

# Retinal Vascular Caliber Changes after Intravitreal Triamcinolone Treatment for Diabetic Macular Edema

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**PURPOSE.** To describe the changes in retinal vascular caliber in response to a single injection of intravitreal triamcinolone (IVTA) in patients with refractory diabetic macular edema.

**METHODS.** Prospective data from a randomized clinical trial were used. The effects of IVTA versus sham injections in patients with refractory diabetic macular edema were evaluated in a randomized clinical trial involving 69 eyes of 43 patients. Of these, 28 eyes (15 IVTA and 13 sham) of 21 patients had gradable retinal photographs at the baseline and 3-month follow-up visit for analysis in the present study. Retinal vascular caliber was measured from digital fundus photographs and summarized as central retinal artery (CRAE) and vein (CRVE) equivalents in all eyes at baseline and at the 3-month follow-up visit.

**RESULTS.** Over the 3 months of the study, there was a significant reduction compared to baseline in retinal arteriolar ( $147.8 \mu\text{m}$  vs.  $140.0 \mu\text{m}$ ,  $P = 0.047$ ) and venular ( $219.5 \mu\text{m}$  vs.  $198 \mu\text{m}$ ,  $P = 0.039$ ) caliber in eyes treated with IVTA. There was no change in retinal arteriolar ( $139.9 \mu\text{m}$  vs.  $139.2 \mu\text{m}$ ,  $P = 0.878$ ) or venular ( $220.3 \mu\text{m}$  vs.  $217.6 \mu\text{m}$ ,  $P = 0.534$ ) caliber in those treated with sham injections.

**CONCLUSIONS.** IVTA has a significant narrowing effect on both retinal arteriolar and venular diameter in eyes with diabetic macular edema (ClinicalTrials.gov number, NCT00148330). (*Invest Ophthalmol Vis Sci.* 2008;49:4707-4711) DOI: 10.1167/iovs.08-1678

Diabetic retinopathy is the most common cause of legal blindness among the working population in the industrialized world today, and sight-threatening retinopathy is mostly commonly due to diabetic macular edema (DME).<sup>1,2</sup> DME results from a series of retinal microvascular changes secondary to endothelial cell dysfunction, thickening of the retinal capillary basement membrane, and reduction in the number of the surrounding pericytes leading to increased permeability and incompetence of retinal vasculature. Although the exact

underlying cause for these retinal changes remains poorly understood, recent studies have indicated a possible role for inflammation and vascular endothelial dysfunction in the pathogenesis of diabetic retinopathy.<sup>3-5</sup>

There is increasing evidence that retinal arteriolar and venular caliber are good indicators of retinal ocular perfusion.<sup>6</sup> Several epidemiologic studies have found larger arteriolar and venular caliber in patients with diabetes and in those with impaired glucose tolerance.<sup>7-10</sup> Larger venular caliber has been additionally linked with increasing severity of diabetic retinopathy and also systemic markers of inflammation.<sup>11</sup> It has been speculated that as a result of increased hydrostatic pressure, larger vessels may lead to increased retinal capillary blood flow and therefore to increased fluid leakage from the retinal capillaries.<sup>12</sup>

Triamcinolone is a synthetic glucocorticoid. In eyes with DME, injections of intravitreal triamcinolone (IVTA) have been shown to improve visual acuity and reduce macular thickening.<sup>13-19</sup> Although the exact mechanisms behind this improvement are not clear, animal studies have suggested that glucocorticoids may have a beneficial effect on retinal vessel diameter.<sup>20-22</sup> There are few clinical studies. In one series, among seven patients with DME, a significant reduction in both retinal arteriolar and venular diameter was seen 1 week after a single injections of IVTA.<sup>23</sup> The purpose of this study was to examine changes in retinal vascular caliber after a single injection of IVTA compared with control subjects in a group of patients with refractory DME.

## METHODS

### Patients

This study was based on data from a prospective, randomized controlled trial comparing IVTA with placebo for the treatment of DME. The study was approved by the South Eastern Sydney Area Health Service and the University of Sydney Research Ethics committees and adhered to the tenets of the Declaration of Helsinki.

