University of KwaZulu-Natal

Intravitreal versus sub-Tenon triamcinolone acetonide for refractory diffuse diabetic macular oedema

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By

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Abstract

Purpose: To compare the safety and efficacy of intravitreal (IVT) and sub-Tenon (ST) triamcinolone acetonide for the treatment of refractory diffuse diabetic macular oedema.

Method: 29 eyes of 22 patients with long-standing, diffuse diabetic macular oedema refractory to argon laser treatment were randomly assigned to a single 4mg injection of IVT triamcinolone acetonide or a 40mg sub-Tenon injection. Patients were subsequently monitored for six to nine months. Outcome measures were visual acuity, intraocular pressure, macular thickness on optical coherence tomography and adverse effects.

Results: There was no significant improvement in visual acuity in either group. A transient decrease in macular thickness was found in the IVT group but not in the ST group. There were no significant adverse effects apart from a mild to moderate intra-ocular pressure rise found more frequently in the IVT group.

Conclusion: IVT and ST triamcinolone acetonide injections for refractory diffuse diabetic macular oedema appear relatively safe and well-tolerated. IVT injection produces a significant temporary decrease in macular thickness in patients with long-standing diffuse diabetic macular oedema while ST injection does not. Neither intervention was shown to significantly improve visual acuity in this group of patients.

Preface

I hereby declare that this dissertation has been my own work and has not been submitted in any form to any other university. The research work was carried out in the Department of Ophthalmology, Nelson R. Mandela School of Medicine, University of KwaZulu-Natal, under the supervision of Dr Linda Visser.

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_____ day of _____ 2009

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Presentations of the results of this study:

Ophthalmic Society of South Africa (OSSA) congress – 2006

Nelson R. Mandela School of Medicine faculty research day - 2006

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Chapter 1

Introduction and literature review

The greater Durban metropolitan region of KwaZulu-Natal has a large diabetic population with a full spectrum of diabetic-related eye disease, posing a considerable public health problem. Macular oedema is a common ocular complication of diabetes worldwide, affecting 29% of diabetics with disease duration of 20 years or more.[1] It remains the most common reason for loss of vision in diabetics. The treatment of diffuse diabetic macular oedema is at present limited and often unsatisfactory, leaving many patients severely debilitated with compromised macular vision.

The current standard of care in the treatment of diffuse diabetic macular oedema is the use of argon laser grid photocoagulation. The Early Treatment Diabetic Retinopathy Study (ETDRS - 1985) showed the benefit of focal laser treatment for clinically significant macular oedema, which reduced the risk of further visual loss by 50%.[2] However only 17% of patients were shown to have an improvement in vision with laser treatment and only 3%

had an improvement of 3 or more Snellen chart lines. Diffuse diabetic macular oedema is notoriously difficult to treat and studies have shown disappointing results from grid argon laser treatment.[3] The experience of the ophthalmology department of the University of KwaZulu-Natal reflects published findings - one of satisfactory results with focal argon laser treatment for focal clinically significant macular oedema but disappointing results with grid laser in diffuse oedema. Diffuse oedema and visual acuity seldom improve despite laser treatment and many patients are considered to have refractory disease.

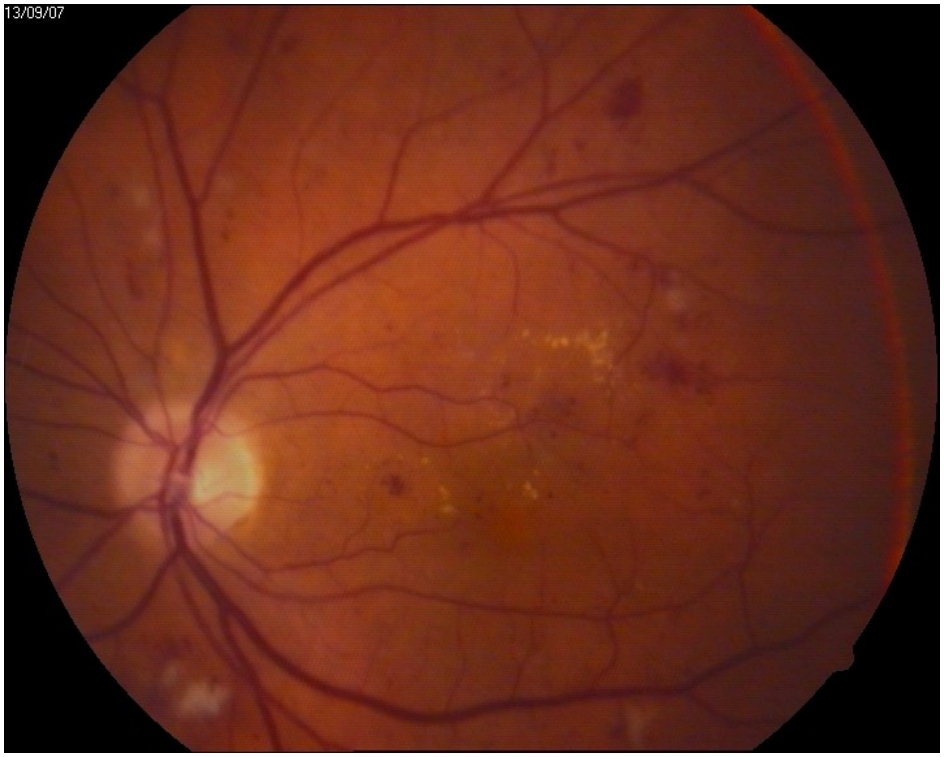


Figure 1 - Diabetic maculopathy with clinically significant macular oedema.

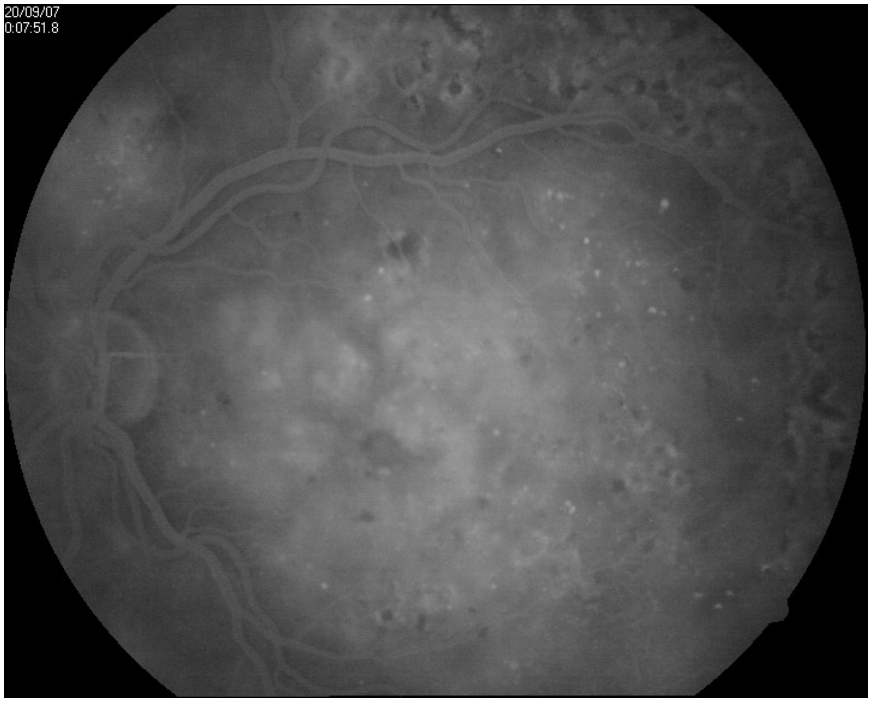


Figure 2 – Fluorescein angiogram - diffuse diabetic macular oedema and previous argon laser retinal scarring.

