

Intravitreal Triamcinolone Acetonide for Diabetic Macular Edema Refractory to Intravitreal Ranibizumab. Nine-month Results

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Abstract: The Purpose of this study was to evaluate the efficacy of IVTA as rescue therapy in patients with DME refractory to intravitreal ranibizumab. This is a prospective interventional non-comparative study that included diabetic patients with persistent CSME and associated visual loss despite previous treatment with intravitreal ranibizumab. Main outcome measures were improvement of BCVA ≥ 3 Snellen lines and improvement of macular central subfield thickness $\geq 250 \mu$ on OCT. Eligible patients received IVTA injection in a concentration of 4 mg in 0.1 ml. Follow-up period was 9 months. Statistical analysis was performed using analysis of variance (F-test) "ANOVA". Statistical significance of measured data was set at significant ($p < 0.05$). The study recruited 50 eyes of 50 patients. Mean baseline macular central subfield thickness was 552.3 μ . Mean BCVA improved by > 5 Snellen lines to reach 20/40 at 1 month follow-up. This improvement was maintained through the 9-month visit. Mean macular central subfield thickness was 314, 308, 307, and 306 μ at 1, 3, 6, and 9 months, respectively. Steroid-induced rise in the IOP was detected in 88% of patients at the 1-month visit. Mean IOP value at subsequent visits was 14 mmHg. At the 9-month visit 16%, 38%, and 18% of patients still relied upon 1, 2, and 3 anti-glaucoma drops, respectively. Eight patients (16%) required filtering surgery. No other ocular complications were detected. In conclusion, IVTA is an effective salvage treatment for DME that is refractory to ranibizumab. Its complications do not seem to be prohibitive given its therapeutic potential.

Key words: IVTA • Refractory DME • Ranibizumab

INTRODUCTION

Diabetic macular edema (DME) is the cardinal cause of visual loss in diabetic retinopathy [1]. The Wisconsin epidemiologic study of diabetic retinopathy reported a 10-year incidence of DME equivalent to 20.1% and 18.6% in juvenile-onset and adult-onset diabetic patients respectively [2]. In terms of risk of visual loss, the early treatment diabetic retinopathy study (ETDRS) reported that the 3-year risk of moderate visual loss due to clinically significant macular edema (CSME) mounted up to 32% of the study population [3].

Over the recent years, our understanding of the pivotal role of vascular endothelial growth factor (VEGF) in the pathogenesis of DME has improved [4,5]. Subsequently, accruing information from several studies demonstrated that intravitreal anti-VEGF agents provided better visual outcome than the classic focal/grid laser treatment proposed by ETDRS. This resulted in shift of treatment paradigm preference for patients with DME and reduced vision from laser treatment to anti-VEGF agents as the new gold standard therapy [6-14].

Still a significant proportion of patients develop refractory edema that is unresponsive to either laser or

anti-VEGF treatment. Though intravitreal triamcinolone acetonide (IVTA) has been proven inferior to laser or anti-VEGF in managing DME [6], still IVTA could be used as rescue therapy for patients who failed laser treatment with encouraging anatomical and functional results that seem to outweigh the potential complications inherent to IVTA use [15-18].

The current study evaluates the efficacy of IVTA as rescue therapy in patients with DME that did not respond to intravitreal ranibizumab and in whom further treatment with ranibizumab was deemed futile.

MATERIALS AND METHODS

Study Population: This is a prospective interventional non-comparative study that included diabetic patients with persistent CSME and associated visual loss despite previous treatment with intravitreal ranibizumab. Recruited patients were male or female subjects, ≥ 18 years of age with either type 1 or type 2 diabetes. One eye per patient was selected. All enrolled eyes had previously received three consecutive injections of ranibizumab (Lucentis, Genentech, Inc., South San Francisco, CA) at a dose of 0.5 mg in 0.05 mL spaced 4 weeks apart. The last lucentis injection was given at least one month earlier. Residual macular edema was defined as CSME $> 250 \mu$ central subfield thickness on OCT and less than 10% improvement from baseline. Persistent visual loss was defined as lack of improvement of BCVA at least 1 Snellen line (5 ETDRS letters) from baseline. Exclusion criteria included inadequately controlled systemic disease that could prevent improvement of macular edema as uncontrolled diabetes, systemic hypertension, anemia or renal disease. Patients with history of glaucoma or those who had active intra-ocular inflammation/infection were also excluded from the study. Main outcome measures were improvement of BCVA ≥ 3 Snellen lines (corresponding to 15 ETDRS letters) and improvement of macular central subfield thickness $\geq 250 \mu$ on OCT.

