The Transient Efficacy of a Single Intravitreal Triamcinolone Acetonide Injection for Diabetic Macular Edema

Howard Desatnik MD, Zohar Habot-Wilner MD, Amir Alhalel MD, Iris Moroz MD, Joseph Glovinsky MD and Joseph Moisseiev MD

Goldschleger Eye Institute, Sheba Medical Center, Tel Hashomer, Israel
Affiliated to Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel

Key words: diabetic macular edema, diabetic retinopathy, laser photocoagulation, triamcinolone acetonide intravitreal injection, optical coherence tomography

Abstract

Background: The major cause of visual impairment in diabetic patients is macular edema. The failure of laser photocoagulation in a large subgroup of patients with clinically significant diabetic macular edema has prompted interest in other treatment methods.

Objectives: To evaluate the long-term efficacy and safety of an intravitreal injection of triamcinolone acetonide for clinically significant diabetic macular edema.

Methods: In a retrospective case series 31 diabetic patients with persistent, recurrent or diffuse clinically significant diabetic macular edema received a single 4 mg (0.1 ml) intravitreal triamcinolone acetonide injection and were followed for at least 6 months. The main outcome measures evaluated were classified as primary: visual acuity and central macular thickness, and secondary: intraocular pressure and cataract progression. Statistical analysis included Student’s t-test, chi-square test and the MacNamar test.

Results: Best visual acuity results were observed 2.6 ± 2.4 months post-injection. At that time the mean foveal thickness had decreased by 37% from a baseline of 455 ± 100 to 288 ± 99 µ (P < 0.001) and the mean visual acuity improved from 6/42 to 6/23 (P < 0.001). Final mean visual acuity after an average of 10 ± 1.8 months follow-up (range 6–13 months) was identical to the baseline, although mean foveal thickness was still significantly lower than the initial thickness (368 ± 166 vs. 455 ± 100 µ, P < 0.01). Statistical analysis did not identify any pre-injection prognostic factors for improved visual acuity. The only complications that occurred were elevated intraocular pressure in 42% of patients and cataract progression in 21%. There was no endophthalmitis.

Conclusions: Intravitreal injection of triamcinolone acetonide for clinically significant diabetic macular edema is effective in reducing foveal thickness and improving visual acuity in the short term. Longer follow-up revealed that visual acuity returned to pre-injection values, even though a modest decrease in the foveal thickness persisted. Further studies are needed to evaluate the long-term efficacy in conjunction with laser photocoagulation treatment.

IMAJ 2006;8:383–387

For Editorial see page 426

Diabetic retinopathy is the leading cause of blindness in patients aged 20–74 years in the United States [1,2]. The major cause of visual impairment in diabetic patients is macular edema, which affects about 30% of patients with disease duration of more than 20 years [3]. In the Early Treatment Diabetic Retinopathy Study, the 3 year risk of moderate visual loss (a doubling of the initial visual angle or a decrease of three or more lines on a logarithmic visual acuity chart) was 30% for patients with clinically significant diabetic macular edema. In the ETDRS study a significant benefit was demonstrated when using focal laser for CSDME. Immediate focal laser photocoagulation reduced moderate visual loss in mild to moderate non-proliferative diabetic retinopathy by approximately 50% [4]. However, 12% of treated eyes still lost 15 or more ETDRS letters at the 3 year follow-up. In contrast, fewer than 3% of the treated eyes showed an improvement in visual acuity of the same magnitude. In addition, 24% of immediately treated eyes had thickening involving the center of the macula at 36 months. These findings suggest that a distinct subgroup of eyes exists with CSDME resistant to conventional laser photocoagulation. Previous studies have demonstrated that eyes with the diffuse form of CSDME show a poor visual prognosis despite laser treatment [4-7]. Focal macular edema is more responsive to laser photocoagulation. The failure of laser photocoagulation in a large subgroup of patients with CSDME has prompted interest in other treatment methods. Surgical treatment with pars plana vitrectomy [8-13] and subtenon or intravitreal triamcinolone acetonide injection had favorable results for diffuse diabetic macular edema [14-18]. However, the impressive anatomic results and improvement in visual acuity after IVTA injection proved to be short lasting (3–6 months). Thus, there is a need for a solution involving either repeated injections or implantation of a corticosteroid slow-release device to prevent recurrent macular leakage and edema, thereby maintaining the improvement and stabilization of visual acuity in the long term. Long-term complications of chronic intravitreal steroid use may be the limiting factor to the chronic use of steroids in these eyes. The most common complications from an IVTA injection were found to be elevated intraocular pressure in 25–50% [19-22] and cataract development or progression in approximately 25% of cases [15,16,19,23]. Cases of endophthalmitis have been reported and the increased incidence (0.5–0.87%) [24,25] may be related to an insufficiently strict aseptic technique for intraocular injection.