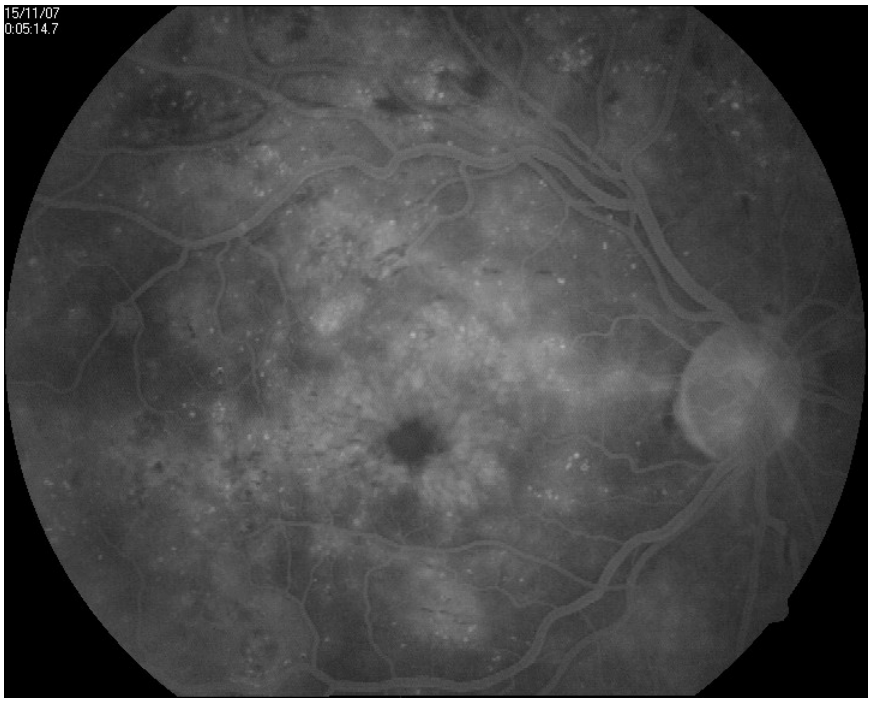


Figure 3 – Fluorescein angiogram - chronic diffuse cystoid diabetic macular oedema.

It is in this context that alternative treatments to laser have been sought. Intravitreal crystalline corticosteroid suspension in the form of triamcinolone acetonide (TA) has been investigated for the treatment of diabetic macular oedema refractory to conventional therapy at several ophthalmology centres worldwide.[4,5,6] Its use proliferated worldwide after Martidis, Duker et al (2002) first published promising results of its use in the treatment of diffuse diabetic macular oedema. They injected 4mg of triamcinolone intravitreally in sixteen eyes with clinically significant diabetic macular oedema that failed to respond to two previous sessions of laser photocoagulation. They found a significant mean improvement in visual acuity of 2.4 Snellen lines at the 1 month follow up, 2.4 lines at 3 months and 1.3 lines at 6 months. The central macular thickness was measured by Optical Coherence Tomography (OCT) and decreased by 55%, 57.5%, and 38% respectively over the same intervals.[5]

Jonas JB, Kreissig I et al (2003) studied 26 eyes which received an intravitreal injection of 25 mg of triamcinolone acetonide for diffuse diabetic macular oedema and followed them for 6 months. Mean visual acuity improved from 0.12 at baseline to a maximum of 0.19 during follow-up.

This was compared to a control group of 16 eyes that underwent macular grid laser and had no significant improvement in visual acuity.[4]

Massim P, Audren F et al (2004) injected 4mg of triamcinolone acetonide into one eye of twelve patients with diffuse diabetic macular oedema unresponsive to laser treatment, the other eye serving as a control.[6] Central macular thickness on OCT improved from an average of 509μ before injection to 207μ at 4 weeks and 207μ at 12 weeks. In the control group central macular thickness was 474 pre-injection, 506μ at 4 weeks and 469μ at 12 weeks. At 24 weeks the oedema had recurred in all eyes and there was no longer a statistically significant reduction.

Triamcinolone has also been used for a variety of other retinal pathologies including cystoid macular oedema secondary to uveitis[7], central and branch retinal vein occlusions[8,9] and the treatment of choroidal neovascular membranes in combination with photodynamic therapy[10].

The pathophysiology of diabetic macular oedema is multifactorial and appears to have an inflammatory component. [20] There is a generalised breakdown in the blood-retinal barrier due to changes in tight junction proteins and leukocyte adherence to vascular endothelium, resulting in increased vascular permeability and accumulation of fluid in the outer plexiform layer of the retina - diffuse oedema. Vascular endothelial growth factor (VEGF) is stimulated by interleukins and other inflammatory mediators and has been shown to increase vascular permeability by phosphorylating the tight junction proteins occludin and zonula occludens-1.[11] The specific mechanisms by which intravitreal steroids achieve their effects are not entirely understood but it has been postulated that triamcinolone is effective in several areas to decrease oedema: Firstly, it decreases the activity of inflammatory mediators - interleukins 5,6 and 8, prostaglandins, interferon-γ and tumour necrosis factor – inhibiting VEGF expression and vascular permeability. Secondly, it has a positive effect on cellular calcium channels, aiding in the active diffusion of fluid across cells and therefore decreasing oedema. Thirdly, triamcinolone has been shown to have a generally favourable effect on the integrity of the blood-retinal barrier, decreasing the osmotic component of oedema.[20]

The results of investigations into the use of intravitreal triamcinolone acetonide for diabetic macular oedema have been largely positive with significant improvements seen in visual acuity and, initially, with a seemingly low incidence of irreversible side effects.[4,5,6] Further retrospective studies of larger numbers of injections have concluded that morbidity is, in fact, quite significant. The most frequent side effect has been shown to be a steroid-induced rise in intraocular pressure in about one third to one half of patients, controllable by topical pressure lowering agents in the majority of cases.[12] However, irreversible steroid-induced glaucoma refractory to medical treatment and requiring filtration surgery is well documented.[13] Corticosteroid-induced glaucoma in general has, in fact, been shown to be irreversible in 3% and has to be managed like primary chronic open angle glaucoma.[14] Endophthalmitis has been shown to occur at a rate of 0.3% per injection and retinal detachment, uveitis, intraocular haemorrhage and vascular occlusions have all been described. Formation or acceleration of cataract within two years is considered universal.[12,13]

The appropriate concentration of intravitreal triamcinolone required for macular oedema treatments has also been the topic of much interest. Jonas JB et al have published a number of papers on the topic of intravitreal triamcinolone using a 25mg intravitreal dosage.[4,17] This dosage was based on the concentration of 0,1ml of the commercially available product and was continued in numerous subsequent studies by Jonas based on this arbitrary fact. (Personal communication). Over time, 4mg has become the generally accepted intravitreal dose as the therapeutic effects are noted to be equivalent to 25mg while possibly causing less steroid-response glaucoma.[6] Recently, Audren F, Lecleire-Collet A et al (2006) showed that there was no statistical difference at 24 weeks post intravitreal injection between 2mg and 4mg with regard to visual acuity, central macular thickness and intraocular pressure, although macular oedema recurred at 16 weeks in the 2mg group but only at 20 weeks in the 4mg group.[15] Lam DS, Chan CK et al (2007) in a randomised prospective trial studied the differences in efficacy and adverse effects of 4mg, 6mg and 8mg doses intravitreally.[16] Visual acuity at 6 months was significantly higher in the 8mg group compared to the 4mg group. The reduction in central macular thickness at 6 months for the 4, 6 and 8mg groups was 28%, 42% and 60% respectively, while ocular

hypertension occurred in 39%, 30% and 55%. These studies suggest that a higher dosage of triamcinolone has a longer duration of effect but may be associated with a higher incidence of glaucoma. At present, a 4mg, 0.1ml injection remains the generally accepted and most widely used intravitreal dosage.