Treatment Protocol and Follow-up: Eligible patients received IVTA injection in a concentration of 4 mg in 0.1 ml that was prepared from a 1ml ampoule containing 40 mg triamcinolone acetonide crystals in suspension.

The ampoule was kept erect for 30 minutes to allow the crystals to precipitate. This was followed by removal of the supernatant vehicle. Then, the drug was re-suspended in one ml BSS, thereby obtaining the required

concentration. A 30-gauge needle with a length of $\frac{1}{2}$ to $\frac{5}{8}$ inches mounted on a one ml tuberculin syringe was used for intravitreal delivery of the drug.

Topical anesthesia was achieved using drops of proparacaine hydrochloride 0.5%, followed by lidocaine 4%. Preparation of the ocular surface then followed using povidone iodine 5% drops. The eyelids and eyelashes were then prepared by povidone iodine 10%. A sterile speculum was then placed under the eyelids. A sterile cotton-tipped applicator was saturated with lidocaine 4% drops and held against the planned intravitreal injection site. Paralimbal paracentesis was performed to reduce the intra-ocular volume. The injection site was measured using a sterile caliper (3.5 mm posterior to the limbus in pseudophakic eyes and 4.0 mm posterior to the limbus in phakic eyes). Triamcinolone acetonide was injected trans-conjunctivally through the inferior pars plana, to keep the suspension in the inferior vitreous region, away from the visual axis, thereby, minimizing post-injection floaters. The needle was introduced into the mid-vitreous cavity, aiming posteriorly and slightly inferiorly. Using a single continuous maneuver, triamcinolone acetonide was injected slowly into the eye. As the needle was withdrawn, the sterile cotton tip applicator was rolled over the entry site to minimize the risk of reflux of both the drug and the vitreous. Indirect ophthalmoscopy was used to confirm proper intravitreal localization of the suspension and perfusion of the optic nerve head. Antimicrobial drops were installed post-injection qid for 3 days.

After the injection, patients were asked to sit up and to keep an upright head position for at least two hours to prevent the cortisone crystals from settling onto the macular region. Safety evaluation of the patients was done the following day and after one week. Follow-up visits were scheduled at 1, 3, 6, and 9 months.

Examination Procedures: Initial evaluation and follow-up visits included Snellen BCVA, anterior segment slit-lamp examination, intra-ocular pressure assessment using Goldmann's applanation tonometry, fundus biomicroscopy using +90 D lens, OCT and fluorescein angiography.

OCT scans were performed using the fourier domain RTVue-100 OCT machine (Optovue Inc., Fremont, CA, USA) and the average of 2 central subfield thickness measurements was used at baseline and at each follow-up visit. Scans were performed using cross lines pattern (1024 pixel horizontal/vertical lines) and MM5 pattern (macular map 5 x 5 mm).

Table 1: Baseline Patient Characteristics

Male	29 (58%)
Female	21 (42%)
Mean Age(years)	50.6
Mean Baseline BCVA	20/200
Mean Baseline Macular Central Subfield Thickness (μ)	552.3
Mean Baseline IOP (mmHg)	14

All procedures and follow-up visits were done at the Research Institute of Ophthalmology (R.I.O.) - Ministry of Scientific Research, Egypt. The study was performed in accordance with the tenets of the Declaration of Helsinki of 1975 (the 2008 revision). The Research Committee of The Research Institute of Ophthalmology approved the protocol of the study. All patients received a thorough explanation of the procedures entailed in the study and signed an informed consent prior to enrollment.

