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Macular function after intravitreal triamcinolone acetonide injection for diabetic macular oedema

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ABSTRACT.

Purpose: **We aimed to evaluate the effect of intravitreal triamcinolone acetonide (IVTA) on macular function in patients with diabetic macular oedema (DMO).**

Methods: **Eleven eyes in 11 patients with DMO were enrolled. In each eye, at baseline and at 30 days after IVTA injection, logMAR visual acuity (VA), macular sensitivity, fixation stability and fixation location by MP-1 microperimetry and optical coherence tomography (OCT) foveal thickness were assessed.**

Results: **Thirty days after IVTA injection, eyes with DMO showed a significant ($p < 0.001$) reduction in foveal thickness and significant ($p < 0.01$) increases in logMAR VA and MP-1 retinal sensitivity ($p < 0.001$). There was also significant ($p = 0.046$) improvement in fixation location and some improvement in fixation stability, although the latter was not significant ($p = 0.08$).**

Conclusions: **In eyes with DMO, short-term improvement in retinal sensitivity and fixation properties can be achieved by IVTA injection.**

Key words: diabetic macular oedema – fixation location – fixation stability – intravitreal triamcinolone acetonide – macular function – microperimetry – MP-1

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Introduction

Diabetic macular oedema (DMO) is one of the most frequent causes of major loss of vision in patients with diabetes mellitus (Klein et al. 1984). The pathophysiological mechanisms leading to DMO are still poorly understood. However, changes in blood–retinal barrier permeability and intravascular hydrostatic pressure are generally believed to be involved in the genesis of DMO (Vinten et al. 2007). The increase in retinal capillary permeability may be caused by a breakdown of the blood–retinal barrier, mediated in part by vascular endothelial growth factor (VEGF). The rationale behind the use of corticosteroids to treat DMO is that they may reduce retinal capillary permeability by increasing the activity and/or density of the tight junctions in the retinal capillary endothelium. It has also been reported that corticosteroids may inhibit the metabolic pathway of VEGF and the expression of the VEGF gene. Corticosteroids are also known to stimulate the production of the glycoprotein called lipocortin that inhibits the activity of phospholipase A2, which releases arachidonic acid from phospholipids, the precursor of prostanoids and leukotrines. Corticosteroids inhibit mRNA responsible for interleukin (IL-1) formation. These actions of corticosteroids on arachidonic acid metabolism and IL-1 formation produce anti-inflammatory, immunosuppressive and antimitogenic effects (Audren et al. 2006; Sivaprasad et al. 2006).

Various studies have shown the benefit of intravitreal triamcinolone acetonide (IVTA) injection in patients with DMO (Jonas & Söfker 2001; Martidis et al. 2002; Karacorlu et al. 2005; Margolis et al. 2008). In these studies, visual acuity (VA) and morphological features before and after IVTA injection were evaluated, but patients' subjective appraisal of their

visual function, which may vary, was not comprehensively discussed.

The purpose of this study was to obtain a measure of foveal function before and after IVTA injection in patients with DMO. To accomplish this, microperimetry was performed in 11 eyes of 11 patients with DMO before and after IVTA injection, and the sensitivity of the fovea determined from the results. Pre-injection sensitivity of the fovea was compared with post-injection sensitivity. Fixation stability and location before and after injection were also determined from the results of microperimetry.

Materials and Methods

Eleven eyes in 11 patients (10 men and one woman) with non-insulin-treated diabetes mellitus and DMO were included. Mean patient age was 59.5 years (range 46–70 years). Mean duration of diabetes mellitus was 11.8 years (range 2–20 years). Eligibility criteria for this study included: the presence of clinically significant DMO (as defined by Early Treatment Diabetic Retinopathy Study [ETDRS] criteria) on fundus examination; the presence of angiographically confirmed DMO, or the presence of DMO confirmed by optical coherence tomography (OCT). Because several conditions may influence microperimetry and VA, we excluded patients with moderate to dense lens opacity, implanted intraocular lenses, corneal opacities, a history of refractive surgery, glaucoma or ocular hypertension, a history of intraocular inflammation such as anterior or posterior uveitis, multifocal choroiditis, a history of retinal detachment, a history of ocular trauma, and optic neuropathy. In this consecutive series, no eyes had received previous laser photocoagulation and all eyes had non-proliferative diabetic retinopathy. Control eyes (CEs) included 11 normal eyes in 11 healthy persons (eight men, three women; mean age 57.9 years). Control eyes did not receive any sham treatment.

