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Functional improvements of diabetic macular edema after treatment with Ranibizumab

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Abstract

Background
Diabetic retinopathy and clinically significant macular edema are largely responsible for the irreversible, debilitating visual impairment. There is evidence suggesting that some of the diabetes-related visual abnormalities are due to neurodegeneration. Use of objective tests for early detection of retinal dysfunction of sight-threatening diabetic retinopathy would be of great value.

Aim
The aim was to study the functional improvements of macular functions after treatments with intravitreal injection of ranibizumab as detected with central visual field and multifocal electroretinogram (mfERG).

Settings and design
A prospective cohort interventional study that included 30 eyes of 30 patients.

Materials and methods
Prospective cohort interventional study including 30 eyes of 30 patients with nonproliferative diabetic retinopathy with diabetic macular edema who were treated with three doses of intravitreal injection of ranibizumab and then performed optical coherence tomography, Central visual field, and mfERG, to assess macular function as detected with visual acuity measuring by LogMAR acuity testing, central visual field and mfERG.

Statistical analysis
Parametric data were analyzed with analysis of variance and whenever appropriate with Student's *t*-test. Nonparametric data were analyzed with χ^2 and/or Mann–Whitney tests. Statistical significance was considered at 95% confidence interval. All *P* values less than 0.05 was considered statistically significant.

Results
After treatment, visual acuity (VA) of 25 eyes improved, whereas five eyes showed stabilization of VA with the same central foveal thickness (CFT). All measurements of the CFT were decreased. The authors could find significant decreases in the average CFT from baseline (376.16 ± 66.23 months) to 261.58 ± 37.55 months at 3 months.

Conclusion
VA correlates closely with CFT and P1 amplitude in the central ring of the mf-ERG, where P1 amplitude shows higher sensitivity than with CFT based on optical coherence tomography.

Keywords: diabetic macular edema, diabetic retinopathy, functional improvements of macular functions, intravitreal injection of ranibizumab, multifocal electroretinogram

Introduction

Diabetic retinopathy is the most common cause of loss of vision in people of working age (20–70 years). In developed countries, diabetic retinopathy and clinically significant

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macular edema are largely responsible for the irreversible, debilitating visual impairment [1,2].

In addition to microvascular pathology, there is evidence suggesting that some of the diabetes-related visual abnormalities are due to neurodegeneration [2].

Functional abnormalities of the retina and vision can occur before clinical signs of retinopathy appear in diabetes. Utilizing the objective tests for early detection of retinal dysfunction of sight-threatening diabetic retinopathy would be of great value [1,2].

The multifocal electroretinogram (mfERG) is an objective and noninvasive method to measure retinal responses to visual stimulation from small, essentially discrete patches of the human retina [3]. It is expected that the functional changes produced by diabetes will be nonuniform across the retina suggesting that the underlying neuroretinal abnormalities may be difficult to detect by full-field ERG [4].

Aim

The aim was to study the functional improvements in macular functions after treatments with intravitreal injection of Ranibizumab as detected with central visual field and mfERG.

Materials and methods

This is a prospective cohort interventional study aiming to study the functional improvements in macular functions after treatments with intravitreal injection of Ranibizumab as detected with visual acuity measured by LogMAR acuity testing, central visual field and mfERG. Retinal imaging using fundus fluorescein angiography (FFA) and spectral domain-optical coherence tomography (SD-OCT) was done to all patients to confirm the diagnosis and exclude ischemic maculopathy.

The study includes 30 eyes of 30 patients with nonproliferative diabetic retinopathy with diabetic macular edema (DME) of more than 300 μm by SD-OCT.

The grading of DME according to the early treatment diabetic retinopathy study group is shown in Table 1.

In this study, we excluded patients with media opacity such as corneal opacity, cataract or vitreous hemorrhage, ischemic maculopathy, patients with any vitreomacular traction, glaucoma patients, and patients with a history of previous treatment of DME with laser or intravitreal injections.