Statistical Analysis: All data were subjected to statistical analysis of variance (F-test) "ANOVA". It is a procedure used for testing the differences among the means of two or more variables. It was noted that if means of subgroups differ greatly from each other, the variance of the combined groups is much larger than the variance of the separate groups. The analysis of variance format for the analysis of differences in means is based on this fact. Duncan's multiple range tests is one of the multiple-comparisons procedures. It uses the "t" distribution corresponding to the number of degrees of freedom for error mean square.

The significance of the measured data was considered non-significant ($p > 0.05$), significant ($p < 0.05$), highly significant ($p < 0.01$), where p is the probability value that reflects null hypothesis.

RESULTS

Patient Characteristics: The study recruited 50 eyes of 50 patients, 29 men and 21 women. All patients completed the required follow-up schedule. Mean age was 50.6 years (range 38-65, SE 1.1). Mean baseline BCVA was 20/200 (range 20/400 – 20/63, SE 0.008). Mean baseline macular central subfield thickness was 552.3 μ (range 462-635 μ , SE 5.07). Mean baseline IOP was 14 mmHg (range 11-18 mmHg, SE 0.25). Table 1.

Anatomical and Functional Outcomes Following IVTA Injection: Mean BCVA improved by > 5 Snellen lines (35 ETDRS letters) to reach 20/40 at 1 month follow-up.

Table 2: Anatomical and Functional Outcomes

Mean Final BCVA	
1 month	20/40
3 months	20/40
6 months	20/40
9 months	20/40
Mean Final Macular Central Subfield Thickness (μ)	
1 month	314
3 months	308
6 months	307
9 months	306
Mean Final IOP (mmHg)	
1 month	32
3 months	14
6 months	14
9 months	14

Improvement was maintained through the 9-month visit. At the last visit 31 patients (62%) maintained BCVA $\geq 20/40$.

Mean macular central subfield thickness was 314, 308, 307, and 306 μ at 1, 3, 6, and 9 months, respectively. These values indicated improvement of mean central subfield thickness by approximately 57% relative to baseline thickness.

Complications: Steroid-induced rise in the IOP was detected in 44 patients (88%) at the 1-month visit. Mean IOP at 1 month was 32 mmHg (range 17-48 mmHg, SE 1.08). Mean IOP value at subsequent visits was 14 mmHg. At the 9-month visit 8 patients (16%), 19 patients (38%), and 9 patients (18%) still relied upon 1, 2, and 3 anti-glaucoma drops respectively to control their IOP. In the remaining 8 patients (16%), IOP rise was recalcitrant to maximum anti-glaucoma topical medication and required filtering surgery which was sufficient to control IOP rise. We did not encounter other ocular complications attributed to IVTA administration. Table 2. Figures 1- 4.

