Macular function by multifocal electroretinogram in diabetic macular edema after intravitreal triamcinolone acetonide injection

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PURPOSE. *The purpose of this study was to assess macular function by multifocal electroretinography (mfERG) in eyes with diabetic macular edema (DME) after intravitreal triamcinolone acetonide (IVTA) injection.*

METHODS. *Fifteen eyes of 15 patients with DME scheduled for 4 mg IVTA injection were prospectively recruited. The response to treatment was monitored functionally by visual acuity (VA) measurement and mfERG and anatomically by foveal thickness measured by optical coherence tomography (OCT). The first-order kernel P1 mfERG responses from 0 to 7 degrees (central) and 7 to 25 degrees (peripheral) were grouped and analyzed. Changes in functional parameters (VAs and the P1 mfERG response amplitudes and peak latencies) and morphometric parameters (OCT foveal thickness) in eyes with DME 1 and 3 months after IVTA injection were compared with baseline values by Student t test.*

RESULTS. *The mean baseline logMAR value for VAs of the patients before treatment was 0.49±0.26. After treatment, it was 0.27±0.23 at 1 month and 0.26±0.18 at 3 months, and differences from pretreatment values were significant (for each, $p<0.001$). There were statistically significant decreases in the mean foveal thickness at 1 and 3 months after treatment compared with pretreatment values (for each, $p<0.001$). There were also statistically significant increases in the mean P1 response amplitude for both central and peripheral groups at all examinations compared with pretreatment (for each, $p<0.001$). The mean P1 peak latencies for both the central and peripheral groups were shortened, but not significantly.*

CONCLUSIONS. *As well as the reduction in DME and improvement in VA, IVTA injection improves macular function as assessed by mfERG in diabetic patients. (Eur J Ophthalmol 2008; 18: 601-8)*

KEY WORDS. *Diabetic macular edema, Intravitreal triamcinolone acetonide, Macular function, Multifocal electroretinogram*

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INTRODUCTION

Diabetic retinopathy is a leading cause of visual impairment in adults, and diabetic macular edema (DME) is the main cause of visual impairment in diabetic patients. The Early Treatment Diabetic Retinopathy Study (ETDRS) proved the value of focal photocoagulation in clinically significant macular edema (CSME) due to focal diabetic edema associated with leaking microaneurysms (1). In cases of CSME with diffuse leakage, grid laser photocoagulation was recommended, but no large prospective trial has yet proved its value. In roughly a quarter of these patients, visual acuity (VA)

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declines by at least three ETDRS lines despite grid photocoagulation (2).

It was demonstrated in a prospective, randomized, controlled trial that a single 4-mg IVTA injection can reduce central macular thickness, as measured by optical coherence tomography (OCT), in patients with CSME who have failed previous focal photocoagulation (3). In another interventional, prospective study by Jonas and Söfker (4), the effect of IVTA on diffuse DME was evident as early as 1 week after injection and persisted for approximately 7 months. A group led by Martidis showed in an interventional case series a statistically significant improvement in vision at months 1, 3, and 6, by 2.4, 2.4, and 1.3 Snellen lines, and a decrease in macular thickness by 55%, 57.5%, and 38%, respectively (5). It was also shown that IVTA injection is effective in the treatment of DME that has had no previous laser treatment (6). In all these studies, VA and morphologic features before and after IVTA injection were evaluated, but patients' subjective appraisal of their visual function, which may differ, was not comprehensively discussed.

The purpose of this study was to obtain a measure of macular function before and after IVTA injection in patients with DME. To accomplish this, mfERG was performed on 15 eyes of 15 patients with DME before and after IVTA injection, and the macular function was determined from the result of mfERG.

