treated with intravitreal antibiotics after the patient presented the day after the injection with panophthalmitis and a...
small hypopyon. The VA had returned to baseline level (20/60) by the 3-month visit.

There were no other significant local adverse events, including retinal detachment or damage to the crystalline lens. One participant experienced progression of epiretinal membranes to a similar extent in both eyes, one of which was treated with laser alone, the other with IVTA.

**Effect of IVTA on the Fellow Eye**

Of the 42 eyes that underwent laser treatment alone, 30 of the fellow eyes received IVTA, since both eyes had been eligible to enter the study. To determine whether IVTA in one eye might have a therapeutic effect on the fellow eye that received laser alone, we compared change in CMT 6 weeks and 6 months after study treatment and in VA at 6 months between the two groups. There was no significant difference between the group of eyes with fellow eyes that received IVTA and the group that did not, in mean reduction in central macular thickness after 6 weeks (17.4 vs. 12.6, P = 0.969, independent t-test).

**DISCUSSION**

In this double-masked, placebo-controlled, randomized clinical trial, we tested the hypothesis that there is a synergistic effect between IVTA and laser photocoagulation for DME. We found that, after 6 months, there was no difference in VA between eyes receiving IVTA before laser treatment and that in those treated with laser alone, despite a greater mean reduction in CMT in eyes treated with IVTA. Although it is very possible that vision would have improved after some of the eyes in the group that received IVTA at the 6-month visit received a second injection, our results do not support a short-term synergistic effect between IVTA and laser photocoagulation. Moreover, there was also no synergistic effect of pretreatment with IVTA on the requirement for further laser at 6 months, according to prospectively defined guidelines. We looked for but did not find any evidence of a confounding effect of IVTA treatment on fellow laser-alone–treated eyes in the significant proportion of study participants who had both eyes entered in the study. Therefore, our study suggests that pretreatment with IVTA does not improve the efficacy of laser photocoagulation for DME.

Most of the eyes in our earlier study of IVTA for advanced DME were unsuitable for laser photocoagulation.† In the

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>IVTA+Laser (n = 42)</th>
<th>Laser Only (n = 42)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual acuity, n (%)</td>
<td>0.787*</td>
<td>0.787*</td>
<td>0.787*</td>
</tr>
<tr>
<td>Gain of ≥10 letters</td>
<td>12 (29)</td>
<td>10 (24)</td>
<td>0.787*</td>
</tr>
<tr>
<td>Gain of 5–9 letters</td>
<td>6 (14)</td>
<td>6 (14)</td>
<td>0.787*</td>
</tr>
<tr>
<td>No change, gain or loss &lt;5 letters</td>
<td>11 (26)</td>
<td>15 (36)</td>
<td>0.787*</td>
</tr>
<tr>
<td>Loss of 5–9 letters</td>
<td>6 (14)</td>
<td>7 (17)</td>
<td>0.787*</td>
</tr>
<tr>
<td>Loss of ≥10 letters</td>
<td>7 (17)</td>
<td>4 (9)</td>
<td>0.787*</td>
</tr>
<tr>
<td>Best corrected visual acuity (gain of ≥5 letters), n (%)</td>
<td>18 (45)</td>
<td>16 (38)</td>
<td>0.807†</td>
</tr>
<tr>
<td>Mean gain in visual acuity, n (letters)</td>
<td>1.55</td>
<td>1.78</td>
<td>0.909†</td>
</tr>
<tr>
<td>Reduction in central macular thickness, μm</td>
<td>98.5</td>
<td>45.8</td>
<td>0.016‡</td>
</tr>
<tr>
<td>Percentage of patients with retreatments</td>
<td>21 (52.5)</td>
<td>22 (56.4)</td>
<td>0.727‡</td>
</tr>
</tbody>
</table>

* From exact Mantel-Haenszel trend test, testing for overall shift across the five categories of change in visual acuity. No evidence of any shift pattern.
† Using generalized estimating equations to allow for correlations between paired eyes.
‡ χ² test for association.
present study, the patient population was more similar to that of the study recently reported by the Diabetic Retinopathy Clinical Research Network (DRCR.net).6 As in the DRCR.net study, improvement in VA in the present study occurred at a higher rate after laser treatment alone than we had anticipated.

