

EXTENDED REPORT

Decreasing efficacy of repeated intravitreal triamcinolone injections in diabetic macular oedema

C K M Chan, S Mohamed, M P Shanmugam, C-W Tsang, T Y Y Lai, D S C Lam

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See end of article for authors' affiliations

Correspondence to:
Professor Dennis S C Lam,
Department of
Ophthalmology and Visual
Sciences, The Chinese
University of Hong Kong,
University Eye Center,
Hong Kong Eye Hospital,
147K, Argyle Street, Hong
Kong; dennislam_pub@
cuhk.edu.hk

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Background/aim: Intravitreal triamcinolone (IVTA) results in transient improvements in diabetic macular oedema (DMO), necessitating repeated injections. The authors report a case series of 10 eyes of 10 patients with DMO, who received a repeat injection of 4 mg IVTA, at least 26 weeks after the first injection of the same dose.

Method: Pre-injection and at 2, 4, 9, and 17 weeks post-injection, best corrected visual acuity (BCVA) and central foveal thickness (CFT) on optical coherence tomography, after the first and repeat injections, were compared using paired *t* test. Side effects were monitored.

Results: BCVA, CFT, intraocular pressure (IOP), and cataract scores were not significantly different before initial and repeat injections (given at 32.5 (SD 3.5) weeks after the first injection). Transient improvements of BCVA and CFT were achieved after both injections. However, after the repeat injection, the BCVA was significantly worse at all time points ($p < 0.05$) and so were the best achieved CFT and the CFT at 4 weeks post-injection ($p = 0.034$ and 0.011 respectively), compared with the initial injection. Post-injection maximum IOPs and increase in cataract scores were not significantly different between the two injections.

Conclusion: A repeat injection of 4 mg of IVTA may not be as effective as an initial injection for the treatment of DMO.

Intravitreal triamcinolone (IVTA) has been used successfully as a primary treatment of diffuse diabetic clinically significant macular oedema (CSMO), as an adjunct to laser photocoagulation and in laser resistant CSMO.^{1–5} However, the beneficial effects of IVTA are transient, lasting up to 9 months,^{6,7} with recurrence of macular oedema, necessitating repeated injections in a proportion of eyes.⁵ The purpose of this case series was to document the effects of a repeated injection of 4 mg of IVTA in eyes with CSMO, which were good responders to a previous injection of the same dose. The safety and efficacy of the repeat injections were compared with the initial injections.

MATERIALS AND METHODS

In this retrospective observational case series, we documented the effect of a second injection of 4 mg of IVTA in 10 eyes of 10 patients who were part of the original clinical trials on IVTA in CSMO conducted by the Department of Ophthalmology and Visual Sciences, the Chinese University of Hong Kong (CUHK). These studies had ethical approval from the CUHK clinical research ethics committee and the research was carried out according to the tenets of the Declaration of Helsinki. Informed consent was obtained from all patients.

The inclusion criteria were: (1) patients over 18 years old with CSMO as defined in the Early Treatment of Diabetic Retinopathy Study (ETDRS)⁸; and (2) central foveal thickness (CFT) of at least 250 μ m as documented on optical coherence tomography (OCT). Exclusion criteria were (1) ocular disease apart from non-proliferative diabetic retinopathy and cataract; (2) vitreomacular traction as demonstrated on OCT; (3) previous ocular surgery apart from cataract surgery; (4) cataract surgery within 6 months or laser photocoagulation within 3 months before entry to the study; and (5) significant media opacities.

Details such as age, sex, and duration of diabetes were gathered from the patient and recorded. Details about

previous laser photocoagulation for diabetic macular oedema (DMO) and duration of CSMO were ascertained by scrutinising the patient's previous ophthalmic records. All patients underwent a complete ophthalmic examination that included best corrected visual acuity (BCVA) recording using the ETDRS chart, slit lamp examination with particular attention to the lens status; fundus examination using indirect ophthalmoscopy and slit lamp fundus biomicroscopy with the 90/78D lens (Volk Optical Inc, Mentor, OH, USA), and the findings were recorded. Intraocular pressure (IOP) was measured with a non-contact tonometer (Xpert NCT Plus, Reichert Ophthalmic Instruments), taken as the average of three readings. If the IOP was greater than 20 mm Hg, it was verified with a Goldmann applanation tonometer (Haag-Streit) and the same (if taken) was used for analysis. All IOP measurements were performed between 2 pm and 5 pm. Cataract grading was performed using the Lens Opacity Classification System (LOCS) III.⁹ To allow easier comparison of cataract grading, a composite score was calculated based on the sum of the scores in the four categories—for example, the maximum grading of NO6/NC6/C5/P5 would give a score of 22. A baseline OCT (StratusOCT, Carl Zeiss, Dublin, CA, USA) was performed. The CFT was the mean thickness at the point of intersection of six radial scans, acquired using the "fast macular thickness map" protocol and the value was automatically generated by the OCT machine using the "retinal map analysis" function. Throughout the study period, BCVA and OCT measurements were performed by technicians, who were unaware of the patients' treatment regimens.