Patients were recruited from the retina clinics of the Sydney Eye Hospital.<sup>13,19</sup> The inclusion criteria for that study were eyes with persistent or recurrent DME involving the central fovea three or more months after adequate laser treatment and best corrected visual acuity in the affected eye of 6/9 or worse. Sixty-nine eyes of 43 patients were entered into the study. Of those patients with both eyes recruited, one eye was randomly assigned to the active treatment group and one eye received sham treatment.

The procedure for injection has been documented previously,<sup>13</sup> but in summary, the eyes were prepared with several drops of amethocaine 1% and 2 drops of 5% povidone iodine. A small amount of 2% lignocaine then was administered subconjunctivally with a 30-gauge needle to the site of the injection. Using a 27-gauge needle, 0.1 mL of triamcinolone acetonide (40 mg/mL; Kenacort 40; Bristol-Myers Squibb, Noble Park, Australia) was injected through the pars plana. A small amount of chloramphenicol ointment then was instilled. Eyes randomized to sham treatment received a subconjunctival injection of saline in a procedure identical to the triamcinolone group. In patients with both eyes in the study, the right eye was treated first followed by the left eye, using a fresh set of sterile drape, speculum, and caliper.

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Supported by grants from the Sydney Eye Hospital Foundation, the Ophthalmic Research Institute of Australia, the Juvenile Diabetes Research Foundation, the Diabetes Australia Research Trust and the National Health and Medical Research Council (Australia).

Submitted for publication January 2, 2008; revised April 1, May 11 and 27, and June 29, 2008; accepted September 12, 2008.

Disclosure: S.S. Wickremasinghe, None; S.L. Rogers, None; M.C. Gillies, None; M. Zhu, None; T.Y. Wong, None

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Of the 69 eyes included in the study, 28 eyes of 21 patients had good-quality gradable retinal photographs at the baseline and 3-month follow-up visit and are included in the analysis.

### Measurement of Retinal Vascular Caliber

Fundus photography was performed with a standardized protocol.<sup>24</sup> Two photographic fields were taken of each eye of each participant: the first centered on the optic disc (ETDRS field 1) and the second centered on the fovea (ETDRS field 2).<sup>25</sup> Images were digitized with a slide scanner (Coolscan V; Nikon Corp., Tokyo, Japan) at a resolution of 150 dpi, saved in the TIFF format, and sent to the University of Melbourne for measurement of retinal vascular caliber and assessment of other retinal disease. Retinal vascular caliber was measured with a computer program (IVAN; University of Wisconsin, Madison), based on a detailed protocol.<sup>26,27</sup> A trained grader who was masked to participant characteristics performed the measurements. For this study, field 1 photographs were selected for measurement. For each photograph, all arterioles and venules coursing through an area one-half to one disc diameter from the optic disc margin were measured and summarized as the central retinal artery equivalent (CRAE) and central retinal vein equivalent (CRVE) using formulas developed by Hubbard et al.<sup>27</sup> and later modified by Knudtson et al.<sup>28</sup> These equivalents are projected calibers for the central retinal vessels, measured away from the optic disc. The reproducibility of retinal vascular measurements has been reported.<sup>26,27</sup>

In a recent study,<sup>29</sup> intragrader reliability was assessed on 200 randomly selected retinal photographs, and the intraclass correlation coefficient (95% confidence interval) was 0.99 (0.98–0.99) for CRAE and 0.94 (0.92–0.96) for CRVE.

### Visual Acuity and Macular Thickness

Visual acuity, central macular thickness (CMT), and intraocular pressure (IOP) were measured at baseline and at 3 months by certified, masked examiners. Best corrected logarithm of the minimum angle of resolution (logMAR) visual acuity was performed with Early Treatment of Diabetic Retinopathy Study (ETDRS) charts. CMT was measured by optical coherence tomography (OCT 3 Stratus; Carl Zeiss Meditec, Inc., Dublin, CA), and IOP was measured by Goldmann applanation tonometry.