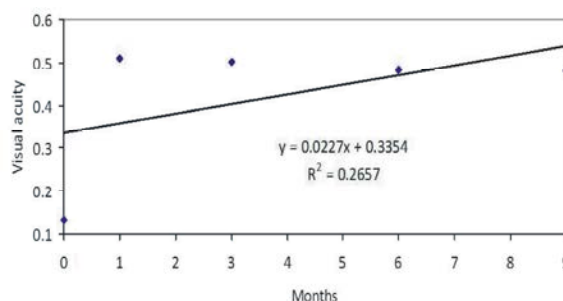


Fig. 1: Relationship between visual acuity and months of follow-up

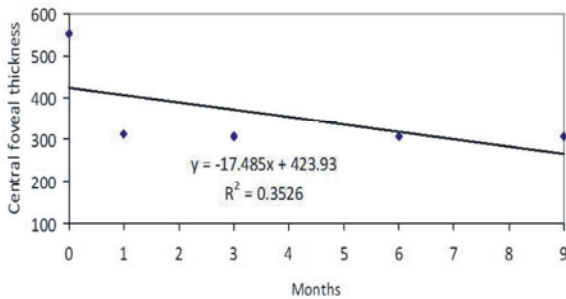


Fig. 2: Relationship between central foveal thickness and months of follow-up

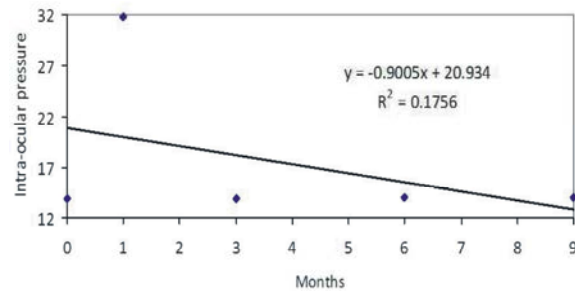


Fig. 3: Relationship between intra-ocular pressure and months of follow-up

Correlation between visual acuity & central foveal thickness at 1 month		BCVA 1m	CFT1m
BCVA1m	Pearson Correlation	1	-.535(**)
	Sig. (2-tailed)		.000
	N	50	50
CFT1m	Pearson Correlation	-.535(**)	1
	Sig. (2-tailed)	.000	
	N	50	50

** Correlation is significant at the 0.01 level (2-tailed)

Correlation between visual acuity & central foveal thickness at 3 months		BCVA 3m	CFT3m
BCVA3m	Pearson Correlation	1	-.434(**)
	Sig. (2-tailed)		.002
	N	50	50
CFT3m	Pearson Correlation	-.434(**)	1
	Sig. (2-tailed)	.002	
	N	50	50

** Correlation is significant at the 0.01 level (2-tailed)

Correlation between visual acuity & central foveal thickness at 6 months		BCVA 6m	CFT6m
BCVA6m	Pearson Correlation	1	-.327(*)
	Sig. (2-tailed)		.020
	N	50	50
CFT6m	Pearson Correlation	-.327(*)	1
	Sig. (2-tailed)	.020	
	N	50	50

* Correlation is significant at the 0.05 level (2-tailed)

Correlation between visual acuity & central foveal thickness at 9 months		BCVA 9m	CFT9m
BCVA9m	Pearson Correlation	1	-.294(*)
	Sig. (2-tailed)		.038
	N	50	50
CFT9m	Pearson Correlation	-.294(*)	1
	Sig. (2-tailed)	.038	
	N	50	50

* Correlation is significant at the 0.05 level (2-tailed)

Fig. 4: Correlation between visual acuity and central foveal thickness at 1-, 3-, 6-, and 9-months follow-up

DISCUSSION

The rationale for using IVTA in management of DME is derived from its anti-inflammatory and anti-angiogenic mechanisms of action. Through these mechanisms IVTA promotes the integrity of the blood-retina barriers through stabilization of the endothelial and basement membranes and attenuation of VEGF-mediated retinal capillary permeability [19-21].

In the current study we demonstrated that IVTA yielded a highly significant anatomical and functional outcome in terms of vision improvement and reduction of macular thickness in patients with persistent DME and vision loss despite standard treatment with ranibizumab. BCVA had improved in all 50 patients (100%) with 62% of patients achieving $\geq 20/40$. Macular central subfield thickness improved in all patients (100%) by a mean of

57%. The favorable outcomes in the current study were maintained through 9-month follow-up period.

In accordance with our findings, Martidis *et al.* [15] reported in a prospective series of 16 eyes with refractory DME treated with IVTA, a reduction of mean macular thickness by 55%, 58%, and 37.5% from baseline at 1-, 3-, and 6-month follow-up respectively. This anatomical outcome was paralleled by improvement in mean BCVA of ≥ 2 Snellen lines in 64% of patients at 1-, and 3-month follow-up each and in 50% of patients at the 6-month visit. Similarly, Sutter *et al.* [16] reported BCVA improvement ≥ 5 ETDRS letters in 55% and mean reduction of foveal thickness by 152 μ in 32% of eyes with refractory DME treated with IVTA. Another study by Gillies *et al.* [17] reported a statistically significant improvement in BCVA by ≥ 5 ETDRS letters in 56% of eyes with refractory DME treated with IVTA versus 26% in the placebo group.