The benefits of intravitreal triamcinolone therapy have been noted to be transient in most patients, usually lasting between 4 and 6 months. A small group of patients appear to have a lasting response to just one injection. Repeated injections have been shown to effectively maintain visual and anatomical results in those patients with recurrent macular oedema.[17]

Sub-Tenon steroid injections are well described for a variety of ophthalmic conditions, including posterior uveitis and cystoid macular oedema.[18,19,20] Their use in diabetic macular oedema is less well accepted although some reports in the literature show modest initial improvements in visual acuity. [20,21] Bakri SJ and Kaiser PK (2005) looked retrospectively at 63 eyes (73 injections) that received 40mg of sub-Tenon triamcinolone for persistent clinically significant diabetic macular oedema. At 1 month 46% of eyes showed no change in vision and 50% showed 1 line or more improvement.

At 3, 6 and 12 months there was a less pronounced improvement from baseline but without statistical significance. No OCT analysis was included in this paper.[20]

Triamcinolone has recently been shown to enter the vitreous trans-sclerally by sub-Tenon injection, however the same study showed the steroid concentration in the vitreous to be six times greater by intravitreal injection.[22] Later, Thomas ER, Wang J et al (2006) showed that the vitreous steroid concentration attained by sub-Tenon injection can vary substantially in each individual, ranging from a clinically significant concentration to zero.[23] These studies suggest that attaining appropriate vitreous concentrations of steroid are less reliable with sub-Tenon injections than direct placement with intravitreal injections.

Peri-ocular steroid injections are not without risk and they have been associated with ptosis, globe perforation, retinal and choroidal vascular occlusions, raised intraocular pressure and cataracts.[24,25] However, the risk of complication remains very low and in a retrospective review of 73 sub-Tenon triamcinolone injections, Bakari and Kaiser (2005) found few complications with only a 4% incidence of ptosis at 3 months post-injection

and in 10% a minor, transient increase in intraocular pressure that was easily controlled with topical hypotensive agents. Fifty percent had the development or progression of cataract at 1 year.[20]

Intravitreal injections are effective in delivering appropriate quantities of steroid close to the target tissue, the retina. One of the major disadvantages of intravitreal steroid injections for diabetic macular oedema is the temporary nature of the therapeutic response and the need for repeated injections every 4 to 6 months in most patients.[17] The incidence of adverse effects in a patient requiring multiple intravitreal injections becomes far more significant with each injection and in this context sub-Tenon injections intuitively have a more favourable risk profile.

At the time of commencement of the design and data collection of this study in 2004, there were no published reports comparing intravitreal and sub-Tenon injections of triamcinolone acetonide. Subsequently four reports have been published in the peer-reviewed literature:

Cardillo JA, Melo LA Jr et al (2005) conducted a prospective, double-masked, randomized controlled trial of twelve patients (24 eyes) with

bilateral diffuse diabetic macular oedema.[26] One eye of each patient randomly received a single 4mg triamcinolone acetonide intravitreal injection and the fellow eye received a 40mg triamcinolone acetonide posterior sub-Tenon's capsule injection. They looked at visual acuity, central macular thickness and complications over a 6 month follow-up period and compared the 2 interventional arms. Significant but transient improvements in central macular thickness and visual acuity were found in both groups, although results were found to be statistically better in the intravitreal group. The mean central macular thickness in eyes with intravitreal injection was found to be significantly thinner than in the sub-Tenon's capsule-injected eyes at 1 month (226μ versus 431μ) and 3 months (242μ and 364μ) The mean visual acuity in the intravitreally injected eyes was significantly better than in the sub-Tenon's capsule-injected eyes at 3 months post injection (0.8 and 1.1) Neither group were found to have any significant side effects in the 6 month follow-up period. The authors suggested a better therapeutic result from intravitreal triamcinolone. This was a particularly informative result, despite the small study size since the two methods of injection were performed on the same patient, thus allowing an excellent comparative analysis.

Bonini- Filho MA, Jorge R, Barbosa JC et al. (2005) looked prospectively at 28 patients with refractory diffuse diabetic macular oedema.[27] Patients randomly received 40mg sub-Tenon triamcinolone acetonide or 4mg intravitreally. Central macular thickness was measured by OCT and found to be significantly reduced in the intravitreal group at several follow-up intervals up to 24 weeks while there was no statistically significant decrease in the sub-Tenon group. Visual acuities were significantly higher in the intravitreal group at each time point. A significant increase in intraocular pressure was found in the sub-Tenon group at weeks 4 and 8 and at week 8 in the intravitreal group. The authors concluded that intravitreal injections were more effective in improving central macular thickness and visual acuity than sub-Tenon injections. Twenty of the 28 eyes had been previously treated with pan retinal photocoagulation for proliferative diabetic retinopathy.

Ozdek S, Bahceci UA et al (2006) did a retrospective analysis of 95 patients (126 eyes) with diffuse diabetic macular oedema refractory to argon laser treatment.[28] Eighty five eyes of 60 patients had received 20mg posterior sub-Tenon TA and 41 eyes of 35 patients had received 4mg intravitreal TA. In the IVT group, 24 eyes were from a primary treatment and 17 eyes were

from subsequent treatments. Sub-Tenon patients were followed for a mean of 4.1 months and IVT patients for 4.6 months. In the sub-Tenon group mean visual acuity improved from 0.19 to 0.22 and the mean central macular thickness decreased from 413µ to 312µ. In the IVT group visual acuity improved from 0.15 to 0.20 and central macular thickness from 494.5µ to 288µ. The authors concluded that sub-Tenon and IVT injections were both effective treatments for diffuse diabetic macular oedema with IVT injections being more efficacious. Importantly, 20% of sub-Tenon injections were found to have no effect at all, supporting the Thomas ER, Wang J et al (2006) paper which showed that some sub-Tenon triamcinolone injections result in minimal or no intravitreal steroid concentration.[23] Of note was that a significant rise in intraocular pressure was found in only 8.2% of the sub-Tenon group and in 24.3% of the IVT injection group.

Finally, Choi YJ, Oh IK et al (2006) did a prospective study of 60 eyes of 60 patients with diffuse diabetic macular oedema.[29] Each patient was assigned to receive a single 4mg intravitreal injection or a single 40mg posterior sub-Tenon injection of triamcinolone acetonide. Visual acuity, intraocular pressure and OCT measurement of central macular thickness were recorded at 1 and 3 months. Both groups showed statistically significant

improvements in visual acuity and central macular thickness from baseline at 1 month and 3 months after injection. The intravitreal group went from a baseline macular thickness of 428μ to 256μ at 1 month and 230μ at 3 months and in the sub-Tenon group from 480μ to 318μ and 271μ. There were no statistically significant differences between the two groups. In the intravitreal group visual acuity measured by the LogMAR system improved from a baseline of 0.73 to 0.57 at 1 month and 0.53 at 3 months and in the sub-Tenon group from 0.78 to 0.65 and 0.62. Again, there were no statistically significant differences between the two groups. Ten eyes (33%) in the intravitreal group had an intraocular pressure rise to 21mmHg or more, while this occurred in only 1 eye (3%) in the sub-Tenon group. The authors found that the posterior sub-Tenon injection of triamcinolone acetonide had a comparable effect to the intravitreal injection and showed a lower risk of elevated IOP. They concluded that sub-Tenon injection of triamcinolone acetonide might be a good alternative to IVT injection for the treatment of diffuse diabetic macular oedema. They also conceded that their results might have been good because the macular oedema was not refractory at baseline.

This study is a prospective, interventional case series to investigate the use of triamcinolone acetonide in the treatment of patients in the Durban metropolitan area of KwaZulu-Natal, South Africa, with diffuse diabetic macular oedema refractory to conventional laser therapy. The drug was made available through Visicare as Kenacort (Bristol Meyers Squibb). Each millilitre contains 40mg triamcinolone acetonide with sodium chloride, 0.99% benzyl alcohol preservative, 0.75% carboxymethylcellulose sodium and 0.04% polysorbate 80.