METHODS

Fifteen eyes of 15 patients (10 men, 5 women) with non-insulin-treated diabetes mellitus and ME were included. The mean age of patients was 59.5 years (range 46–70 years), and the duration of diabetes mellitus ranged from 2 to 7 years (mean 5.8 years). The eligibility criteria for this study included 1) the presence of CSME due to diabetic retinopathy on fundus examination; 2) the presence of angiographically confirmed DME; and 3) the presence of ME confirmed by OCT. Because several diseases may influence mfERG and VA, we excluded patients with moderate to dense lens opacity, 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. Eyes

TABLE I - CLINICAL CHARACTERISTICS OF PATIENTS WITH DIABETIC MACULAR EDEMA BEFORE AND AFTER INTRAVITREAL TRIAMCINOLONE ACETONIDE (IVTA) INJECTION

		VA (logMAR)			mfERG-c P1 amplitude (nV/deg2)			mfERG-p P1 amplitude (nV/deg2)			mfERG-c P1 peak time (ms)			mfERG-p P1 peak time (ms)			OCT mean foveal thickness (µm)		
Patient	Age, yr	B	1 mo	3 mo	B	1 mo	3 mo	B	1 mo	3 mo	B	1 mo	3 mo	B	1 mo	3 mo	B	1 mo	3 mo
1	65	0.7	0.4	0.4	13	15.5	21.5	10.3	11.4	16	40.2	39.8	37.7	35.7	39.8	40.8	330	296	210
2	55	0.3	0.2	0.2	31.9	47.7	30.2	16.6	23.9	15.5	41	36.7	35.7	41	36.7	35.7	589	216	238
3	60	0.2	0	0	24.2	32.2	29.6	14	19.4	17.8	42	36.7	35.7	42	36.7	35.7	532	224	230
4	64	0.5	0.3	0.4	16.2	17.6	14.1	8.9	11.7	7.6	42	40.8	40.8	41	38.7	40	648	312	455
5	61	0.7	0.2	0.2	7.5	10.9	13.8	3.7	6.2	7.1	45.9	41.8	42.8	43.8	40.8	40.8	412	238	245
6	61	0.2	0	0	15.6	18.1	22.3	10	8.9	9	37.7	37.7	39.8	36.7	36.7	36.6	386	214	255
7	53	0.7	0.3	0.3	8	10.6	13.2	9.4	10	11	41.8	37.7	37.7	38.7	37.7	37.7	439	204	280
8	61	0.4	0.3	0.2	13.5	14.8	29	6.3	10.9	14	43.8	38.7	40.8	37.7	35.7	36.7	423	214	210
9	66	1.2	1	0.7	6.9	16.9	17.6	7.2	11.2	12.7	35.7	40.8	39.8	36.7	34.7	36.7	538	316	330
10	67	0.4	0.2	0.2	11.2	21.1	19.5	6.9	9.7	13	37.7	38.7	40.8	39.8	37.7	37.7	496	350	270
11	65	0.3	0.2	0.2	30.6	35	34	17.7	28.3	28	36.7	35.7	35.7	35.7	35.7	34.7	510	269	240
12	66	0.7	0.4	0.5	8.6	13.3	9	6	6.9	6.6	34.7	33.6	33.6	37.7	36.7	37.7	519	217	397
13	55	0.4	0.2	0.2	10.4	17.7	17.3	7.2	11.8	11.8	36.7	38.7	38.7	37.7	37.7	37.7	418	298	290
14	58	0.4	0.2	0.2	11.7	21.5	19	7	10.5	12.5	37.7	38.7	38.7	39.8	37.7	40.8	510	245	234
15	67	0.3	0.2	0.2	11.2	20.1	17	6.5	7.7	6	36.7	36.7	37.7	37.7	37.7	38.7	455	236	310

VA = Visual acuity; mfERG-c = mfERG central; mfERG-p = mfERG peripheral; OCT = Optical coherence tomography; B = Baseline (pretreatment); 1 mo = 1 month after IVTA injection; 3mo = 3 months after IVTA injection

with DME were compared with 15 eyes of 15 age-matched control subjects (mean age 61 years, range 47–69 years). Written informed consent was obtained from all subjects, and the study was conducted in accordance with the tenets of the Declaration of Helsinki.

The patients underwent complete ophthalmic examination, including corrected VA measurement (with ETDRS chart), slit lamp biomicroscopy, indirect ophthalmoscopy, color fundus photography, fluorescein angiography, and OCT. Best-corrected VA, expressed as logMAR, was obtained from a distance of 4 m. Fluorescein angiograms were performed on a Heidelberg scanning laser ophthalmoscope (Heidelberg Engineering, Heidelberg, Germany). OCT examinations were done using the OCT 3000 scanner (Carl Zeiss Ophthalmic System Inc., Humphrey Division, Dublin, CA). All OCT examinations were done by the same operator and all scans had a scan length of 6 mm. The foveal thickness was defined as the distance between the vitreoretinal interface and the retinal pigment epithelium in the center of the fovea.