Follow-up period was 2 years. Those patients were enrolled in an open-label extension study of 5-year duration [18]. At the conclusion of the study, the authors found that improvement in BCVA by ≥ 5 ETDRS letters was maintained in 42% of patients initially treated with IVTA versus 32% in patients initially treated with placebo. That difference was not statistically significant. There was also no statistically significant difference in reduction of mean central macular thickness. It is worthy of note that patients enrolled in these fore-mentioned studies had refractory DME after adequate laser treatment, whereas in our study patients had refractory DME after treatment with ranibizumab.

In comparison, a systematic review of randomized controlled trials that studied patients with refractory DME concluded that IVTA resulted in improvement in BCVA at 3 months after injection but the effect was not sustained at 6 months. The study concluded that IVTA could produce short-term improvement in BCVA but this beneficial effect does not persist on the long-term [22].

The widespread use of IVTA in DME is limited due to its potential side-effects that have been established in several studies, particularly rise of IOP [23-28]. At the onset of the current study none of our patients had glaucoma. We detected approximately two-fold rise in IOP in 88% of our patients one month after IVTA administration. By the end of the follow-up period 72% of enrolled patients relied on topical anti-glaucoma medication to control their IOP. Eight patients (16%) required glaucoma filtering surgery.

In comparison, Martidis *et al.* [15] reported in their study an average rise of IOP by 45%, 20%, and 13% at the 1-, 3-, and 6-month follow-up intervals. One eye progressed to cataract. Sutter *et al.* [16] had elevation of IOP in 30% of their treated cases, with 24% of patients requiring topical anti-glaucoma medication. They had one case of cataract and one case of infectious endophthalmitis. The follow-up period was 3 months.

In Gillies study at 2 years [17], 68% of treated eyes had IOP rise, with 44% requiring glaucoma medication and 5.9% undergoing trabeculectomy. Cataract surgery was needed in 54% of treated eyes. One patient developed infectious endophthalmitis. In the 5 years open-label extension study [18], 9% of initial IVTA group underwent trabeculectomy, 56% were on glaucoma medication and 71% had cataract surgery.

In the systematic review provided by Yilmaz *et al.* [22], IVTA resulted in significant higher IOP values in treated patients when compared to no treatment.

In the DRCRnet study [29] IOP rise developed in 16% and 33% of the groups treated with IVTA compared to 4% of patients who were treated with laser. Cataract surgery was needed in 23% and 51% of patients in both IVTA groups as compared to 13% in patients who did not receive IVTA. At the three-year follow-up study [30], 83% had undergone cataract surgery in IVTA group versus 31% in the laser group. IOP had risen by more than 10mm Hg at any visit in 33% of IVTA group versus 4% for the laser group. IOP lowering treatment was being used in 12% of the IVTA group versus 3% of the laser group and 5% of patients in the IVTA group underwent glaucoma surgery.

The comparison of the incidence and rate of complications between the current study and other studies should be made while bearing in mind that in our study IVTA injection was administered only once. With the exception of Sutter *et al.* study [16] the treatment protocols for the fore-mentioned studies entailed multiple injection of IVTA.

Limitations of the current study included small number of patients and relatively short follow-up period of time. Had the follow-up period been longer, the favorable anatomical and functional results of the current study would have declined; also we would have needed a larger number of IVTA injections to maintain the currently reported outcome. Another important limitation was absence of control group. Though we treated only one eye per patient so that the fellow eye could serve as control given that enrolled patients had persistent chronic macular edema after ranibizumab, the presence of a separate group of patients acting as control would have added to the strength of the study.

The current study demonstrated that a single IVTA injection resulted in significant anatomical and functional improvement that was maintained for at least 9 months. The fact that patients selected for enrollment had refractory DME and visual loss despite standard treatment with ranibizumab supports consideration of this therapeutic line especially when laser therapy is inapplicable due to center-involving macular edema. Randomized controlled trials with longer follow-up and larger patient cohort are warranted for better assessment of the potential benefits of IVTA versus its potential risks in this group of patients.

CONCLUSION

IVTA is an effective salvage treatment for DME that is refractory to ranibizumab. Complications of IVTA do not seem to be prohibitive given its potential to improve central vision in those patients.

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