Abbreviations: BCVA, best corrected visual acuity; CFT, central foveal thickness; CSMO, clinically significant macular oedema; DMO, diabetic macular oedema; ETDRS, Early Treatment of Diabetic Retinopathy Study; IOP, intraocular pressure; IVTA, intravitreal triamcinolone; LOCS, Lens Opacity Classification System; OCT, optical coherence tomography; VEGF, vascular endothelial growth factor

Table 1 Patient demographic data and macular morphology

Patient no	Age	Sex	Lens status	Previous macular laser (focal/grid)	Morphology of macular oedema on OCT*	
					Before first injection	Before repeat injection
1	71	F	IOL	Y	E1/E3 TO	E1/E2 TO
2	61	M	Phakic	Y	E1/E2 TO	E1/E2 TO
3	73	F	IOL	Y	E1 TO	E1 TO
4	71	F	IOL	Y	E1 T1	E1 T1
5	58	M	Phakic	Y	E1 TO	E1 TO
6	67	F	Phakic	N	E1/E3 T1	E1/E3 T1
7	68	M	Phakic	N	E2 TO	E1 TO
8	54	F	Phakic	N	E1/E2 TO	E2 TO
9	57	F	Phakic	Y	E2 TO	E1 TO
10	69	M	Phakic	Y	E1/E3 TO	E1/E3 TO

IOL, intraocular lens. *Morphology of macular oedema based on OCT classification.¹⁰ In summary E1, simple thickening (diffuse), E2, cystoid thickening; E3, neuroepithelial detachment; TO, absence of epiretinal hyper-reflectivity; T1, presence of continuous line of flat hyper-reflectivity and adherent to the retina without significant retinal distortion. Note some eyes can have more than one pathological change.¹¹

Intravitreal injection procedure

The procedure was performed using standard aseptic techniques. After sterilisation with 5% povidone-iodine, 2% lidocaine hydrochloride gel (Xylocaine, AstraZenec) was applied as a local anesthetic. Triamcinolone acetate 4 mg (0.1 ml of 40 mg/ml) (Kenacort A, Bristol-Myers Squibb, Anagni, Italy) was injected through the pars plana (4 mm post-limbus in phakics and 3.5 mm post-limbus in pseudophakics) using a 27 gauge needle. Indirect ophthalmoscopy and IOP examination were performed after the procedure. Levofloxacin eye drops (Cravit, Santen, Osaka, Japan) was given immediately then four times a day for 2 weeks.

After the first injection, the patients were seen at weeks 2, 4, 9, 17, and 26 and 3 monthly thereafter until a repeat injection was given, with additional visits as required. At each study visit, the patients underwent a complete dilated ophthalmic examination including BCVA, OCT, and IOP. Cataract grading was performed at 4, 9, and 26 weeks. The criteria for re-injection were (1) responsive to the first IVTA injection, defined as reduction of CFT by more than 100 µm or improvement of BCVA by more than one ETDRS line on the logMAR chart; (2) recurrence of CSMO with CFT greater than 250 µm, accompanied by a deterioration of BCVA of at least one ETDRS line from best achieved value, after the first injection; (3) lack of significant adverse events after the first IVTA injection, including a maximum IOP rise to more than 21 mm Hg and (4) patient willing to undergo repeat injection. The repeat injection of 4 mg IVTA was given at least 26 weeks after the initial injection, with a repeat of the baseline investigations, if not done within 1 month before the second injection. The patients were then seen at weeks 2, 4, 9, and 17 after the second injections. Only eyes with at least 17 weeks of follow up after the second injection were included for analysis.