### Statistical Methods

Retinal vascular calibers (CRAE and CRVE) were assessed as continuous variables. Normality was assessed for all analyses, and appropriate nonparametric methods were applied as necessary. The relationship between baseline and 3-month vessel caliber was assessed by paired two sample *t*-test, to account for within-eye pairing of measurements. The relationship between treatment group and change in caliber over 3 months was assessed by one-way ANOVA. Changes in other ocular factors (IOP, CMT, VA) were assessed by one-way ANOVA, or Kendall's rank correlation to account for non-normality. Significance levels were

set at  $P < 0.05$ . All data analysis was performed (Intercooled Stata version 9.0 for Windows, 2005; StataCorp, College Station, TX).

### RESULTS

Overall 28 eyes of 21 patients were included in the study. The baseline characteristics of the patients receiving an injection of IVTA versus those receiving sham injection are shown in Table 1. No statistically significant differences between the two groups were noted. Of the 21 patients, 7 had both eyes (14 eyes) and 14 had one eye recruited into the study. Of these patients, there were no statistically significant differences between those with both or one eye included, in terms of age ( $65.0 \pm 10.4$  years vs.  $61.5 \pm 12.9$  years,  $P = 0.504$ ), male sex (50.0% vs. 42.9%,  $P = 0.757$ ) and HbA1c ( $8.42\% \pm 1.20\%$  vs.  $8.10\% \pm 1.30\%$ ,  $P = 0.576$ ), although, those with only one eye included had a median duration of diabetes of 12.0 years compared with 15.5 years in those with both eyes included,  $P = 0.039$ . Of the original 43 patients, no significant differences in baseline characteristics (age, sex, HbA1c, and duration of diabetes) were noted in those patients who were included compared with those who were excluded from the study.

At baseline, there were no statistically significant differences in visual acuity (61.5 letters compared with 67.6 letters), CMT ( $426 \mu\text{m}$  vs.  $475.3 \mu\text{m}$ ), arterial diameter ( $147.8 \mu\text{m}$  vs.  $139.9 \mu\text{m}$ ), or venular diameter ( $219.5 \mu\text{m}$  vs.  $220.3 \mu\text{m}$ ) between the IVTA and sham groups, respectively.

Table 2 shows the changes in visual acuity, retinal arteriolar caliber (CRAE), retinal venular caliber (CRVE), and CMT measurements at baseline and at 3 months in individual patients treated with IVTA and sham injections. Although the absolute reduction in the mean CRAE ( $-7.8 \mu\text{m}$ ) and CRVE ( $-21.8 \mu\text{m}$ ) was greater in the IVTA-treated eyes than in the sham treated eyes ( $-0.7$  and  $-2.7 \mu\text{m}$ , respectively), the difference between the groups did not reach statistical significance for either CRAE ( $P = 0.222$ ) or CRVE ( $P = 0.065$ ). In eyes treated with IVTA, however, there was a statistically significant reduction in both arteriolar ( $147.8 \mu\text{m}$  vs.  $140.0 \mu\text{m}$ ,  $P = 0.047$ ) and venular caliber ( $219.5 \mu\text{m}$  vs.  $198 \mu\text{m}$ ,  $P = 0.039$ ) compared with baseline. There was no reduction in either arteriolar ( $139.9 \mu\text{m}$  vs.  $139.2 \mu\text{m}$ ,  $P = 0.878$ ) or venular caliber ( $220.3 \mu\text{m}$  vs.  $217.6 \mu\text{m}$ ,  $P = 0.534$ ) in those treated with sham injections (Table 3).

In the seven patients with both eyes included in the study (seven with IVTA and seven fellow eyes with sham injections), there was a significant change in absolute arteriolar ( $-11.25 \pm 15.82 \mu\text{m}$  vs.  $-4.19 \pm 18.24 \mu\text{m}$ ,  $P = 0.028$ ) but not venular diameter ( $-23.47 \pm 24.33 \mu\text{m}$  vs.  $-1.73 \pm 23.05 \mu\text{m}$ ,  $P = 0.128$ ) in eyes with IVTA.