ETDRS = Early Treatment Diabetic Retinopathy Study
CSDME = clinically significant diabetic macular edema
IVTA = intravitreal triamcinolone acetonide
The purpose of the present study was to evaluate the long-term efficacy and safety of a single intravitreal triamcinolone acetonide injection as treatment for clinically significant diabetic macular edema.

Patients and Methods
We conducted a retrospective chart review of 31 consecutive diabetic patients (31 eyes) who received a single 0.1 ml (4 mg) IVTA injection (Kenalog®, Bristol-Myers Squibb, Italy) during the period September 2002 to February 2003 and were followed for at least 6 months. All patients had a complete eye examination and optical coherence tomography studies (OCT 3, Carl Zeiss Ophthalmic System Inc, CA, USA) immediately before the injection and several times during the follow-up period (usually at day 0, 2 weeks, 2–3 months, 4–6 months, and every 3 months thereafter). All patients had persistent diffuse clinically significant diabetic macular edema. The data retrieved from the charts included age, gender, history of previous laser treatments, anti-glaucoma medications (when applicable), and details of the ophthalmic examination, including visual acuity, slit-lamp examination, tonometry, dilated fundus examination and OCT 3. Visual acuity was measured with Snellen charts. The series mean visual acuity at the different follow-up visits, the difference in visual acuity between the series means, the individual visual acuity changes, and all statistical analyses were calculated after converting the Snellen visual acuity to logMAR units. Since this was a retrospective study the endpoints for a significant visual acuity change chosen were halving or doubling of the visual angle (equal to a change of about three ETDRS lines), calculated by conversion to logMAR units. Eyes with less than this visual acuity change were defined as stable. In order to facilitate understanding the results, the mean and median visual acuity results of the series at the different follow-up examinations were reconverted to Snellen acuities. Central foveal thickness was measured in microns by the OCT 3 studies.

Statistical analyses included Student's t-test for continuous variables, chi-square test for non-continuous variables, and MacNamar test for identifying prognostic factors for a significant visual acuity change, as defined above.

Patients
Nineteen males and 12 females were included in the study series. The age range was 40–88 years (mean 64 ± 11, median 64.5 years). Nineteen eyes were phakic and 12 were pseudophakic with a posterior chamber intraocular lens. Eighteen eyes had non-proliferative diabetic retinopathy and 13 had proliferative diabetic retinopathy treated with panretinal photocoagulation. Prior macular laser treatment was performed in 21 eyes, between one and four times per eye. Four eyes had primary open angle glaucoma controlled with topical therapy. The follow-up range was 6–13 months (mean 10.0 ± 1.8, median 11 months). Twenty-one patients (68%) had at least 10 months follow-up.