For the injection of triamcinolone acetonide (Kenacort-A; 40 mg/mL, Bristol-Myers Squibb Co., Princeton, NJ) 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. 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 mfERG and anatomically by OCT foveal thickness after injection.

Serial mfERG recording was performed in all subjects before IVTA injection and 1 and 3 months after injection. The mfERGs were recorded using the RETI-scan (Roland Consult, Weisbaden, Germany). Multiple retinal areas were stimulated with a stimulus array of 67 hexagons with a binary m-sequence. The overall stimulus pattern subtended an angle of approximately 30 degrees on either side of fixation. The

TABLE II - MORPHOMETRIC DATA AND PSYCHOPHYSICAL AND ELECTROPHYSIOLOGIC PARAMETERS OBSERVED IN CONTROL EYES AND EYES WITH DIABETIC MACULAR EDEMA WITH INTRAVITREAL TRIAMCINOLONE ACETONIDE (IVTA) INJECTION

Parameter	Control eyes (n=15)	Eyes with diabetic macular edema (n=15)		
		Baseline	1 mo	3 mo
Mean foveal thickness (µm)	215.20±14.61	480.33±82.42 p<0.001	256.60±46.53 p<0.001	279.60±69.45 p<0.001
VA (logMAR)	0.0±0.0	0.49±0.26, p<0.001	0.27±0.23 p<0.001	0.26±0.18 p<0.001
mfERG-c P1 amplitude (nV/deg2)	37.67±4.50	14.70±7.90, p<0.001	20.86±10.07 p<0.001	20.47±7.27 p<0.001
mfERG-c P1 peak time (ms)	34.65±1.00	39.35±3.27 p<0.001	38.18±2.15 p=0.14	38.40±2.49 p=0.25
mfERG-p P1 amplitude (nV/deg2)	18.32±3.17	9.18±4.02 p<0.001	12.56±6.31 p<0.01	12.57±5.58 p<0.01
mfERG-p P1 peak time (ms)	34.77±2.64	38.78±2.38 p<0.001	37.38±1.56 p<0.05	37.86±1.98 p=0.20

Data were collected at baseline and 1 and 3 months after IVTA injection. The data for eyes with macular edema at baseline were compared with data for control eyes, by Student t test. The data for eyes with macular edema at 1 and 3 months after IVTA injection were compared with baseline, by Student t test.

n = Number of eyes enrolled, at baseline (pretreatment); 1 mo = 1 month after IVTA injection; 3 mo = 3 months after IVTA injection; VA = Visual acuity; mfERG-c = mfERG central; mfERG-p = mfERG peripheral.