All eyes underwent complete ophthalmic examination, including corrected VA measurement (with an ETDRS chart), slit-lamp biomicroscopy, indirect ophthalmoscopy, colour fundus photography, fluorescein angiography (FA) and OCT. Best corrected VA, expressed as logMAR, was obtained at a distance of 4 m. Fluorescein angiograms were performed on a Heidelberg scanning laser ophthalmoscope (Heidelberg Engineering GmbH, Heidelberg, Germany). Optical coherence tomography examinations were performed using the OCT 3000 scanner (Carl Zeiss Ophthalmic Systems, Inc., Humphrey Division, Dublin, CA, USA). All OCT examinations were carried out by the same operator and all scans were made with a scan length of 6 mm. Foveal thickness was defined as the distance between the vitreoretinal interface and the retinal pigment epithelium in the centre of the fovea.

Before the IVTA injection, topical proparacaine hydrochloride was applied to the ocular surface, followed by preparation with 5% povidone iodine. A cotton-tipped applicator soaked in proparacaine hydrochloride was then applied to the injection site 4 mm posterior to the limbus. The injection consisted of 0.1 ml (4 mg) of a commercially available suspension of triamcinolone acetonide (Kenacort-A; 40 mg/ml, Bristol-Myers Squibb Co., Princeton, NJ, USA). Indirect ophthalmoscopy was used to confirm proper intravitreal localization of the suspension. Patients were examined on days 1 and 7 to detect any infection.

The response to treatment was monitored functionally by VA and microperimetry assessment and anatomically by OCT foveal thickness after injection. Potential corticosteroid-induced and injection-related complications such as increases in intraocular pressure (IOP), cataract and endophthalmitis were also observed.

Macular sensitivity was evaluated using MP-1 microperimetry (Version MP1 SW 1.4.1 SP1; Nidek Technologies SRL, Padua, Italy). The MP-1 provides a 45-degree non-mydriatic view of the fundus with automated correction for eye movements. Goldmann III stimuli and a 4–2 staircase strategy were used, and a circular test grid with 74 stimulus locations covering an area of 20 degrees was applied. The stimuli were projected on a white background with background illumination set to 1.27 cd/m^2 and a stimulus presentation time of 200 millisecond (ms). The perimetric strategy of the current MP-1 software starts at an initially defined threshold level for each stimulus. A 4–2 staircase strategy is then carried out, and the threshold value last seen is taken as the final threshold. Although the examiner can define the initial threshold value, the actual threshold of the examined eye remains unaccounted for. In addition, the instrument tests the same luminance levels at all test locations before moving on to the next luminance level. Differential light threshold values were compared by calculating 74 points of mean sensitivity in a polygon averaged automatically by the MP-1 microperimetry software.

To assess fixation, fundus movements are tracked during examination while the patient gazes at the fixation target. The autotracking system calculates horizontal and vertical shifts relative to a reference frame and draws a map of the patient's eye movements during the examination. The recorded fixation points are classified into three categories for fixation stability analysis (stable, relatively unstable and unstable). Fixation is regarded as stable if $> 75\%$ of the fixation points are inside the 2-degree diameter circle, as relatively unstable if $< 75\%$ are inside the 2-degree diameter circle but $> 75\%$ are inside the 4-degree diameter circle, and as unstable if $< 75\%$ of the fixation points are inside the 4-degree diameter circle. To assess fixation location, a standard, circular, central fixation area 2 degrees in diameter (approximately 700 μm) centred on the fovea is defined. Eyes with $> 50\%$ of the preferred fixation points located within the central area are classified as having predominantly central fixation. Eyes with $> 25\%$ but $< 50\%$ of preferred fixation points located within the central area are classified as having poor central fixation. Eyes with $< 25\%$ of the preferred fixation points located within the central area are classified as having predominantly eccentric fixation. Fixation locations are classified automatically by the MP-1 software after a landmark has been positioned in the centre of the foveal avascular zone. We performed MP-1 microperimetry before treatment to collect baseline data. The subsequent MP-1 assessment was performed at 30 days after IVTA injection. We repeated the procedure, choosing an MP-1

microperimetry follow-up program which used the same test parameters as in the baseline evaluation.