How efficacious is intravitreal and sub-Tenon triamcinolone acetonide for the treatment of diffuse diabetic macular oedema in our patient population with respect to macular thickness and visual acuity? What is the incidence of complication of these interventions? How do these two modes of delivery compare with regard to efficacy and incidence of complications?

Chapter 2

Materials and methods

A prospective, randomised comparative study was undertaken. The study had approval from the Ethics Committee of the Nelson R Mandela School of Medicine.

Nineteen patients with symptomatic, clinically significant diffuse diabetic macular oedema based on assessment by fundoscopy with a 90 dioptre lens and showing no response to two or more macular grid laser therapies were included in the study. Patients excluded from the study: Those with pre-existing glaucoma or ocular hypertension, known steroid responders, concomitant macular pathology affecting visual acuity, macular ischaemia, an unclear fundal view (e.g. significant cataract, vitreous haemorrhage) and proliferative diabetic retinopathy or severe non-proliferative diabetic retinopathy requiring pan retinal argon laser.

INCLUSION:	**• Diffuse diabetic macular oedema - 2 previous failed grid argon laser treatments**
EXCLUSION:	**• Pre-existing glaucoma/ocular hypertension** **• Steroid responders** **• Poor fundal view** **• Macular ischaemia (FFA)** **• Other macular pathology causing low VA** **• Cataract surgery within the last 6 months** **• Severe non-proliferative diabetic retinopathy or proliferative diabetic retinopathy**

Table I – Study inclusion and exclusion criteria.

After obtaining written consent, patients underwent fluorescein fundal angiography to exclude macular ischaemia as a cause of reduced visual acuity. A proforma with demographic and clinical information (age, sex, race, diabetic history etc) was completed. Patients were examined with respect to their visual acuity, as measured by logarithm of minimal angle of resolution (Logmar) test, intraocular pressure and macular thickness by optical coherence tomography (OCT – Zeiss-Humphrey instruments, San

Leandro, California) measurement. OCT examinations consisted of six radial cuts centred on the fovea. The central macular thickness was taken as the 1000μ circle centred on the foveola and was automatically calculated by the OCT software.

Patients' eyes were then alternately assigned to two experimental groups. Eyes assigned to group A received a single pars plana intravitreal injection of 4mg triamcinolone acetonide in the eye clinic by conventional sterile technique. Group B received a single 40mg sub-Tenon triamcinolone injection.

OUTCOME MEASURES:	**• Visual acuity (Logmar)** **• Fundoscopy** **• OCT** **• IOP** **• Observation of complications**

Table II – Study outcome measures.

The intravitreal injection technique:

The injection was preceded by softening of the globe by gentle massage. The eye was anaesthetised with topical benoxinate and sterilised with 5% povidone iodine into the conjunctival sac. The periorbital area was cleaned with a betadine solution followed by sterile draping of the head and neck and the use of a sterile wire speculum to keep the lids open and the eyelashes away from the injection site. A sterile cotton tipped applicator soaked in benoxinate was applied to the injection site for 5 minutes and the injection site was identified with a calliper - 4mm posterior to the limbus in phakic patients and 3.5mm in pseudophakic patients. Thereafter, 4mg (0.1ml) of triamcinolone acetonide (Kenacort, Bristol Myers Squibb) was injected via the pars plana, posterior to the superior limbus. Patients then received one drop of chloramphenicol immediately after the procedure and four times daily for the following 5 days. Correct placement of the steroid and normal retinal arterial circulation was confirmed on indirect fundoscopy.

The sub-Tenon injection technique:

Benoxinate drops were used to anaesthetise the eye and 5% povidone iodine was instilled into the conjunctival sac. The periorbital area was cleaned with

a betadine solution followed by sterile draping of the head and neck and the use of a sterile wire speculum to keep the lids open. A small bleb of lignocaine was injected inferonasally under the conjunctiva and a cut-down made with Westcott scissors through conjunctiva and Tenon's capsule to bare sclera, 8mm posterior to the limbus. Forty milligrams (1ml) of triamcinolone acetonide (Kenacort) was injected into the sub-Tenon's space using an olive-tipped canula, with particular attention to avoiding reflux of steroid.

Follow up examinations were done at day 1, 2 weeks, 6 weeks, 12 weeks, 24 weeks and 36 weeks after injection. At each visit visual acuity, macular thickness by OCT scan, intraocular pressure and complications arising from the intervention were recorded, as well as a clinical evaluation of the macula and optic disc by fundoscopy. Appropriate intraocular pressure lowering measures were undertaken if there was any clinically significant rise in intraocular pressure.

All examinations, investigations and treatments were performed by the author.

Chapter 3

Results

Twenty nine eyes of 22 patients were initially enrolled in the study. Fifteen eyes received intravitreal triamcinolone and 14 eyes received sub-Tenon injections. One patient absconded after the 6 week follow up visit (2 study eyes), one patient died of renal failure after the 6 week follow up (2 study eyes) and one patient died of cardiac disease after the 6 week follow up (1 study eye). Thus 24 eyes of 19 patients were followed for 6 to 9 months post injection with 13 eyes in the intravitreal group and 11 eyes in the sub-Tenon group.

There were no statistically significant differences between the two groups at baseline in terms of patient macular thickness as measured by OCT ($p=0.914$) and visual acuity ($p=0.459$).

		Levene's Test for Equality of Variances		t-test for Equality of Means						
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
									Lower	Upper
OCT	**Equal variances assumed**	.232	.634	.109	23	.914	7.96	73.322	-143.717	159.640
	Equal variances not assumed			.107	20.744	.915	7.96	74.088	-146.229	162.152
VA	**Equal variances assumed**	.083	.776	.754	23	.459	.0929	.12335	-.16222	.34812
	Equal variances not assumed			.764	21.673	.453	.0929	.12168	-.15962	.34552

Table III - Independent Samples Test – comparing macular thickness and visual acuity at baseline between the 2 treatment groups.
For OCT p=0.914 and for VA p=0.459, therefore no significant differences between the groups at baseline.

Eighteen patients were Indian, 3 African, and 1 Coloured. The mean patient age was 65 (range 52 to 80). All patients had type 2, non-insulin dependent diabetes mellitus. Macular oedema was present in all patients for at least two years and was considered longstanding and refractory to treatment.

The mean central macular thickness at baseline in the intravitreal group was 458µ. Macular thickness at the follow up intervals was 368 (n=14), 370 (n=14), 408 (n=13), 512 (n=13) and 508 (n=10) at 2, 6, 12, 24 and 36 weeks post-injection respectively. Mean visual acuity at the follow up intervals was 0.764 at baseline and 0.68, 0.66, 0.60, 0.70 and 0.88 at 2, 6, 12, 24 and 36 weeks post-injection respectively. The mean central macular thickness at

baseline in the sub-Tenon group was 450µ. At follow up macular thickness was 480 (n=14), 462 (n=12), 530 (n=10), 563 (n=11) and 471 (n=7) at 2, 6, 12, 24 and 36 weeks post-injection respectively. Mean visual acuity was 0.66 at baseline and on follow up, 0.70, 0.72, 0.64, 0.78 and 0.80 at 2, 6, 12, 24 and 36 weeks post-injection respectively. There were statistically no significant differences between the changes in mean value for macular thickness or visual acuity between the intravitreal and sub-Tenon groups using the ANOVA repeated measures test.