TABLE 1. Baseline Characteristics of the Eyes

	IVTA (n = 13)	Sham (n = 15)	P
Age (y)	61.8 (10.9)	65.1 (11.2)	0.43
Sex, male, n (%)	5 (38.5)	7 (46.7)	0.66
Diabetes duration (y)	16.5 (9.1)	12.8 (5.4)	0.26
HbA1c (%)	8.0 (0.92)	8.20 (1.29)	0.63
Visual acuity (letters)*	61.5 (9.5;43–77)	67.6 (10.1;40–78)	0.115
CMT ( $\mu\text{m}$ )*	426.0 (146.7;268–717)	475.3 (98.3;358–620)	0.423
IOP (mm Hg)*	15.8 (2.8;13–23)	16.0 (2.9;11–20)	0.887
CRAE ( $\mu\text{m}$ )*	147.8 (28.4;72.1–184.5)	139.9 (20.5;109.5–179.4)	0.402
CRVE ( $\mu\text{m}$ )*	219.5 (43.5;122.5–302.4)	220.3 (26.5;187.8–290.0)	0.955

Data shown are proportional; *P* relates to the  $\chi^2$  test statistic.

\* Data are expressed as the mean  $\pm$  SD; *P* relates to the one-way ANOVA statistic.

TABLE 2. Visual Acuity, CMT, and Retinal Vascular Caliber at Baseline and after 3 Months in Triamcinolone- and Sham-Treated Eyes

Eye	IVTA							Sham									
	Baseline			3 Mo				Baseline			3 Mo						
	VA	CRAE ( $\mu\text{m}$ )	CRVE ( $\mu\text{m}$ )	CMT ( $\mu\text{m}$ )	VA	CRAE ( $\mu\text{m}$ )	CRVE ( $\mu\text{m}$ )	CMT ( $\mu\text{m}$ )	VA	CRAE ( $\mu\text{m}$ )	CRVE ( $\mu\text{m}$ )	CMT ( $\mu\text{m}$ )	VA	CRAE ( $\mu\text{m}$ )	CRVE ( $\mu\text{m}$ )	CMT ( $\mu\text{m}$ )	
LE	67	184.45	234.69	—	80	182.30	187.11	—	LE	69	154.11	236.31	—	64	144.71	225.98	—
LE	52	147.16	174.54	—	67	141.82	225.33	—	LE	53	109.48	205.53	—	38	122.31	190.26	—
RE	53	169.97	302.37	—	57	168.15	238.21	—	RE	40	179.43	204.25	—	—	140.80	212.71	—
RE	70	134.94	202.19	—	80	123.36	194.52	212	LE	65	151.35	234.77	—	66	139.45	221.27	345
LE	68	142.72	223.18	—	68	147.38	197.94	—	RE	72	115.07	208.91	—	69	149.44	223.86	—
RE	43	133.29	214.35	484	43	129.85	211.57	436	RE	78	132.75	188.44	—	82	133.42	190.11	278
LE	65	162.45	207.91	330	76	167.63	218.40	283	LE	76	131.37	226.87	410	65	135.97	232.45	462
RE	64	151.20	220.10	268	75	144.63	228.15	261	RE	75	141.75	187.76	498	75	158.56	199.18	416
LE	52	165.08	214.86	389	63	124.57	161.77	188	RE	77	151.74	233.12	358	81	156.28	227.17	325
RE	62	165.89	245.80	717	67	150.74	192.55	234	RE	62	121.06	190.35	359	60	117.63	198.06	261
RE	57	72.10	122.47	294	60	79.94	114.28	233	RE	65	125.23	231.83	605	64	108.70	218.61	445
LE	70	125.35	217.15	522	78	107.11	167.96	229	RE	68	150.35	224.47	543	61	152.42	221.41	566
RE	77	167.40	274.26	404	81	152.54	237.46	354	RE	73	150.19	237.49	461	74	141.99	225.98	305
									RE	69	116.02	204.23	620	71	127.44	229.60	461
									LE	72	169.03	290.04	424	68	159.60	247.33	414

Concurrent with the changes in CRAE and CRVE, there were significant improvements in visual acuity (+7.3 letters) in the IVTA group compared with the sham group ( $-2.6$  letters;  $P < 0.001$ ) and significant decreases in CMT in the IVTA ( $-55.5 \mu\text{m}$ ) and sham groups ( $-82.0 \mu\text{m}$ ). There was no difference in the change from baseline, between the IVTA- and sham-injection groups with respect to CMT ( $P = 0.413$ ). IOP was not significantly different between the two groups at baseline and at 3 months, nor was there a significant change in IOP over the 3-month period (Table 4).