Results from CEs and DMO eyes observed at baseline were compared using Student's *t*-test. Values for functional (VA and MP-1 microperimetry) and morphometric parameters (OCT) observed in eyes with DMO 30 days after IVTA injection were compared with baseline (pretreatment) values using the paired *t*-test. Pearson and Spearman correlations were used to correlate foveal thickness with visual function parameters (VA and MP-1 microperimetry results). The MP-1 microperimetry fixation location and fixation stability in DMO eyes at baseline were compared with the same parameters in CEs using Wilcoxon's test. Equivalent data observed in DMO eyes at 30 days after treatment were compared with baseline values using Mann–Whitney *U*-test.

Test–retest data for MP-1 microperimetry results are expressed as the mean difference between three records obtained in separate sessions ± the standard deviation (SD) of the difference. The 95% confidence interval (CI) of test–retest variability in normal and study subjects was established with the assumption of a normal distribution.

Table 1. Clinical characteristics of patients with diabetic macular oedema at baseline (pretreatment) and 30 days after treatment.

		Visual acuity, logMAR		MP-1 microperimetry sensitivity, dB		MP-1 microperimetry 'fixation location'		MP-1 microperimetry 'fixation stability'		OCT foveal thickness, μ	
Patient	Age, years	Baseline	30 days	Baseline	30 days	Baseline	30 days	Baseline	30 days	Baseline	30 days
1	65	0.7	0.4	5.0	8.4	3	3	2	3	330	296
2	61	0.4	0.2	11.4	18.4	3	3	2	2	423	214
3	66	1.5	1.0	12.4	14.3	1	2	1	2	538	316
4	53	0.3	0.2	10.2	13.0	3	3	3	3	589	216
5	58	0.2	0	8.8	10.8	3	3	3	3	532	224
6	58	0.3	0.1	8.9	10.5	3	3	3	3	382	254
7	66	0.5	0.3	8.7	13.2	2	2	2	2	648	312
8	61	0.7	0.5	4.2	6.4	2	3	2	3	412	238
9	68	0.3	0.1	8.8	11.5	2	3	2	2	386	214
10	70	0.5	0.3	6.1	9.0	3	3	3	3	314	282
11	46	0.7	0.5	8.5	13.0	2	3	2	2	426	228

For fixation location: 3 = predominantly central; 2 = poor central; 1 = predominantly eccentric.
For fixation stability: 3 = stable; 2 = relatively unstable; 1 = unstable.
OCT = optical coherence tomography.

Table 2. Visual acuity, MP-1 microperimetry sensitivity and foveal thickness according to optical coherence tomography in eyes with diabetic macular oedema at baseline compared with control eyes, by Student's *t*-test.

		Baseline	30 days	p-value (paired *t*-test)
Visual acuity	Control eyes (n = 11)	0.00 ± 0.00	0.33 ± 0.28	t = 7.47, p < 0.001
	DMO eyes (n = 11)	0.55 ± 0.36		
	p (Student's t-test)	t = 5.08, p < 0.001		
MP-1 microperimetry sensitivity, dB	MP	14.71 ± 1.55	11.68 ± 3.25	t = 6.76, p < 0.001
	MP	8.45 ± 2.52		
	p (Student's t-test)	t = 7.02, p < 0.001		
OCT foveal thickness, μ	MP	219.00 ± 13.15	254.00 ± 40.29	t = 5.94, p < 0.001
	MP	452.73 ± 108.29		
	p (Student's t-test)	t = 7.1, p < 0.001		
				Wilcoxon test
MP-1 microperimetry fixation stability	Control eyes	Median = 3.00	Median = 3.00	z = 1.73, p = 0.08
	DMO eyes	Median = 2.00		
	Mann–Whitney U-test	z = 2.16, p = 0.03		
MP-1 microperimetry fixation location	Control eyes	Median = 3.00	Median = 3.00	z = 2.00, p = 0.046
	DMO eyes	Median = 3.00		
	Mann–Whitney U-test	z = 2.47, p = 0.013		

Data observed in DMO eyes at 30 days after treatment were compared with equivalent data obtained at baseline, by paired *t*-test. MP-1 microperimetry fixation location and fixation stability of DMO eyes at baseline were compared with the same parameters in control eyes, by Wilcoxon's test. Equivalent data observed in DMO eyes at 30 days after treatment were compared with baseline data, by Mann–Whitney *U*-test.
n = number of eyes enrolled.
For fixation location: 3 = predominantly central; 2 = poor central; 1 = predominantly eccentric.
For fixation stability: 3 = stable; 2 = relatively unstable; 1 = unstable.
DMO = diabetic macular oedema; MP = microperimetry; OCT = ocular coherence tomography.