Intravitreal	Baseline:	2 weeks	6 weeks	12 weeks	24 weeks	36 weeks
Macular thickness: (µ)	**458**	**368**	**370**	**408**	**512**	**508**
No. of eyes:	14	14	14	13	13	10

Table IV - Changes in macular thickness after intravitreal triamcinolone

Sub-Tenon	Baseline:	2 weeks	6 weeks	12 weeks	24 weeks	36 weeks
Macular thickness: (μ)	**450**	**480**	**462**	**530**	**563**	**471**
No. of eyes:	15	14	12	10	11	7

Table V - Changes in macular thickness after sub-Tenon triamcinolone

In the intravitreal group 9 of the 13 eyes that were followed to 6 months had a rise in intraocular pressure above 21mmHg. In 1 eye this was above 30mmHg. Four eyes (31%) required pressure lowering treatment. In 2 eyes, 1 topical pressure lowering drop was needed and in 2 eyes 2 medications were needed. In the sub-Tenon group, 3 of the 13 eyes that were followed to 6 months had a rise in intraocular pressure above 21mmHg with only 1 eye (8%) requiring 1 topical medication. In both groups, pressures returned to normal by 6 months and all drops were discontinued.

There were no other significant adverse events in either group.

Macular thickness Intravitreal group		
	Macular thickness:	**Change in thickness from baseline:**
Baseline:	458µ	
Week 2:	368µ	**20% decrease**
Week 6:	370µ	**26% decrease**
Week 12:	408µ	**11% decrease**
Week 24:	512µ	**12% increase**
Week 36:	508µ	**11% increase**

Table VI - Percentage change in central macular thickness after intravitreal triamcinolone.

Visual Acuity (LogMAR) Intravitreal group		
Baseline:	0.76	
Week 2:	0.68	**Gained 4 letters**
Week 6:	0.66	**Gained 5 letters**
Week 12:	0.6	**Gained 8 letters**
Week 24:	0.7	**Gained 3 letters**
Week 36:	0.88	**Lost 6 letters**

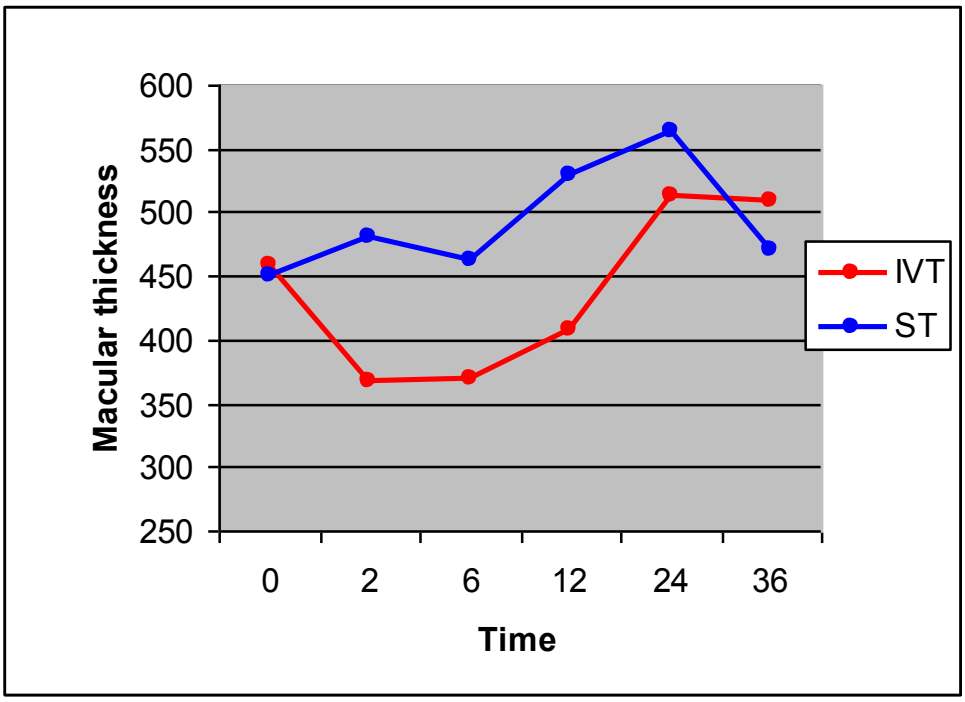
Table VII - Change in visual acuity after intravitreal triamcinolone.

Macular thickness Sub-Tenon group		
	Macular thickness:	**Change in thickness from baseline:**
Baseline:	450µ	
Week 2:	480µ	**7% increase**
Week 6:	462µ	**3% increase**
Week 12:	530µ	**18% increase**
Week 24:	563µ	**25% increase**
Week 36:	471µ	**5% increase**

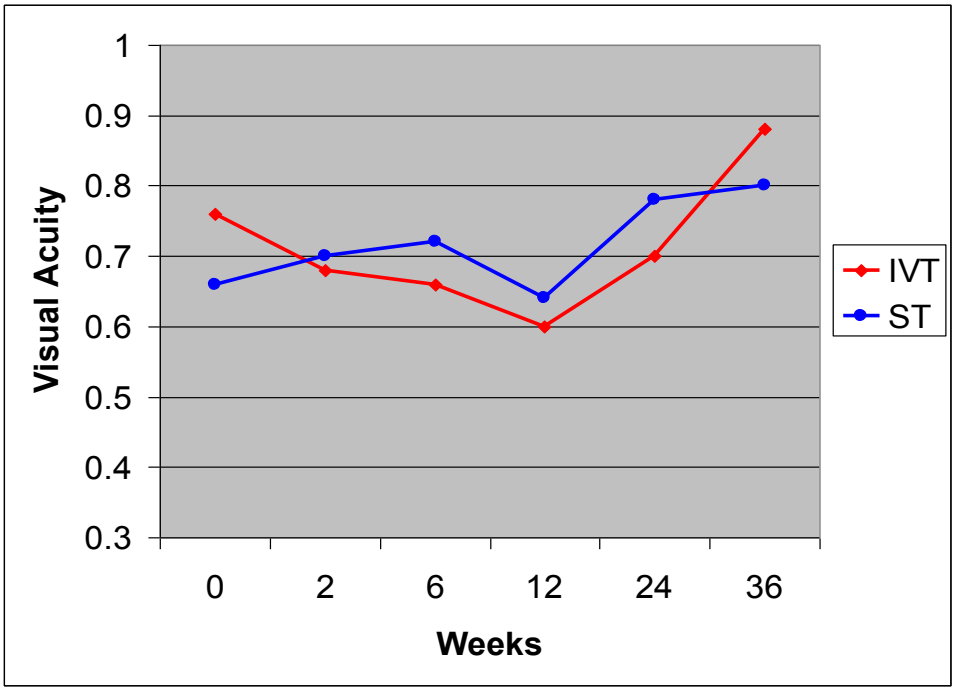
Table VIII - Percentage change in central macular thickness after sub-Tenon triamcinolone.

Visual Acuity (LogMar) Sub-Tenon Group		
Baseline:	0.66	
Week 2:	0.70	**Lost 2 letters**
Week 6:	0.72	**Lost 3 letters**
Week 12:	0.64	**Gained 1 letters**
Week 24:	0.78	**Lost 6 letters**
Week 36:	0.80	**Lost 7 letters**

Table IX - Change in visual acuity after sub-Tenon triamcinolone.

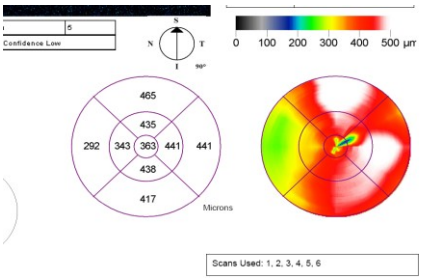


Graph I - Change in macular thickness after IVT and sub-Tenon triamcinolone.

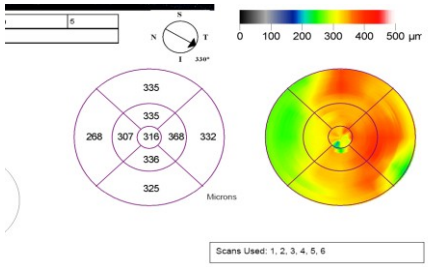


Graph II - Change in visual acuity after IVT and sub-Tenon triamcinolone.