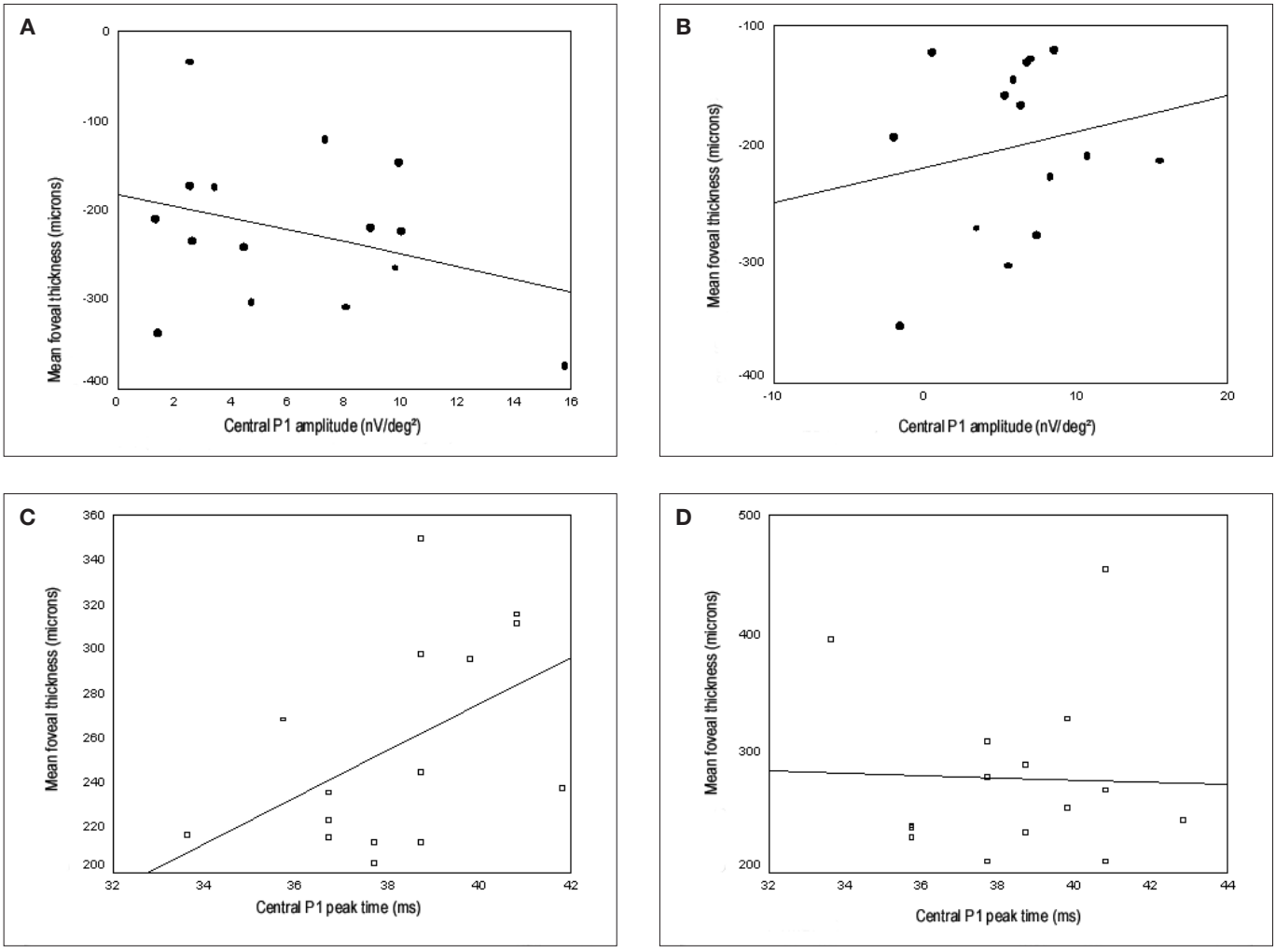

Fig. 1 - (A) *Differences from baseline in the mean foveal thickness (μm) in eyes with diabetic macular edema (DME) 1 month after intravitreal triamcinolone acetonide (IVTA) injection, plotted against the differences in multifocal electroretinography (mfERG)-c (central) P1 amplitudes, y=–181.34–6.87x (r^2=0.11, p=0.23).* **(B)** *Differences from baseline in the mean foveal thickness (μm) in eyes with DME 3 months after IVTA injection, plotted against the difference in mfERG-c (central) P1 amplitudes, y=–218.03+2.99x (r^2=0.03, p=0.50).* **(C)** *Differences from baseline in the mean foveal thickness (μm) in eyes with DME 1 month after IVTA injection, plotted against the difference in mfERG-c (central) P1 peak times, y=–211.54+10.45x (r^2=0.12, p>0.05).* **(D)** *Differences from baseline in the mean foveal thickness (μm) in eyes with DME 3 months after IVTA injection, plotted against the difference in mfERG-c (central) P1 peak times, y=–192.82–8.30x (r^2=0.13, p>0.05).*

luminance of the stimulus was 120 cd/m² for the bright flashes and 1 cd/m² for the dark flashes. The stimulus was displayed on a black-and-white monochrome cathode ray tube monitor.