Results

The clinical characteristics of eyes with DMO observed at baseline and at 30 days post-treatment are reported in Table 1. Comparisons of functional and morphological data at baseline and 30 days after treatment are reported in Table 2. Eyes with DMO showed significantly lower ($p < 0.001$) logMAR VA and MP-1 microperimetry sensitivity and significantly higher ($p < 0.001$) OCT foveal thickness than CEs. Eyes with DMO showed lower fixation location and fixation stability than CEs ($p = 0.013$, $p = 0.03$, respectively). At baseline, in eyes with DMO, fixation localization was predominantly central in six, poor central in four and predominantly eccentric in one eye; fixation stability was stable in four, relatively unstable in six and unstable in one eye. Thirty days after IVTA injection, eyes with DMO showed a significant ($p < 0.001$) reduction in foveal thickness. There was also a significant ($p < 0.01$) increase in logMAR VA and MP-1 retinal sensitivity ($p < 0.001$). Figures 1 and 2 show, respectively, the FA and MP-1 results for patient 2 at baseline and at 30 days post-treatment.

At baseline, fixation location was predominantly central in patients 1, 2, 4, 5, 6 and 10 and poor central in patient 7. Fixation location had not changed at 30 days after treatment in these eyes. In patient 3, fixation changed from predominantly eccentric at baseline to poor central and in patients 8, 9 and 11 fixation changed from poor central at baseline to predominantly central at 30 days after treatment. Eyes with DMO showed significant improvement in fixation location ($p = 0.046$) at 30 days post-treatment compared with at baseline.

At baseline, fixation stability was stable in patients 4, 5, 6 and 10 and relatively unstable in patients 2, 7, 9 and 11. Fixation stability had not changed at 30 days after treatment in these eyes. In patients 1 and 8, relatively unstable fixation at baseline had changed to stable fixation at 30 days post-treatment, and in patient 3 unstable fixation at baseline had changed to relatively unstable fixation at 30 days after treatment. Eyes with DMO showed some improvement in fixation stability from baseline to 30 days after treatment although this was not significant ($p = 0.08$).

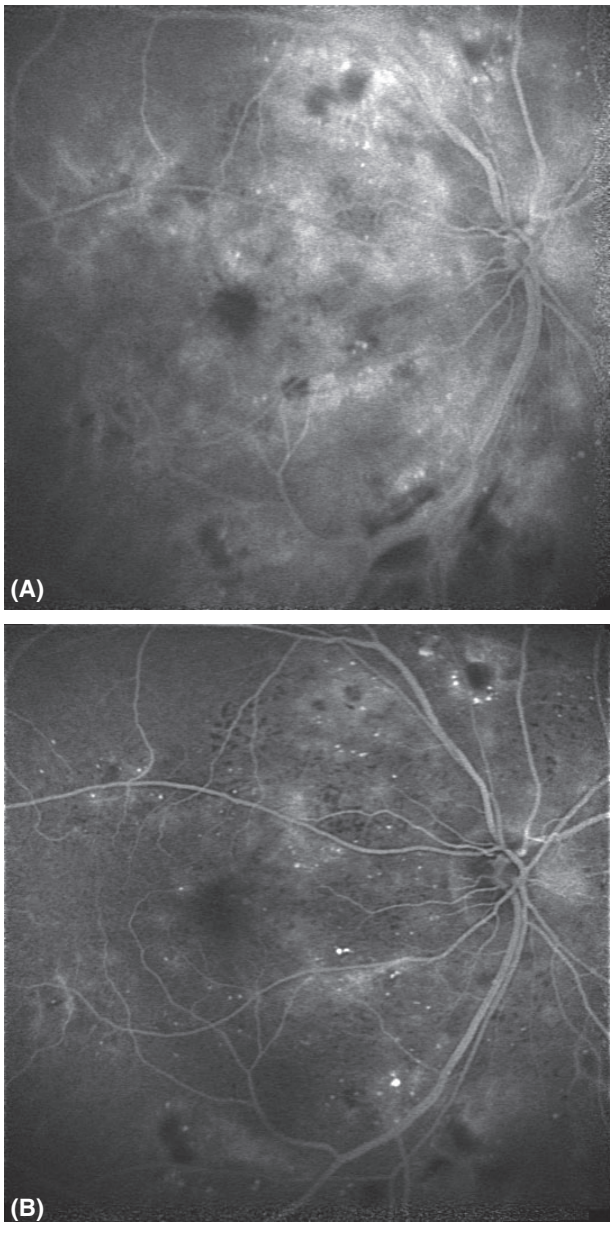

Fig. 1. Fluorescein angiography in patient 2 at (A) baseline (at 3.52 seconds) and (B) 30 days after treatment (at 3.23 seconds). Diabetic macular oedema was seen to have decreased at 30 days after treatment.