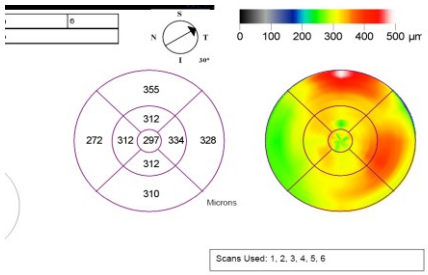
Intravitreal - Baseline



Intravitreal - Week 2



Intravitreal - Week 6



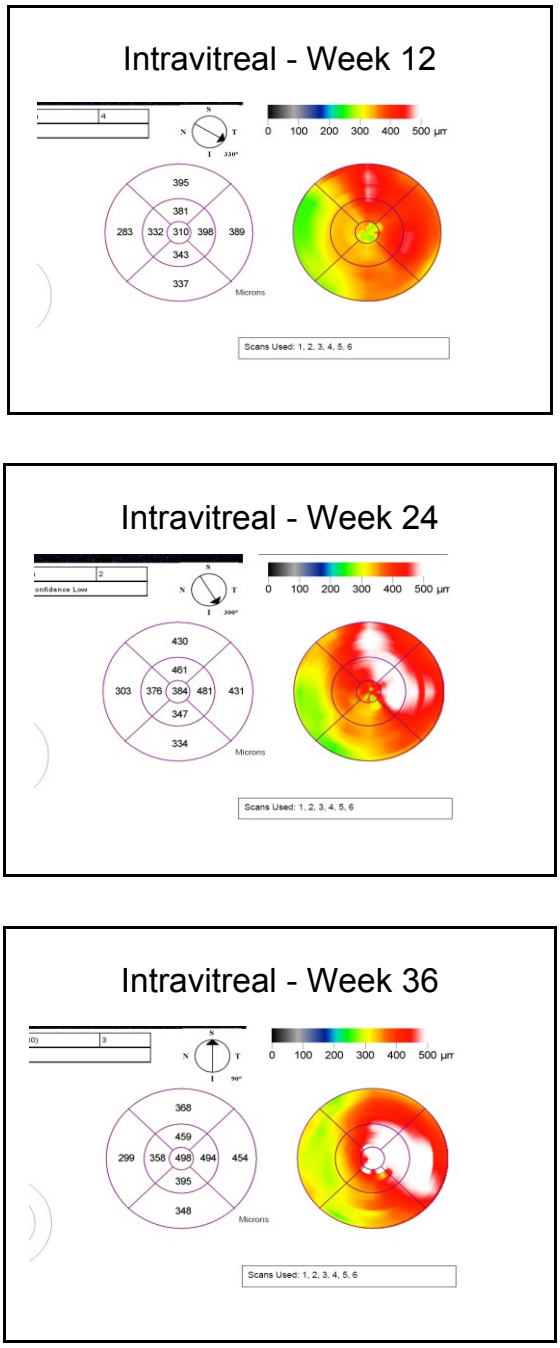
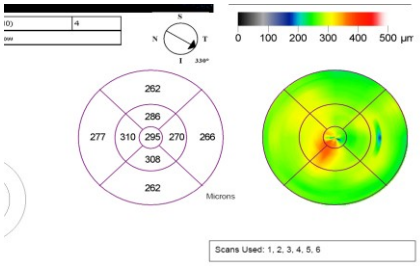
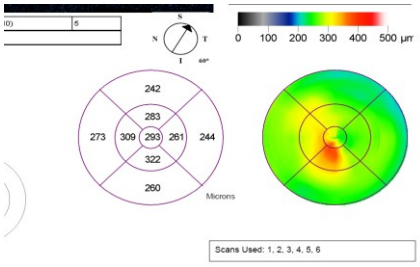


Figure 4 - OCT map of macular thickness – intravitreal triamcinolone acetonide. Macular thickness reduced after triamcinolone injection at weeks 2 and 6. Recurrence of oedema starting again at week 12.

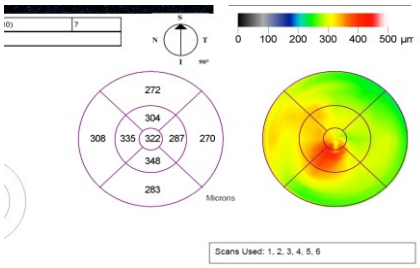
Sub-Tenon - Baseline

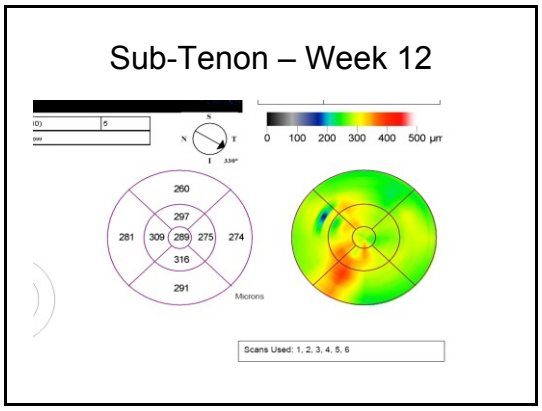


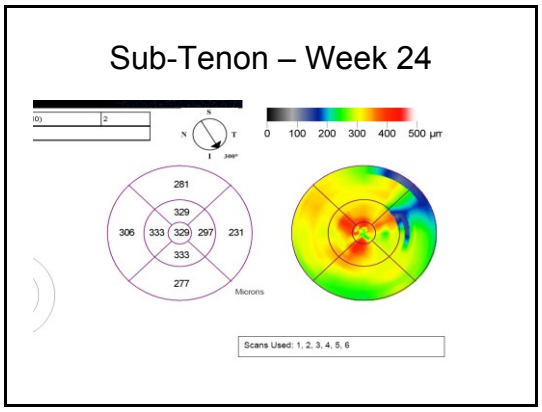
Sub-Tenon – Week 2



Sub-Tenon – Week 6







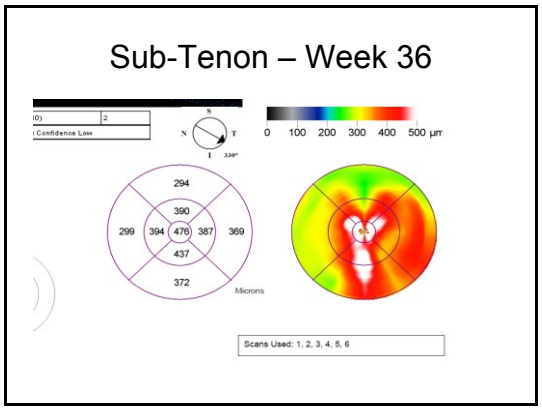


Figure 5 - OCT map of macular thickness – sub-Tenon triamcinolone acetonide. Macular thickness does not reduce after triamcinolone injection. Progressively worsens over the follow-up period.