Statistical analysis was performed with the SPSS for Windows Release 10.1.0. The paired *t* test was used to analyse the differences between the initial and repeat responses in BCVA, CFT, cataract grading, and IOP, as well

as analysing any changes from baseline. A difference was considered statistically significant if $p < 0.05$.

RESULTS

To date, 103 eyes of 100 patients with DMO had been injected with 4 mg of IVTA as part of various clinical studies. Ten eyes of 10 patients met the criteria as set out above and all completed at least 26 weeks and 17 weeks of follow up after their initial and repeat injections, respectively. The patients' average age was 65.1 (range 54–73). The patients' demographic data and the macular morphology of the eyes are summarised in table 1. No eyes underwent cataract extraction surgery or macular laser photocoagulation between the first and repeat injection or during the follow up period. The pre-injection BCVA, CFT, IOP, and cataract scores were not significantly different between the first and repeat injections (see table 2). The mean duration to re-injection was 32.5 (SD 3.5) weeks after the first injection.

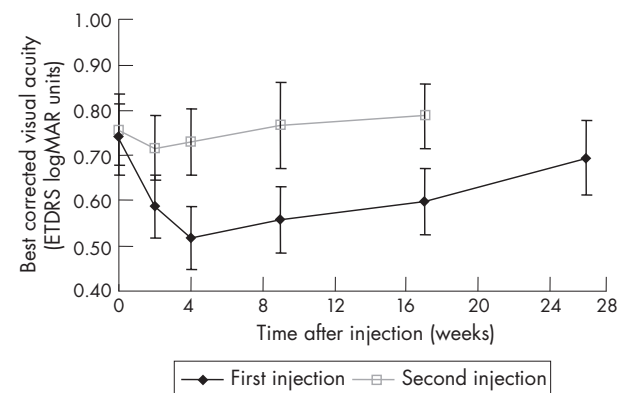


Figure 1 Changes in best corrected visual acuities after the first and repeat intravitreal triamcinolone injections. Error bars show standard error of the mean.

Table 2 Baseline characteristics before the first and repeated intravitreal triamcinolone injections

Pre-injection	First injection		Repeat injection		p Value
	Mean	SD	Mean	SD	
Best corrected visual acuity (ETDRS logMAR units) (approximate Snellen equivalent)	0.74 (20/110)	0.25	0.76 (20/115)	0.25	0.79
Central foveal thickness	475	123	448	158	0.66
Intraocular pressure	12.3	3.1	12.3	2.5	0.99
Cataract score	6.6	1.5	7.5	2.1	0.20

Best corrected visual acuity

The changes in BCVA are summarised in table 3 and figure 1. After the initial injection, there were statistically significant improvements of mean BCVA at 2, 4, and 9 weeks, compared to baseline ($p = 0.012$, 0.003 and 0.030 , respectively). However, there was subsequent gradual deterioration. After the repeat injection, the BCVA did not improve significantly at any time point, although the mean best achieved BCVA was better than pre-injection ($p = 0.01$). The mean BCVA at each time point (at 2, 4, 9, and 17 weeks) and the mean of the individual best achieved BCVA, were significantly worse after the repeat injection than the initial injection ($p < 0.05$ and $p = 0.001$ respectively).

Central foveal thickness

The changes in CFT are summarised in table 4 and figure 2. Statistically significant improvements in CFT were seen at 2, 4, and 9 weeks after the first and repeat injections compared to pre-injection values. The optimal effects on CFT were seen at 4 weeks after the both injections, at which time the CFT was significantly worse after the repeat injection ($p = 0.011$). The mean of best achieved CFT for individual eyes was also thicker after the repeat injection ($p = 0.034$).

Side effects

The maximum mean IOP achieved was 16.1 (SD 2.6) mm Hg and 18.9 (4.6) mm Hg after the first and repeat injections, respectively, and these were not significantly different ($p = 0.16$). However while none of the eyes had a maximum IOP of over 21 mm Hg after their first injection, two eyes did after their repeat injections. Both of these eyes reached a maximum of 26 mm Hg and were controlled with timolol eye drops 0.5% (Nyolol, Ciba Vision, Faure, France) alone. The average increase in cataract score was 0.9 (1.6) at 26 weeks after the first injection and 0.1 (0.2) at 9 weeks after the second injection (cataract grading was not performed at 17 weeks). No other significant adverse events were noted.