Table 3 reports the correlations between foveal thickness and logMAR VA, MP-1 microperimetry sensitivity, fixation stability and fixation location in eyes with DMO in terms of the differences between baseline values and those obtained at 30 days after IVTA injection. There was no significant correlation ($p > 0.05$) between foveal thickness and parameters of visual function.

Test–retest mean sensitivity data for MP-1 microperimetry in control subjects were: mean 0.43 dB, SD 0.46 dB, 95% CI 0.14–0.73 dB. Equivalent data in eyes with DMO were: mean 0.22 dB, SD 0.49 dB, 95% CI − 0.15 to 0.60 dB. Test–retest fixation stability data for MP-1 microperimetry in control subjects were: for 2 degrees, mean − 2.33%, SD 5.69%, 95% CI − 5.95 to 1.28%; for 4 degrees, mean − 1.00%, SD 1.65%, 95% CI − 2.04 to 0.05%. Equivalent data in eyes with DMO were: for 2 degrees, mean 0.22%, SD 6.57%, 95% CI − 4.83 to 5.27%; for 4 degrees, mean − 0.89%, SD 6.15%, 95% CI − 2.81 to 0.90%.

No cataract progression and endophthalmitis were encountered during

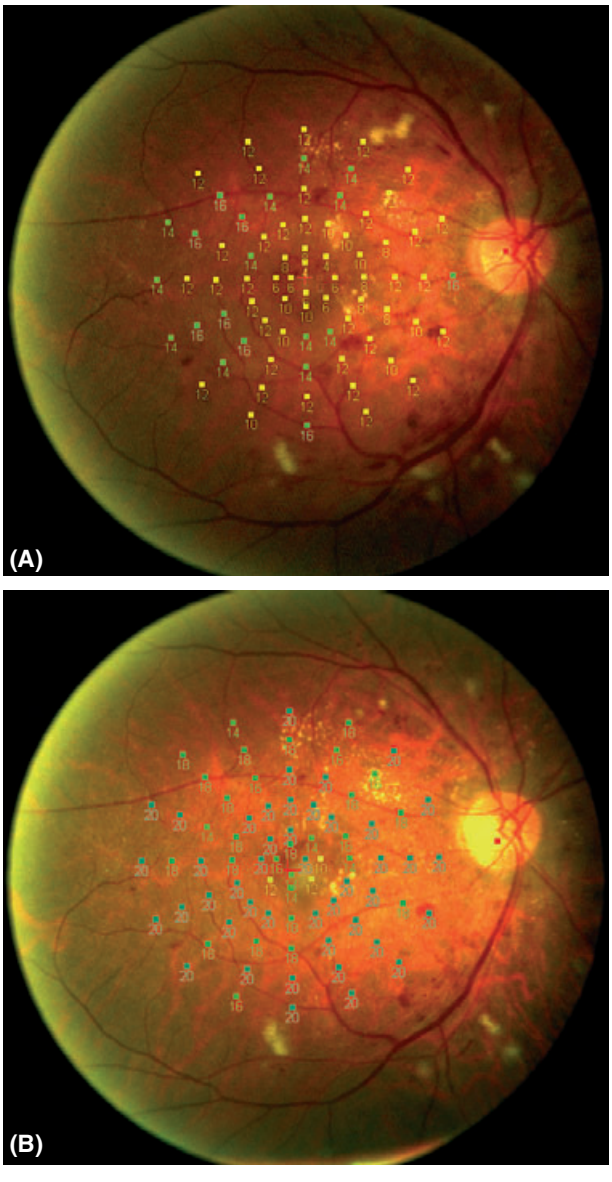

Fig. 2. MP-1 microperimetry in patient 2 at (A) baseline and (B) 30 days after treatment. Macular sensitivity was examined by testing the mean decibels at 76 points of the central 20 degrees of the macula. The intensity of the stimulus inversely corresponded to the tested retinal sensitivity, expressed as a gradual change in colour from dark red (corresponding to 0 dB) to dark green (corresponding to 20 dB). At baseline, patient 2 showed a lower macular sensitivity in MP-1 microperimetry than control eyes, but sensitivity had increased at 30 days post-treatment.