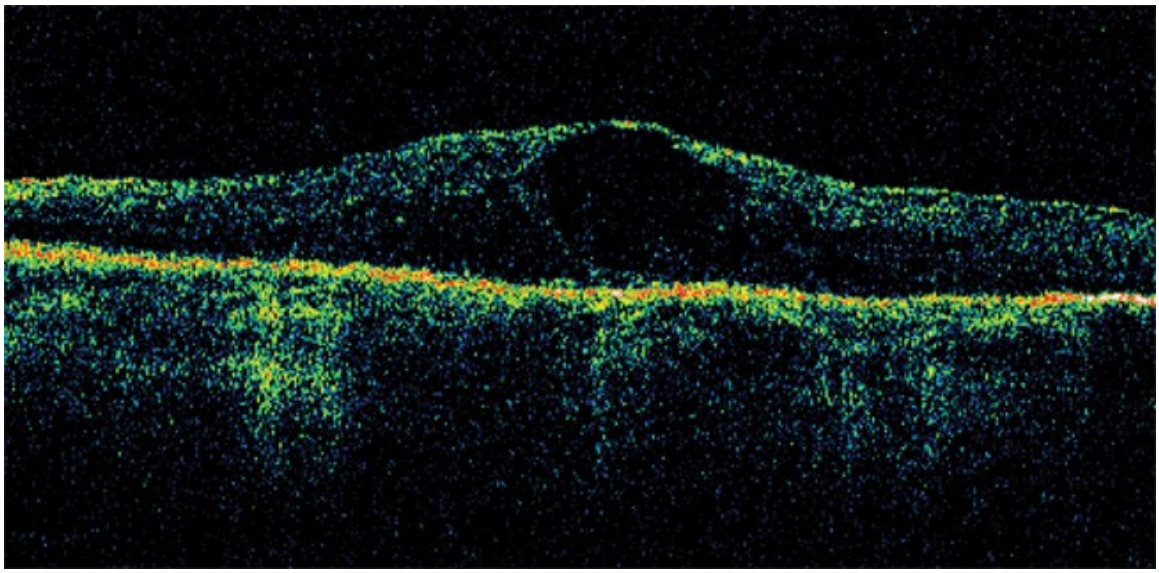


Figure 6: Optical coherence tomography image - diabetic macular oedema.

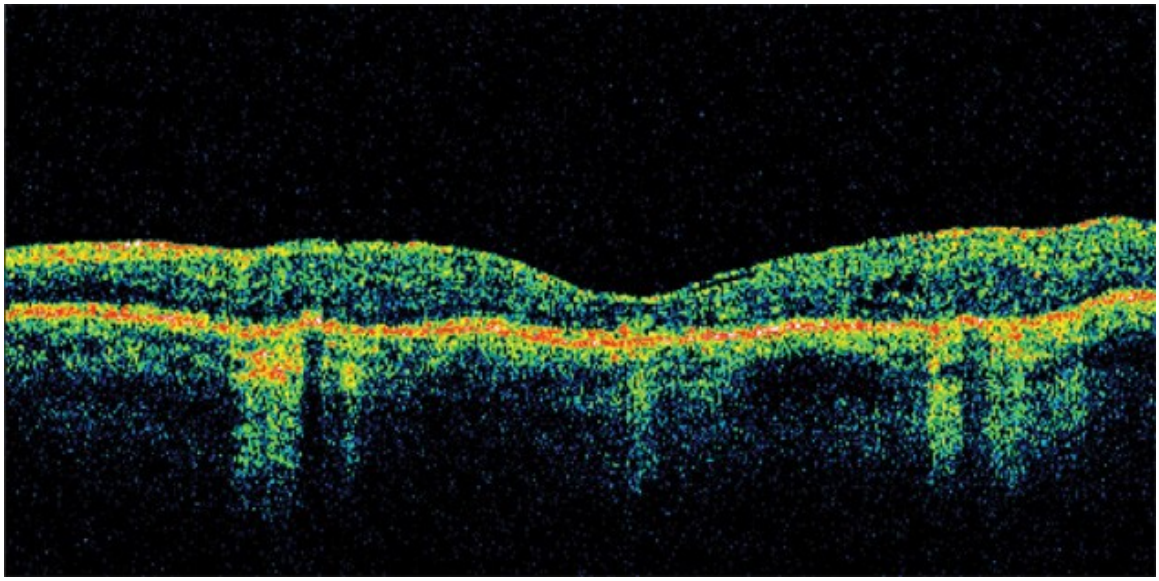


Figure 7: Optical coherence tomography image – oedema resolved 6 weeks post 4mg intravitreal triamcinolone acetonide.

Chapter 4

Discussion

In this study, intravitreal triamcinolone for longstanding diffuse diabetic macular oedema refractory to laser treatment resulted in a small and transient but clinically significant improvement in visual acuity and central macular thickness. It was superior to sub-Tenon injections which had no apparent effect on macular thickness or visual acuity. Neither intervention was found to have any serious adverse side effects over the 9 month follow-up period. A modest increase in intraocular pressure, seen with greater frequency in the intravitreal group, was transient and well controlled with topical medications.

There were no statistically significant differences between the sub-Tenon and intravitreal groups but the improvements in macular thickness and visual acuity in the intravitreal group were clinically superior

In the intravitreal group there was a modest decrease in macular thickness for the first 12 weeks post-injection – to a maximum mean decrease of 26% at week 6. A modest temporary improvement in visual acuity was also seen

for the first six months - with a maximum mean improvement of 8 letters (1.5 Snellen lines) at week 12. By week 24 the macular oedema had recurred. Martidis et al[5] reported 55%, 58% and 38% reductions in mean macular thickness at 1, 3 and 6 months follow up in their groundbreaking intravitreal triamcinolone study. They also saw a mean improvement of 2.5 Snellen lines at 1 and 3 months. Massin et al[6] reported similar transient reductions in central macular thickness with macular oedema recurring by week 24. Jonas et al[4] reported a mean visual acuity improvement from 0.12 at baseline to a maximum of 0.19 during follow-up.

In this study, therefore, the transient improvements in visual acuity and central macular thickness seen with intravitreal injections, although far more modest, reflect findings from previous studies of intravitreal triamcinolone injections for refractory diffuse diabetic macular oedema. There is a clear trend towards an initial improvement in visual acuity and a reduction in central macular thickness, followed by recurrence of oedema and deterioration in visual acuity by 6 months post-injection.

In the sub-Tenon group there was no mean improvement in macular thickness in the 9 months following injection and this did not clinically appear to be a useful intervention. In fact, there was a mean loss of visual acuity at each time point, except at week 12 where there was a gain of just 1 letter. In contrast, Bakri and Kaiser[20] reported improvements in visual acuity from a mean baseline of 20/80 to 20/50 at 1 month, stabilizing to 20/65 at 3 months, 20/68 at 6 months and 20/63 at 12 months. OCT was not performed in this study. There do not appear to be any other studies in the literature looking at the effect of posterior sub-Tenon injections for diffuse diabetic macular oedema alone.

Four previous studies have looked at the difference between the effect and safety of intravitreal and sub-Tenon injections for diffuse diabetic macular oedema.[26-29]

	Cardillo, Melo et al		Bonini-Filho, Jorge et al		Ozdek, Bahceci et al		Choi, Oh et al		Zaborowski	
	IVT	ST	IVT	ST	IVT	ST	IVT	ST	IVT	ST
Central macular thickness (%)										
1 month	56	16	41	6	40	18	41	34	26	3
3 months	53	29	31	5	42	24	46	44	11	18
6 months	15	16	23	0	25	25			12	25
Visual acuity (letters)										
1 month	7	1	10	6	3	1	8	7	5	3
3 months	12	0	5	0	3	0	10	8	8	1
6 months	2	0	0	0	0	0			3	6

Decreased central macular thickness/improved visual acuity
Increased central macular thickness/worse visual acuity

IVT = intravitreal
ST = sub-Tenon

Table X – A comparison of the results of the 4 previous intravitreal versus sub-Tenon injection studies.

In all four studies, the reductions in central macular thickness with intravitreal injections are comparable to the results of Martidis and Duker[5]. In this study a trend towards improvement was seen but was far less impressive than the previous four studies. Reported improvements in visual acuity were reasonably modest. Cardillo, Melo et al[26] reported a maximum mean improvement in visual acuity of 12 letters (2.5 Snellen lines) at 3 months. Bonini-Filho, Jorge et al[27] reported a maximum of 10 letters (2

Snellen lines) at 1 month. Choi, Oh et al[29] reported a maximum of 10 letters (2 Snellen lines) at 3 months. Ozdek, Bahceci et al[28] had the least impressive improvements reporting a 3 letter improvement at 1 and 3 months.