Before mfERG recording, patients' pupils were fully dilated with eyedrops containing 0.5% tropicamide and 0.5% phenylephrine. All subjects were placed in ordinary room light for 15 minutes for light adaptation before testing. Gold foil scleral electrodes were used for mfERG recording. Room lights were maintained throughout the recordings. The mfERG recordings were divided into eight segments, and any segments with blinking, large eye movements, or losses of fixation were discarded and recorded again. Retinal signals were filtered with low-frequency and high-frequency cutoffs of 10 Hz and 300 Hz, respectively, and amplified with a gain of 100,000.

The first-order kernel mfERG responses were analyzed. Individual mfERG responses for the hexagons were grouped into the two concentric areas centered on the fovea, with a central ring of 0 to 7 degrees (central group) and a peripher-

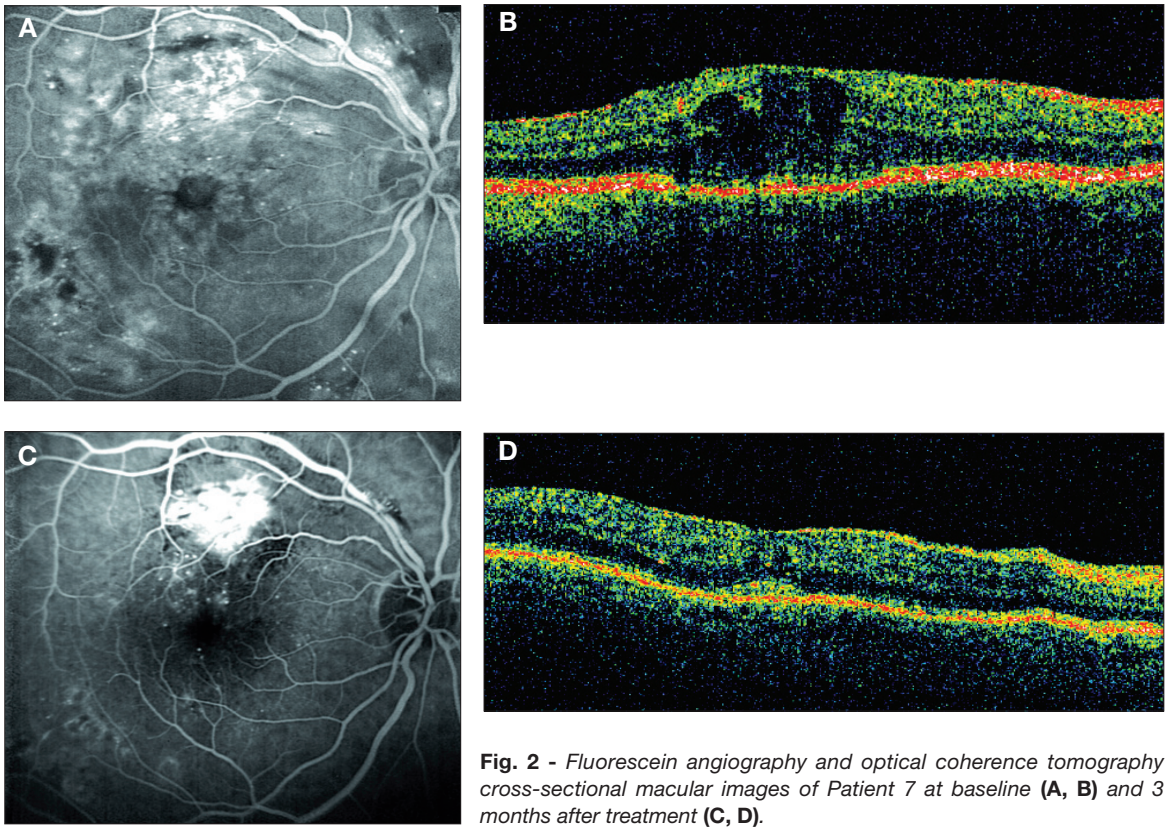

Fig. 2 - *Fluorescein angiography and optical coherence tomography cross-sectional macular images of Patient 7 at baseline* **(A, B)** *and 3 months after treatment* **(C, D)**.