Table 3. Visual acuity, MP-1 microperimetry sensitivity and foveal thickness according to optical coherence tomography in eyes with diabetic macular oedema 30 days after treatment, correlated with baseline data.

	Differences (baseline–30 days)	Pearson correlations (p, r)
Visual acuity	0.23 ± 0.10	$r = -0.24$, p = 0.48
MP-1 sensitivity	− 3.23 ± 1.58	$r = -0.08$, p = 0.79
		Spearman correlations (p, ρ)
MP-1 fixation stability	Median = 0.00	$\rho = 0.19$, p = 0.56
MP-1 fixation location	Median = 0.00	$\rho = 0.06$, p = 0.86
OCT foveal thickness	198.73 ± 110.93	

OCT = optical coherence tomography.

follow-up. Four eyes (36%) with IOP > 21 mmHg at a given examination were treated with a topical beta-blocker at the subsequent examination.

Discussion

Diabetic macular oedema is the leading cause of severe visual impairment in the Western population (Klein et al. 1984). The condition affects visual function as part of the disease process and severely compromises the highly developed functions of the macula, such as perception of details, central fixation, colour vision and reading ability. Visual acuity is the standard measurement of vision commonly used in clinical practice (Brown et al. 1999; Lamoureux et al. 2004). However, high-contrast VA measurement is often a poor predictor of general visual performance. Important daily tasks such as recognition of faces and symbols, orientation and reading are extremely dependent on the preservation of the central visual field.

The purpose of our study was to obtain a measure of foveal function before and after IVTA injection in patients with DMO. To accomplish this, microperimetry was performed in eyes with DMO before and after IVTA injection, and the sensitivity of the fovea was determined from microperimetry results.

Various studies have shown the benefits of IVTA injection in patients with DMO (Jonas & Söfker 2001; Martidis et al. 2002; Karacorlu et al. 2005). In these studies, VA and morphological features before and after IVTA injection were evaluated, whereas patients' subjective appraisal of visual function, which may vary, was not comprehensively discussed (Jonas & Söfker 2001; Martidis et al. 2002; Karacorlu et al. 2005). After intravitreal injection of 4 mg triamcinolone, Martidis et al. (2002) found improvements in VA of 2.4, 2.4 and 1.3 Snellen lines at 1, 3 and 6 months, respectively. Another study of subjects undergoing IVTA injection, by Karacorlu et al. (2005), found VA increases at 3 and 6 months, respectively, in 66.6% and 83.2% of DMO patients who did not undergo laser treatment. In all these studies, foveal thickness was measured with OCT before and after IVTA injection and reductions in

foveal thickness demonstrated the effectiveness of treatment. The results of our study show similarities to these data. Thirty days after IVTA injection, eyes with DMO showed a significant increase in logMAR VA. There was also a significant reduction in foveal thickness. At 1-month follow-up, mean foveal thickness had decreased from 452.73 ± 108.29 μm to 254.00 ± 40.29 μm.

The microperimetric data also show changes in retinal sensitivity after treatment. Thirty days after IVTA, mean retinal sensitivity had increased from 8.45 ± 2.52 dB to 11.68 ± 3.25 dB. Similarly, fixation location improved significantly after treatment. Treated eyes also showed improvement from baseline in fixation stability, although this was not statistically significant. It is clear that improvements in microperimetric parameters that are closely related to the central visual field positively affect the patient's daily activities. We have already pointed out that important daily tasks such as recognition of faces and symbols, orientation and reading are extremely dependent on the preservation of the central visual field (Rohrschneider et al. 2005; Okada et al. 2006). For example, it has been shown that stability of fixation is directly related to reading ability (Midena et al. 2004). High-contrast VA measurement, the standard measurement of vision in both clinical practice and many studies, is a poor predictor of general visual performance. For these reasons, our data are important because they indicate improvements in retinal sensitivity and fixation properties after IVTA injection in eyes with DMO. Because of the limitations of our pilot study (in terms of its short follow-up and small study sample), it was not possible to assess longterm changes in the central visual field, especially after recurrences of DMO and after retreatments. Thus, as well as showing short-term improvements in retinal sensitivity and fixation properties after IVTA injection in eyes with DMO, our study also shows that further study with a longer follow-up and a large series is needed.

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