Our study contrasts with several related clinical trials which have in fact reported a synergistic effect of combining steroid therapy with laser photocoagulation for macular edema. Tunc et al.12 reported that eyes with diffuse DME undergoing laser had better VA outcomes after 18 weeks if treatment was preceded by a posterior sub-Tenon’s capsule injection of triamcinolone. Whether the added beneficial effect would have lasted for 6 months, which was the duration of the present study, is uncertain. Kang et al.9 randomized 86 eyes with diffuse DME to receive IVTA, either alone or followed by grid laser. They found improvement in VA and CMT in both groups after 3 weeks; however, after 6 months, these improvements were maintained in the combined group only, suggesting again that laser treatment acted synergistically with IVTA and resulted in a more prolonged benefit of the latter. Mean VA and CMT were worse after 6 months than at 3 months in the present study; however, we did not include a group receiving IVTA alone. Such a group may have deteriorated to a greater extent after 6 months. Since laser photocoagulation is the standard treatment.
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for DME, we chose to study whether IVTA improves its efficacy rather than vice versa, as in the study by Kang et al.19 Avitabile et al.15 randomized 60 eyes with cystoid macular edema secondary to either diabetes or retinal occlusive disease to receive IVTA, laser photocoagulation, or both. Since VA and macular thickness outcomes were consistently better in the two groups receiving triamcinolone for up to 9 months and there was no apparent difference between the laser plus triamcinolone and the triamcinolone-alone groups, they suggested that triamcinolone is superior to laser for this indication. However, it is not clear from their report what the status of the macular edema was after the first dose of triamcinolone had worn off in the groups receiving triamcinolone with and without adjunctive laser treatment.

Our data are more consistent with those in the study by Lam et al.,10 who reported a randomized controlled trial of 111 patients with DME randomized to grid laser photocoagulation, 4 mg of IVTA, or 4 mg of IVTA combined with sequential grid laser approximately 1 month later. As in the present study, IVTA combined with laser produced greater reduction in CMT than did laser treatment alone; however, there was no significant difference in VA after 6 months. A limitation was that their report did not provide data on the proportions from each group that warranted further intervention for persistent or recurrent edema—information that is important to both patients and clinicians.

It has been noted that change in CMT is a poor surrogate marker for change in VA in eyes with DME,14 probably because of the influence of confounding variables, such as the degree of irreversible structural damage to the fovea which is difficult to measure and for which it is difficult to control. Thus, the functional significance of the apparent better anatomic results in the group receiving triamcinolone combined with laser in the present study is uncertain.

The rationale for combining IVTA with laser comes from current understanding of the mechanisms of action of laser photocoagulation for DME. Laser energy is absorbed by the retinal pigment epithelium rather than the retinal capillaries.15,16 Since it has been established that preretalinal oxygen tension is increased over laser scars,17,18 it has been proposed that destruction of the RPE/photorceptor complex results in improved oxygenation of the inner retina, leading to retinal vasoconstriction and thus reduced leakage.19 Improved oxygenation of the inner retina would also presumably result in reduced expression of vascular endothelial growth factor. An alternative hypothesis, which is strengthened by the observation that subthreshold micropulse diode laser photocoagulation can reduce DME without apparently terminally injuring RPE cells,20,21 is that laser stimulates the RPE to produce trophic factors that restore the damaged blood-retinal barrier.22–25 Whatever the mechanism, bringing the retinal capillaries closer to the site of action of laser treatment would be expected to improve the efficacy of the latter, which could also be applied with lower energy. This synergism would also be expected to pertain to other drugs that reduce macular thickness before laser photocoagulation, such as the VEGF inhibitors. One possible explanation for the apparent lack of synergism evident from the present study could be that IVTA’s beneficial effect on macular edema is offset by a modulation of the response to photocoagulation in a way that reduces its long-term efficacy. Whether this will also be found with VEGF inhibitors remains to be seen.

Steroid-related adverse events were seen at a rate similar to those in previous reports. These consisted mainly of elevated IOP. No significant progression to cataract was found; however, cataract generally does not occur until a year or so after an injection of IVTA in most eyes in which it develops.7 Culture-negative endophthalmitis, one case of which was seen in the present study, is an uncommon event after injection of the commercially available preparation of triamcinolone acetonide that we used. It usually, but not always, clears without a deleterious effect on vision.24

There are some limitations and strengths of the present study that are worth noting. With 42 patients per group, this was not a large study. A much larger study may not have reached different conclusions, however, because the differences in event rates between the two treatment groups with respect to change in VA and need for retreatment were small. Strengths of the study include strict adherence to randomization procedures and double-masking as well as the use of objective outcome criteria.

The results of our present study suggest that pretreatment of eyes with DME with IVTA before laser treatment may not have beneficial effects on vision at 6 months or on the need for further treatment, despite a better anatomic outcome reflected by reduction in mean CMT. Thus, there appears to be no short-term synergistic effect of IVTA on laser treatment for eyes with DME.

Acknowledgments

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References


11. Age-Related Eye Disease Study Research Group. The age-related eye disease study (AREDS) system for classifying cataracts from...