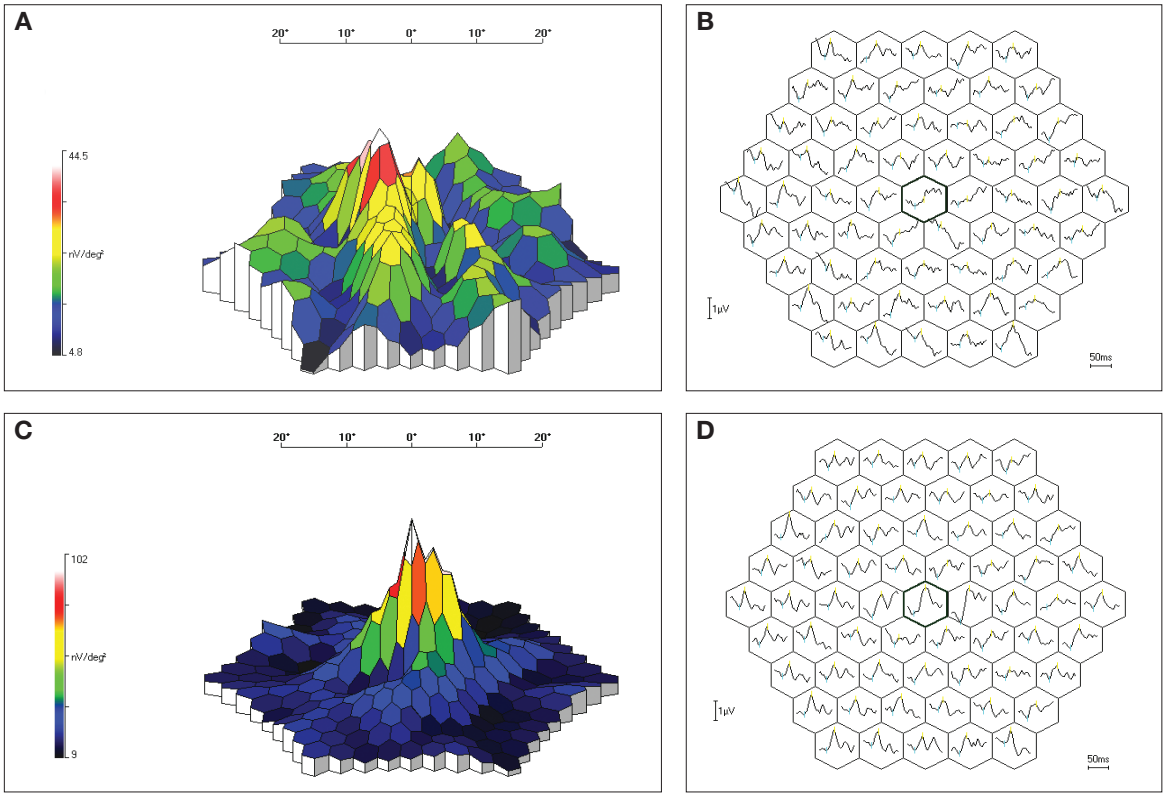

Fig. 3 - *Multifocal electroretinography of Patient 7 at baseline* **(A, B)** *and 3 months after treatment* **(C, D)**.

al ring 7 to 25 degrees (peripheral group). The first positive peak (P1) response amplitudes and P1 peak latencies for the central and peripheral groups were then measured.
Results from control eyes and eyes with DME at baseline were compared by Student *t* test. Changes in functional parameters (VAs and the P1 mfERG response amplitudes and peak latencies) and morphometric parameters (OCT foveal thickness) in eyes with DME 1 and 3 months after IVTA injection were compared with baseline (pretreatment) values by Student *t* test. The P1 mfERG response amplitudes and peak latencies in the central area and OCT foveal thickness were correlated with a linear correlation test.