DISCUSSION

To our knowledge, all published studies so far have demonstrated the beneficial effects of IVTA on patients with DMO are transient, regardless of the dose used, which means patients have to undergo repeated injections. From our experience, not all patients are suitable for re-injections; some patients do not respond to IVTA, some patients have adverse events (for example, increased IOP, pseudo-endophthalmitis), and some patients do not wish to have repeat injections owing to the lack of perceived improvement despite objective documentation of better BCVA. In this study, we performed repeat IVTA injections in patients who responded well to the first injection of IVTA, and should theoretically represent the better end of the clinical response spectrum to IVTA. A previous paper by Jonas *et al* described the response of four eyes with diffuse CSMO whose visual

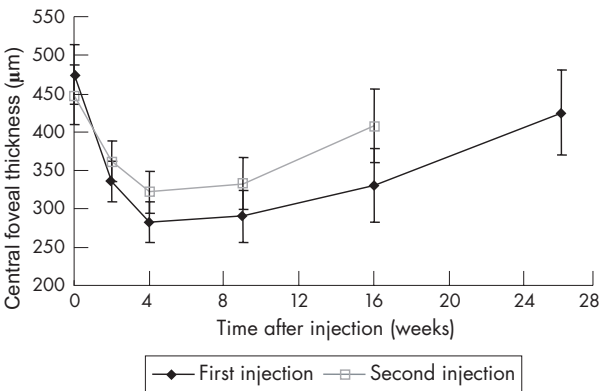


Figure 2 Changes in central foveal thickness after the first and repeat intravitreal triamcinolone injections. Error bars show standard error of the mean.

acuties improved after an initial and repeat IVTA injection of 20 mg.¹² However the patient numbers were too small for statistical analysis. Recently the same group described a larger series of 22 eyes in 19 patients who received two to three injections of 20 mg of IVTA and demonstrated the visual acuity improvements were not significantly different between the injections.¹³ No OCT data were given in these two studies. Other authors described good responses after repeated IVTA injections for idiopathic cystoid macular oedema (4 mg)¹⁴ and exudative age related macular degeneration (25 mg)¹⁵ in case reports or small case series. Concurring with their studies, we also found the BCVA improved after the repeat injections of the more conventional dose of 4 mg of IVTA, but the BCVAs were significantly worse than the initial injection at all time points. There was some anatomical reduction of macular oedema, but the best achieved CFT and the CFT at 4 weeks were also significantly worse after the repeat injection (note: the optimal effects of IVTA on CFT were achieved at 4 weeks after first and repeat injections). We postulate that there are several mechanisms, which could underlie the worse response, after the repeat injections, in CFT and the disproportionate lack of BCVA improvement compared with CFT.

Most of our patients (7/10) were phakic, and IVTA is known to accelerate cataractogenesis.^{16, 17} It was expected that increased lens opacity would contribute to the poorer response in BCVA after the second injection, even with the same amount of CFT reduction. However, there was no significant worsening of the cataract score after the repeat injection. Macular ischaemia can contribute to loss of vision in diabetic patients, in addition to the oedema component, but regrettably, there was no fluorescein angiographic documentation in this study and it was not possible to decipher the relative contributions of the two components.

Table 3 Changes in mean best corrected visual acuities after the first and repeat intravitreal triamcinolone injections					
Best corrected visual acuity (ETDRS logMAR units) (approximate Snellen equivalent)	First injection		Repeat injection		p Value
	Mean	SD	Mean	SD	
Pre-injection	0.74 (20/110)	0.25	0.76 (20/115)	0.25	0.786
2 weeks	0.59 (20/75)	0.22	0.72 (20/105)†	0.23	0.030*
4 weeks	0.52 (20/65)†	0.22	0.73 (20/105)	0.23	0.006*
9 weeks	0.56 (20/70)	0.23	0.77 (20/115)	0.30	0.023*
17 weeks	0.60 (20/80)	0.23	0.79 (20/120)	0.23	0.038*
26 weeks	0.69 (20/100)	0.26			
Best achieved BCVA	0.48 (20/60)	0.24	0.66 (20/90)	0.24	0.001*

BCVA, best corrected visual acuities; *statistically significant difference between the first and repeat injections, †timing of best achieved response.