IVTA injection technique
All injections were performed in the operating room, and a single Kenalog® (triamcinolone acetonide) (Bristol-Myers Squibb, Italy) syringe was used for each patient. Topical Lidocaine HCL 200 mg/10 ml (esracain 2%, Rafa Laboratories, Israel) was applied to the ocular surface for 1–2 minutes, and the eyelids and the conjunctival sac were sterilized with 5% povidone iodine. The eye was draped and an eye speculum was placed. The Kenalog suspension was aspirated from the syringe after vigorous shaking, and 4 mg (0.1 ml) was injected into the vitreous cavity at the inferotemporal quadrant. In phakic eyes the injection site was 4 mm from the limbus and in pseudophakic eyes 3.5 mm from the limbus. No paracentesis was performed either before or after the injection. The eye was patched with chloramphenicol 5% ointment (synthomycin 5%, Rekah, Israel) for 3 hours. All patients received olofoxacin 3 mg/ml drops (OfloX® Allergan, Westport, Ireland) 3 times a day for 5 days following the injection.

Results
The major visual acuity and foveal thickness data are presented in Table 1.

<table>
<thead>
<tr>
<th>Table 1. Summary of visual acuity and foveal thickness data</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Baseline</td>
</tr>
<tr>
<td>Best post-IVT</td>
</tr>
<tr>
<td>(2.6 months)</td>
</tr>
<tr>
<td>Final</td>
</tr>
<tr>
<td>(10.0 months)</td>
</tr>
</tbody>
</table>
Final post-injection data

The final visual acuity ranged from 6/9 to 6/240, with a mean of 6/42 (logMAR 0.84 ± 0.42) and a median of 6/40 (logMAR 0.82). The final visual acuity was therefore identical to the initial one. The central foveal thickness was 140–800 μ (mean 368 ± 166 μ), a 19% decrease in foveal thickness compared to pre-injection foveal thickness, and this difference was statistically significant (t-test, P < 0.01).

At the end of the follow-up, 4 eyes (13%) had a moderate visual gain (halving of the visual angle), 4 eyes (13%) had a moderate visual loss (doubling of the visual angle), and the other 23 eyes (74%) were defined as stable. The follow-up time for these three groups of eyes was 9.75 ± 2.6, 9.75 ± 1.5, and 10 ± 1.8 months respectively, and the difference was not statistically significant. Figure 1 demonstrates the individual final visual acuity results for all patients, in logMAR values compared with the initial visual acuity.

A statistical analysis using the MacNamar test failed to identify any prognostic factor for improved final visual acuity, but poor initial acuity (6/30–6/60) approached statistical significance.

Complications

The most common complication was elevated intraocular pressure. Ten of the 27 normotensive eyes (37%) had pressure elevation to 25 mmHg or more, and required topical anti-glaucoma therapy. One eye required argon laser trabeculoplasty. Seven of these 10 eyes still required topical therapy by the end of the follow-up. The mean initial IOP in the normotensive eyes was 17 ± 3 mmHg, the mean highest IOP was 23 ± 6 mmHg, and the difference was statistically significant (P < 0.001). The mean IOP at the end of the follow-up was 17 ± 4 mmHg, almost identical to the initial IOP, but with seven of the eyes still on topical therapy. Three of the four eyes (75%) with primary open angle had significant IOP elevation, to 28 mmHg or more, and were controlled with additional topical and oral anti-glaucoma medications. Cataract progression was observed in 4 of 19 phakic eyes (21%). Endophthalmitis, retinal tears, retinal detachment, lens damage or vitreous hemorrhage did not occur in any of these eyes.