## DISCUSSION

In this prospective randomized controlled study of eyes with DME, IVTA had a significant narrowing effect on both retinal arteriolar and venular diameter compared with that in control eyes receiving sham injections.

Triamcinolone is a synthetic glucocorticoid and has a variety of actions, including anti-inflammatory effects, and several groups have shown a beneficial effect of IVTA on visual acuity and macular edema in patients with refractory DME.<sup>13,16,17,30-33</sup> Recent studies have also highlighted a previously unsuspected role of inflammation in the pathogenesis of DME. It has been hypothesized that vascular endothelial growth factor (VEGF) can trigger early retinal inflammation by inducing the expression and upregulation of intracellular adhesion molecules,<sup>34</sup> which may in turn lead to leukocyte adhesion and stasis within the retinal vascula-

ture. With subsequent reperfusion, endothelial cell injury, and dysfunction may ensue.

There is evidence that retinal venular caliber may also be influenced by systemic inflammation<sup>7,35-37</sup> and in patients with diabetes and those with impaired fasting glucose, retinal venular caliber has been noted to be larger than in individuals with normal fasting glucose.<sup>7-10</sup> It has been speculated that inflammation and endothelial dysfunction may explain the underlying association of larger venular caliber with diabetes and impaired fasting glucose.<sup>38</sup> It has been postulated that that in the diabetic retina, hyperglycemia, and hypoxia initiate retinal vasodilatation, leading to vascular hyperperfusion,<sup>39,40</sup> with subsequent elevation of transmural hydrostatic pressure and consequent leakage across the vessel wall. Although an attractive explanation, the counter argument that vascular dilatation in patients with diabetes improves retinal perfusion and oxygenation, rather than having a detrimental effect, cannot be dismissed.

The present study showed that 3 months after a single IVTA injection in patients with refractory DME there were significant reductions in both the retinal arteriolar and venular diameter compared with that in eyes receiving sham injection. This finding would support our hypothesis, although the absolute changes in the vessel diameter between the two groups did not reach statistical significance. In the seven patients treated in one eye with IVTA and sham in the other, there was a significant change in CRAE at 3 months in the IVTA-treated eyes

TABLE 3. Retinal Vascular Caliber at Baseline and after 3 Months in Triamcinolone- and Sham-Treated Eyes

	IVTA ( $n = 13$ )				Sham ( $n = 15$ )				
	Baseline	3 Mo	$P^*$	Change over 3 Mo	Baseline	3 Mo	$P^*$	Change over 3 Mo	$P^\dagger$
CRAE ( $\mu\text{m}$ )	147.8 (130.7 to 165.0)	140.0 (123.4 to 156.6)	0.047	-7.8 (-15.6 to -0.1)	139.9 (128.6 to 151.3)	139.2 (130.7 to 147.7)	0.878	-0.7 (-10.0 to 8.6)	0.222
CRVE ( $\mu\text{m}$ )	219.5 (193.2 to 245.8)	198.1 (176.9 to 219.3)	0.039	-21.4 (-41.6 to -1.3)	220.3 (205.6 to 235.0)	217.6 (208.5 to 226.7)	0.534	-2.7 (-11.8 to 6.4)	0.065

Data are the mean (95% confidence interval).

\*  $P$  relates to the paired two-sample  $t$ -test statistic.

†  $P$  relates to the two-sample  $t$ -test statistic.