RESULTS

Pretreatment and posttreatment clinical measurements are presented in Table I. After 3 months follow-up, VA had improved in all eyes, with a mean of 2.5 and 2 lines at 1 and 3 months after treatment, respectively. The mean baseline logMAR value for VAs of the patients before treatment was 0.49±0.26. After treatment it was significantly different from the pretreatment value (for each, $p<0.001$). The mean baseline foveal thickness was 480.33±82.42 μm. Thickness had decreased at 1 and 3 months after treatment (for each, $p<0.001$) (Tab. II).
There were statistically significant increases in the mean P1 response amplitude for both central and peripheral groups at all examinations compared with pretreatment (for each, $p<0.001$) (Tab. I). The mean P1 peak latencies were shortened but not significantly in both the central and peripheral groups at all examinations compared with pretreatment. During follow-up, no patient had recurrence of ME.
Scatter plots of the foveal thickness as a function of the P1 response amplitudes and peak latencies for central area are shown in Figure 1. The correlations between the foveal thickness and P1 response amplitudes and peak latencies for the central area were not significant. The OCT cross-sectional macular images, fluorescein angiography, and mfERGs of Patient 7 are shown in Figures 2 and 3.

DISCUSSION

DME is retinal thickening caused by accumulation of intraretinal fluid, primarily in the inner and outer plexiform layers, resulting from hyperpermeability of the retinal vasculature (1). ME affects approximately 29% of diabetic patients with a disease duration of 20 years or more and is responsible for a significant degree of visual loss in this population (1). Various studies have shown the benefit of IVTA injection in patients with DME (4-6). In these studies, VA and morphologic features before and after treatment were evaluated, whereas patients' subjective appraisal of visual function, which may differ, was not comprehensively discussed. It was acknowledged that DME 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, color vision, and reading ability. But 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 strongly dependent on the preservation of the macular function.
mfERG is a technique developed by Sutter and Tran (7) that allows mapping of retinal function in the posterior pole through simultaneous stimulation of different areas of the retina. In contrast to a conventional full-flash ERG, which uses a global flash stimulus to stimulate the entire retina, mfERG utilizes an array of alternating flickers of hexagonal stimuli to stimulate individual retinal areas, and mfERG responses are obtained using cross-correction between the raw recording and a pseudorandom m-sequence. The mfERG recording can provide an objective assessment of retinal function, and its sensitivity in detecting functional abnormalities has been demonstrated in various macular disorders, including age-related macular degeneration and central serous chorioretinopathy (8-10). It is also well known that mfERG can assess retinal function in patients with diabetic retinopathy (11-13). Yamamoto et al (14) showed that the mfERG from the macular area was a good objective indicator of macular function in patients with DME and was strongly correlated with morphologic changes in the macula. Using mfERG as an objective method of assessing retinal function may therefore be a useful tool in documenting the functional changes after treatment in patients with DME. It has been shown that in spite of unchanged values of retinal thickness and VA, panretinal photocoagulation seems to cause a functional impairment in the adjacent untreated macula, shown by reduced amplitudes measured by the mfERG (15). It has also been shown that both the implicit times and the amplitudes of the mfERGs are changed after grid laser photocoagulation for DME, although the results of psychophysical tests suggested little or no change in visual function (16). It was thought that damage to the outer retina caused by photocoagulation could account for the in-

creased delay in implicit times and reduction of amplitudes. On the other hand, although the improvement of the mfERG was limited to the implicit times, no electrophysiologic deterioration was observed after pars plana vitrectomy in patients with DME (17).

The results of the present study have shown that besides the reduction in ME and improvement in VA, IVTA injection improves macular function assessed by mfERG in diabetic patients. After IVTA injection there were statistically significant increases in the mean P1 response amplitude for both central and peripheral groups at all examinations compared with pretreatment. Although mean P1 peak latencies for both the central and peripheral groups were shortened they did not reach significant values and a significant negative correlation was not observed between the foveal thickness and P1 response amplitudes and peak latencies for the central area. This result may show that not only the reduction of foveal thickness but also other factors such as structural changes in the retina may play a role in the improvement of macular function after IVTA injection.

It is clear that the improvement of mfERG parameters that are closely related to macular function positively affect the patient's daily activities. It is well known that important daily tasks such as recognition of faces and symbols, orientation, and reading are strongly dependent on the preservation of macular function (18, 19). 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 from the point of view of improvement of macular function after IVTA injection in eyes with DME. Because of the limitations of our pilot study - short follow-up and a small study sample - it was not possible to assess the changes in macular function in the long term, especially after recurrences of ME and after retreatments. Besides showing short-term improvement in macular function after IVTA injection in eyes with DME, our study also shows that further study with longer follow-up and a large series is needed.

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