Discussion

The results of this retrospective case series demonstrate significant short-term improvement in visual acuity and in foveal thickness in patients with CSDME with a single 4 mg intravitreal injection of Kenalog. Almost all eyes demonstrated a significant reduction in foveal thickness, including those that were refractory to previous laser photocoagulation. The median time to best visual acuity was 2 months, halving of the visual angle (equal to improvement of about three ETDRS lines) was observed in 42% of the eyes, and in 19% the acuity improved by an amount equal or greater to four ETDRS lines. At 2.6 months post-injection, the mean time of the best-observed visual acuity, the foveal thickness had decreased by 37% compared to the pre-injection measurement. This finding concurs with the results of other studies. Ciardella and co-authors [18] showed a decrease in central macular thickness of 42% at 1 month post-injection after a single intravitreal injection of 4 mg triamcinolone, and 47% at 3 months post-injection. Martidis et al. [16], using the same dose of triamcinolone, showed a decrease in central macular thickness of 55% and 57% from baseline values at 1 and 3 months respectively. However, in our case series, by 10 months post-injection the central macular thickness had increased as the macular edema recurred, with a concomitant decline in visual acuity to pre-injection levels. Among our patients, 74% had stable visual acuity while 13% had doubling of the visual angle and 13% had a halving of the visual angle. A similar pattern of recurrent macular edema followed by a decline in visual acuity after reaching its maximum positive effect at 1–3 months was demonstrated by Martidis [16] and Ciardella [18] and their teams. Of interest is that at the end of the follow-up period the mean visual acuity returned to baseline levels despite a persistent reduction in the foveal thickness. This discrepancy probably indicates that central foveal thickness is only one of the factors involved in determining visual acuity outcome after treatment for CSDME. Jonas et al. [15] reported similar results using a much higher dose (25 mg) of IVTA for diffuse macular edema. In their study, a significant decrease in fluorescein leakage was noted after IVTA injection in patients in whom fluorescein angiography was available. After 7 months follow-up, visual acuity had improved from 0.12 to 0.19, in contrast to our series where 74% had stable acuity (+/- 1 Snellen line) at the end of the follow-up (10 months).

Laser photocoagulation for CSDME, according to the ETDRS protocol, rarely resulted in visual improvement especially of a large magnitude in the long term. Our case series, like previously mentioned series, demonstrated that a single IVTA is very effective in the short term. However, due to the temporary nature of the efficacy of IVTA for diabetic macular edema, using laser photocoagulation to augment IVTA may reduce the incidence of recurrent edema (after IVTA injection) and in so doing provide visual stabilization in the long term. There appears to be a role for combined treatment of recalcitrant macular edema – namely, the benefits of different mechanisms of action of intravitreal...
triamcinolone, followed by focal laser photocoagulation. This approach could offer the advantages of both greater visual acuity improvement (from the IVTA injection) and longer-term visual acuity stability (from more efficacious laser photocoagulation).

The most common complications after IVTA injection, in order of frequency, are intraocular pressure elevation and cataract formation. Bacterial endophthalmitis is the most dreaded complication, and it must be differentiated from pseudohypopyon and sterile endophthalmitis. Our series had a 37% (10/27) incidence of elevated IOP (> 25 mmHg) in normotensive eyes, similar to the reported incidence of 25–41% from three of the largest series in the literature [19-21]. Even though the IOP returned to baseline levels at 6 months, 7 of 10 patients in our series were still on topical anti-glaucoma medication at the end of follow-up. One patient needed argon laser trabeculoplasty to control his IOP. It is likely that with longer follow-up, as reported by Jonas and collaborators [22], the IOP would normalize without anti-glaucoma medications. Three of the four glaucomatous eyes in our series (75%) developed elevated IOP (average 28 mmHg) after IVTA injection, and were controlled with additional glaucoma medications. This finding suggests that glaucoma is a relative contraindication to IVTA injection, and that this treatment should be considered for eyes with glaucoma only when the benefit markedly outweighs the risk. Jonas and co-workers reported an increase in IOP of more than 50% (> 21 mmHg) at 1–2 months post-injection (25 mg IVTA) and a return to baseline levels at 6 months, without further medication [22]. Four of 19 phakic patients in our series (21%) developed cataract progression. The reported incidence for cataract progression ranges from 6 to 57% [15,16,19,23] and depends on follow-up duration.

None of the patients developed endophthalmitis in our study group. In addition, no cases of infectious endophthalmitis were observed in our institution, which has performed over 600 IVTA injections in the past 3 years. All the IVTA injections were done in the operating room with a sterile technique as for intraocular surgery. Culture-proven endophthalmitis after IVTA has been reported with an incidence of 0.87% [24] and 0.5% [25]. Lack of attention to a meticulous sterile technique has been suggested as a possible cause of a higher incidence than expected of endophthalmitis after IVTA injection. No patients developed retinal tears, retinal detachment or vitreous hemorrhage in this series.