In this study, the visual acuity improvements with intravitreal injections were surprisingly good and comparable to the 4 previous studies despite the unimpressive reductions in central macular thickness. A 5 letter improvement was found at 1 month (1 Snellen line) and an 8 letter improvement (1.5 Snellen lines) was found at 3 months.

With sub-Tenon injections, Cardillo, Melo et al and Ozdek, Bahceci et al reported no real improvement in mean visual acuity, while Bonini-Filho, Jorge et al reported a 6 letter improvement at 1month and Choi, Oh et al reported 7 letters at 1 month and 8 letters at 3 months.
Cardillo, Melo et al, Ozdek, Bahceci et al and Choi, Oh et al all reported improvements in central macular thickness which were statistically inferior to the intravitreal injections. Bonini-Filho, Jorge et al found no improvement from baseline.

In this study, sub-Tenon's injections were more in keeping with the results of Bonini-Filho et al and there was no significant mean improvement in central macular thickness or visual acuity.

Choi, Oh et al found that there was statistically no difference between the sub-Tenon and intravitreal groups. Sub-Tenon injections were considered a good and safer alternative to intravitreal injections. Their patients differed from other studies in that the diffuse diabetic macular oedema was not refractory. Cardillo, Melo et al concluded that there was a clear short-term trend favouring intravitreal injection although both interventions had a favourable transient benefit. Ozdek, Bahceci et al found a pronounced effect with intravitreal injections and less effective but significant benefits with posterior sub-Tenon's. Bonini-Filho, Jorge et al found significant benefits with intravitreal steroid but not with sub-Tenon injections. They believed that triamcinolone reflux might be partly to blame for the poorer sub-Tenon results, as well as an inadequate positioning of the steroid next to the macular area. They felt that the sclera and choroid acted as a significant barrier to triamcinolone diffusion into the vitreous.

There are several possible explanations for the poor results in this study:

1. The group of patients studied in the Department of Ophthalmology of the University of KwaZulu-Natal have notoriously poor metabolic and hypertensive control. There may actually be degrees of treatment resistance with diabetic macular oedema and these metabolic factors may limit the efficacy of steroid treatment. Metabolic factors were not quantified but may warrant further study as to their role in the efficacy of steroid treatment. A subsequent study might exclude patients with poor glycaemic and blood pressure control.
2. All the studied patients had diabetic macular oedema for at least 2 years and in many cases for much longer. Again, there might be degrees of treatment resistance in diabetic macular oedema and the duration of oedema may play a role in the sensitivity to steroid treatment.
3. There was a definite study bias towards a more severe, refractory disease. Referred patients from fellow clinicians to the study project typically had profound macular oedema and did not necessarily represent the typical patient population of diabetics with macular oedema refractory to 2 macular grid laser treatments.

Unlike the 4 previous studies comparing intravitreal and sub-Tenon injections, this study continued to 9 months of follow up in most patients. An interesting finding was that at 9 months, central macular thickness and visual acuity was worse than baseline in both the intravitreal and sub-Tenon groups.

	Zaborowski	
	IVT	**ST**
Central macular thickness (%)		
9 months	**11% increase**	**5% increase**
Visual acuity (letters)		
9 months	**6 letters decrease**	**7 letters decrease**

Table XI – Changes in central macular thickness and visual acuity following triamcinolone treatment.

This suggests the interesting possibility of a steroid withdrawal, rebound type effect. No study has yet looked at the 9 month outcome of patients who were treated with triamcinolone acetonide injections but not re-treated. This data is suggestive of a deleterious effect of once-off triamcinolone injections and may support continued injections for the recurrence of oedema. The possibility of a steroid withdrawal, rebound effect warrants further study.

Most previous studies have shown either very poor efficacy with sub-Tenon triamcinolone as a treatment for diffuse diabetic macular oedema or modest benefits statistically inferior to intravitreal injections. The results of this study do not support the use of sub-Tenon triamcinolone acetonide for longstanding diffuse diabetic macular oedema refractory to laser treatment. Why is intravitreal delivery apparently more effective than sub-Tenon? The most likely reason is poor localisation of steroid adjacent to the macula due to reflux or poor injection technique. Intravitreal injections deliver a very predictable dose of steroid into the vitreous but it is unpredictable with sub-Tenon injections. This was seen experimentally by Thomas ER, Wang J et al (2006)[23] where sub-Tenon injections of triamcinolone produced a wide variety of vitreous steroid concentrations ranging from levels comparable to intravitreal injections to no detectable steroid at all. On average, the vitreous concentration with sub-Tenon injections was much lower than with intravitreal injections. There is certainly a degree of technical skill in ensuring that the full 40mg bolus of steroid is successfully delivered sub-Tenon and adjacent to the macula. Intravitreal injections are technically simple and there is little doubt about the ease of achieving a high concentration of the drug in the vitreous. Intuitively one also feels that the

sclera and choroid pose a natural barrier to diffusion of the steroid into the vitreous. This is overcome to a degree by injecting ten times the intravitreal dose in sub-Tenon's injections.

One of the main outcome measures of this study was to report any adverse effects of the triamcinolone treatments. In both study groups there were no major adverse effects although there was a rise in intraocular pressure above 21mmHg in 9 of the 13 eyes in the intravitreal group. In 4 eyes (31%) topical pressure lowering treatment was required. In the sub-Tenon group, 3 of 11 had a rise in intraocular pressure above 21mmHg with only 1 eye (8%) requiring topical medication. In both groups, pressure lowering was successful and pressures returned to normal by 6 months with all drops discontinued. The increased frequency of ocular hypertension in the intravitreal group would be expected if intravitreal injections caused a higher intraocular concentration of steroid. In a meta-analysis of 272 patients who received 20mg intravitreal injections, 41.2% had pressures >21mmHg, 11.4% >30mmHg, 5.5% >35mmHg and 1.8% >40mmHg.

The effect of the steroid on cataract formation was not specifically studied but posterior sub-capsular cataracts are a well-recognised complication and

were shown to have a prevalence of 45% after 1 year after a single 4mg intravitreal injection of triamcinolone.[30] No endophthalmitis, sterile or infective, was encountered although the study size was small and other studies have found the incidence of infective endophthalmitis to be up to 0.87%, with sterile endophthalmitis up to 1.6%.[31]

Chapter 5

Conclusions

The results of this study should be viewed with caution as the study size was small with a large number lost to follow up. Patient eyes were alternately assigned to either treatment arm and therefore this was not a randomised controlled study allowing potential selection bias.

Triamcinolone acetonide appears to be of limited value in the treatment of longstanding diabetic macular oedema refractory to laser treatment. While intravitreal injections showed a clinically significant trend towards a transient improvement in visual acuity and central macular thickness, this effect was modest. Sub-Tenon injections had no effect on visual acuity or central macular thickness. Intravitreal injections appear to be more effective than sub-Tenon injections, probably due to a more predictable delivery of steroid into the vitreous. The results of this study do not support the use of sub-Tenon injections for longstanding, refractory disease.

Poor clinical results may be due to permanent damage to the retinal pigment epithelium and photoreceptors due to disease chronicity, making

improvements in visual acuity modest at best. The macular oedema may also become more refractory with time. Intravitreal triamcinolone may be more effective earlier in the disease process. Poor metabolic control may play a role in a weak response to steroid treatment.

Once the decision has been made to treat, the clinician should be prepared to repeat injections if and when oedema returns. Single injections may actually worsen the disease in the long-term, possibly through a rebound-type effect of steroid withdrawal and should be used with caution. This effect warrants further study.

Single injections of sub-Tenon and intravitreal triamcinolone for diffuse diabetic macular oedema refractory to laser are relatively safe short to medium term, but patients will probably require management of secondary ocular hypertension which is usually self-limiting.

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