TABLE 4. Difference in Other Ocular Factors after 3 Months in Triamcinolone- and Sham-Treated Eyes

	IVTA	Sham	P
Visual acuity (letters)	(n = 13 eyes)	(n = 14 eyes)	
At 3-mo visit*	68 (63, 78)	67 (64, 74)	0.680
Change from baseline to 3 mo†	+7.3 (+4.3 to +10.3)	-2.6 (-5.8 to +0.6)	<0.001
IOP (mm Hg)	(n = 13 eyes)	(n = 14 eyes)	
At 3-mo visit*	17 (14 to 19)	14.5 (12 to 16)	0.119
Change from baseline to 3 mo†	0 (-3 to +4)	-1.5 (-2 to 0)	0.305
CMT ( $\mu\text{m}$ )	(n = 9 eyes)	(n = 11 eyes)	
At 3-mo visit*	270.0 (209.7 to 330.3)	388.9 (325.8 to 452.0)	0.007
Change from baseline to 3 mo†	-55.5 (-247 to -47.5)	-82 (-156 to -10)	0.413

\* Values shown are median (interquartile range); P relates to Kendall's  $\tau$  test statistic.

† Values shown are mean (95% confidence interval); P relates to one-way ANOVA test statistic.

compared with the sham-treated eyes. We found no statistically significant difference in CRVE in these patients, although there was a large absolute difference noted.

Similar findings, in terms of reduction of retinal arteriolar diameter 1 week after IVTA were found by Vinten et al.<sup>23</sup> (94.9% of baseline,  $P = 0.05$ ). In addition, they noted a statistically significant reduction in venular diameter (89.2% of baseline,  $P = 0.02$ ). Analogous to our study, Vinten et al. had seven patients, each of which had one eye treated with IVTA and the fellow assessed as the control. In their study blood-retinal barrier permeability was also assessed, and, concurrent with the reductions in arteriolar and venular diameter, there was a significant reduction in blood-retinal barrier permeability. This reduction was not seen in the untreated fellow eye. In keeping with this increase in blood-retinal barrier permeability in patients with DME, Sander et al.<sup>41</sup> documented increased permeability in patients progressing from nonclinically significant to clinically significant macular edema. This change was noted to precede any changes in retinal thickness or retinal vascular caliber.

Our results are consistent with the previously reported improvements in visual acuity and CMT with IVTA. There was a good correlation between improved visual acuity and CMT with the reduction in vessel caliber in patients treated with IVTA. Although there is an association between IVTA and a concurrent reduction in CMT and an improvement in visual acuity, it is not possible from our results to determine whether the IVTA is directly responsible for the change, or whether the reduction in vessel caliber is a response to the improvement in retinal thickening. Nonetheless, it is plausible that the anti-inflammatory effects of triamcinolone as well as its role in inhibiting the VEGF induced inflammatory changes in vascular permeability<sup>42</sup> plays a role. As such, IVTA may lead to a reduction in vascular caliber and consequent reduction in pressure gradient across the walls of the retinal vessels<sup>12</sup> and to an ensuing reduction in vascular leakage.

The principle strength of this study is that the data were taken from a double-masked, placebo-controlled randomized clinical trial.<sup>13</sup> Unfortunately, due to a significant number of the original cohort having ungradable photographs, the overall number of patients included in the study was low. Although it is possible that IVTA has no effect on CRAE and CRVE, with the reduction in vessel caliber being a result of regression to the mean, we believe that this is unlikely, since there was no statistically significant difference in the baseline arteriolar diameter between patients in the two treatment groups. In addition, regression to the mean would not explain the concurrent reduction in venular diameter seen in the IVTA-treated patients. We feel that the most likely reason for the lack of statistical significance in the change of retinal vascular diameter, despite the large difference in absolute measurement after IVTA compared with sham injection, is due to the small group

of patients. A larger randomized masked trial may be able to clarify these issues further. Another possible limitation is that patients in the placebo group were given sham injections rather than intravitreal injections of placebo. As such, we are not able to say for sure whether the reduction in vessel caliber is related to the IVTA or whether it relates to the intravitreal injection itself.

In summary, this study suggests that in patients with refractory DME, there is reduction in both the retinal arteriolar and venular caliber after injection of IVTA. The significance of these findings is unclear and may be the mechanism of action of triamcinolone-induced improvements in DME or may merely represent a response to the reduction in DME itself.

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