Statistical analysis failed to identify any prognostic factor for improved visual outcome of more than three Snellen lines at the end of the follow-up, probably due to the small size of our series. Only poor initial visual acuity (6/30–6/60) approached prognostic significance (P = 0.06) for improved visual acuity of more than three Snellen lines. Multiple factors are involved in determining the visual acuity in eyes with CSDME, including macular perfusion and adequacy of laser photocoagulation, duration of the macular edema and degree of diabetes control, as well as other systemic factors such as systemic hypertension, renal function and cardiac status. Determining the individual contribution of each factor to the prognosis following IVTA injection may be possible only in a large prospective study.

Our case series had a number of limitations that may curtail the drawing of definitive conclusions. The case series is relatively small and retrospective in nature, and there was no control group. A historical control group from the ETDRS was used for comparison of results with the natural history of CSDME treated by laser photocoagulation. Visual acuity was not measured using standard ETDRS charts but with Snellen charts. LogMAR conversion was used to overcome this flaw. Also, the visual acuity results were not refracted best-corrected at each visit. The response to IVTA injection was assessed using OCT examinations and as a result most patients did not undergo pre-injection fluorescein angiography for evaluation of macular perfusion and assessment of the adequacy of previous laser photocoagulation. The duration of macular edema was also not available. The extent of diabetic control, duration of diabetes as well as systemic hypertension, renal status and cardiac function were not recorded for all patients.

Despite the above-mentioned limitations, our findings nevertheless provide some useful and important information on the short and long-term anatomic and functional effects of IVTA that can be used to plan and assess the most beneficial and efficacious ways to use IVTA for diabetic macular edema. A single IVTA injection is very effective in causing macular edema absorption, but only for a limited period. Thus it may be necessary to perform repeated injections in order to maintain the benefit of IVTA injections. However, the high incidence of raised IOP and cataract progression may limit repeated injections. Augmenting the initial anatomic and visual acuity success of IVTA by combining IVTA injection with laser photocoagulation may be helpful in reducing the need for repeated IVTA injections. In addition, laser may be applied more effectively, especially to leaking microaneurysms, when the macula becomes thinner (less edematous due to less leakage) after IVTA injection. A prospective trial comparing the results of combined treatment with either treatment alone needs to be performed and could clarify whether IVTA injection is a valuable addition to our standard treatment of CSDME with laser photocoagulation.

References


We have enslaved the rest of the animal creation, and have treated our distant cousins in fur and feather so badly that beyond doubt, if they were able to formulate a religion, they would depict the Devil in human form.

William R. Inge (1860-1954), English clergyman, scholar and author

**Capsule**

**Cerebral emboli as a potential cause of Alzheimer’s disease**

Purandare and collaborators tried to compare the occurrence of spontaneous cerebral emboli and venous to arterial circulation shunts in patients with Alzheimer’s disease or vascular dementia and controls without dementia. The study was conducted through secondary care old age psychiatry services in Manchester, and included 170 patients with dementia (85 with Alzheimer’s disease, 85 with vascular dementia) and 150 age and gender-matched controls. Patients on anticoagulant treatment, patients with severe dementia, and controls with marked cognitive impairment were excluded. Spontaneous cerebral emboli were detected in 32 patients (40%) with Alzheimer’s disease and 31 (37%) of those with vascular dementia compared with just 12 each (15% and 14%) of their controls, giving significant odds ratios adjusted for vascular risk factors of 2.70 for Alzheimer’s disease and 5.36 for vascular dementia. These spontaneous cerebral emboli were not caused by carotid disease, which was equally frequent in dementia patients and their controls. A venous to arterial circulation shunt indicative of patent foramen ovale was found in 27 (32%) Alzheimer’s disease patients and 25 (29%) vascular dementia patients compared with 19 (22%) and 17 (20%) controls, giving non-significant odds ratios of 1.57 and 1.67.

**Br Med J** 2006;332:1119

Eitan Israeli