Table 4 Changes in mean central foveal thickness after the first and repeat intravitreal triamcinolone injections

Mean central foveal thickness (µm)	First injection		Repeat injection		p Value
	Mean	SD	Mean	SD	
Pre-injection	475	123	448	158	0.658
2 weeks	335	83	362	121	0.488
4 weeks	283†	84	321†	64	0.011*
9 weeks	290	108	333	122	0.091
17 weeks	331	150	408	193	0.189
26 weeks	425	174			
Best achieved central foveal thickness	236	66	279	91	0.034*

*Statistically significant difference between the first and repeat injections.

†Timing of best achieved response.

The discrepancy between the improvement of CFT and BCVA may also be explained by the development of cystoid spaces in macular area caused by long lasting oedema. However, in our study we were unable to analyse the results of eyes with different macular morphology separately owing to the small numbers involved. Incidentally, Larsson *et al* also found the reduction of foveal thickness did not correlate strongly with the improvement in visual acuity after IVTA injection.¹⁸

There are many pathophysiological mechanisms that contribute to the development of DMO, including protein kinase C-β activation, increased vascular endothelial growth factor (VEGF) production, oxidative stress, and accumulation of intracellular sorbitol and advanced glycosylation end products.¹⁹ Corticosteroids block blood-ocular barrier breakdown and oedema by modulating the signalling or effector proteins downstream of the VEGF receptor in animal models,²⁰ but the other mechanisms may be unaffected by corticosteroids and could contribute to the ongoing deterioration of the macular oedema.

Tachyphylaxis has been described in dermatology with topical application of steroids²¹ and a study by Shaikh and Blumenkrantz,²² using systemic steroids to treat macular oedema associated with CRVO found poor response to subsequent treatment and attributed tachyphylaxis as one of the reasons for the same. Similar tachyphylaxis may occur with repeated intravitreal steroid injections, thereby explaining the decreasing response to further injections.

Two patients developed mild IOP rises after the repeat injection (up to 26 mm Hg) when their first injections were uneventful, however the mean maximum IOP was not significantly different between the two injections. This concurs with studies by Smithen *et al*²³ and Jonas *et al*.²⁴ using repeated injections of 4 mg and 20–25 mg of IVTA, respectively. Their studies demonstrated similar ocular hypertensive responses after first and repeat IVTA injections.

The drawbacks of this retrospective study are small patient numbers, lack of fluorescein angiography; heterogeneous conditions of the eyes involved (macular morphology, lens status, duration of macular oedema, previous macular laser treatment, intervals between the two injections); and the lack of documentation of systemic control of diabetes and other risk factors (for example, blood pressure, proteinuria). The follow up periods were also short after the repeat injection; however, it can be argued that if the repeat injection is not effective in improving the BCVA, the patients should be offered an alternative treatment—for example, conventional macular photocoagulation, especially for laser naïve eyes, without undue delay. If supplementary treatment was given in some patients, this would render direct comparison between injection episodes difficult.

In conclusion, this study demonstrated repeated 4 mg IVTA injections may not be as effective as initial injections,

even in initial good responders. This is contrary to the results of Jonas's studies using repeated IVTA injections of 20 mg in patients with DMO.^{12–13} It is not clear whether this discrepancy can be attributed to the difference of the IVTA dose used. Even if the ocular hypertensive effects were similar between the injections, the cumulative effects of the intraocular steroids would lead to increased cataractogenesis and each injection exposes the eye to the small but serious risk of infective endophthalmitis. Therefore IVTA injections alone may not be the ideal long term treatment solution for CSMO. This calls for larger scaled studies investigating the long term effects of combining IVTA with other possible treatments—for example, laser photocoagulation or pegaptanib.²⁵

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Authors' affiliations

C K M Chan, S Mohamed, M P Shanmugam, C-W Tsang, T Y Y Lai, D S C Lam, Department of Ophthalmology and Visual Sciences, The Chinese University of Hong Kong, Hong Kong

C K M Chan, S Mohamed, M P Shanmugam, C-W Tsang, T Y Y Lai, D S C Lam, Hong Kong Eye Hospital, 147K Argyle Street, Kowloon, Hong Kong

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Presentation: The data in this paper were presented in part at the Annual Scientific Meeting of the Hong Kong Ophthalmological Society (3–5 Dec 2005, Hong Kong) and the 21st Congress of the Asia Pacific Academy of Ophthalmology (10–14 June 2006, Singapore).

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