Table 1: Diabetic macular edema definition in the early treatment diabetic retinopathy study

Disease severity level	Finding observable upon dilated ophthalmoscopy
Diabetic macular edema apparently absent	No apparent retinal thickening or hard exudates in posterior pole
Diabetic macular edema apparently present	Thickening of the retina with hard exudates of one disk diameter of the center of the macula
Clinically significant macular edema	Retinal thickening at or within 500 μm of the center of the macula and/or hard exudates at/or within 500 μm of the center of the macula, if associated with thickening of the adjacent retina on the disk area in size at least part of which within one disk diameter of the center of the macula

Methodology in detail

Preoperative history taking

(1) Onset of diabetes.
(2) Prior ocular surgeries, laser treatment, or ocular surgery.
(3) Other eye diseases or medications.

Preoperative examinations

(1) Best corrected visual acuity (BCVA).
(2) Slit lamp biomicroscopy.
(3) Preoperative OCT using Topcon 3D OCT- 2000 FA Plus (Topcon. Medical Systems, Tokyo, Japan) Zeiss Humphrey Field Analyzer 3 (Carl Zeiss Meditec, Inc., Dublin, CA, USA).
(4) mfERG will be performed using the RETI scan system (Roland Consult, Brandenburg Berlin, Germany).
(5) Central visual field (central 10°) using the Zeiss Humphrey Field Analyzer 3 (Germany).

Treatment

Treatment is with 3-onthly doses of intravitreal Ranibizumab 0.5 mg (0.05 ml of 10 mg/ml solution).

Technique of injection

(1) After complete sterilization of the lid and conjunctiva in the operating theater under topical anesthesia (benoxinate eye drops), intravitreal injection of 0.5 mg (0.05 ml of 10 mg/ml solution) of Ranibizumab is given using a 29 G needle 4 mm behind the limbus.
(2) Then an antibiotic eye ointment and a sterile patch is applied to the eye.
(3) This procedure may have possible risks such as elevation of intraocular pressure and injury of the ocular structure which may induce cataract or vitreous hemorrhage or intraocular infection (endophthalmitis).
(4) Postoperative medications: topical antibiotic eye drops (Gatifloxacin 0.5%) for 1 week.
(5) Follow-up: at 1 day, 1 week, and 1 month postoperatively.

Outcomes of treatment

(1) Assessment of improvements of BCVA (logMAR).
(2) Assessment of improvements of macular thickness using OCT.
(3) Assessment of the role of mfERG in the evaluation of macular function in patients with DME by comparing amplitude and implicit time of P1 in the central two rings from the ring analysis before and after treatment with Ranibizumab.
(4) Assessment of central visual field (10-2) regarding the MD, pattern SD, and descriptive analysis for the visual field before and after treatment with Ranibizumab.
(5) Correlation between changes in mfERG and changes in central macular thickness by OCT.

(6) Correlation between changes in mfERG and changes in BCVA after injection.

Sample size

Thirty eyes of 30 patients.

The study followed the ethical values in collecting data, data analysis, and in keeping honesty. Informed consent will be taken. All identifiable information about patients' health status, medical condition, diagnosis, prognosis, treatment, and all other information of a personal kind will be kept confidential.

Results

The duration of diabetes mellitus ranged from 6 to 15 years (average 9.2 years). At baseline, the mean HbA1c ± SD was 8.25%±1.41. The systolic blood pressure and diastolic blood pressure were 133.5 ± 10.5 and 85.3 ± 9.8 mmHg, respectively. There was no significant change in fasting blood glucose in all examinations.

All patients underwent 10-2 perimetry well according to the reliability indices false-positive and false-negative responses. We have found that the frequency of false-positive answers ranged from 0 to 28%, the median was 7%, and the mode value was 0%. Only two subjects had frequencies of false-positive answers larger than 15%. Frequencies of false-negative response ranged from 0 to 16%, with a median and mode value of 0%.

White-on-white perimetry (WWP) correlated significantly to the level of diabetic retinopathy when considering total loss as expressed by MD values (P = 0.0001) (Figs. 1–3). The regression model fit was good for WWP (r_2 = 0.23). As expected, MD values were worse (more negative) in eyes with more advanced retinopathy.

Localized visual field loss, as measured by the number of significantly depressed points at the P less than 0.01 level in pattern deviation maps, increased by 0.67 points per early treatment diabetic retinopathy study step (P = 0.002) with WWP.

The number of injections was three. No serious ocular adverse effects or complications were seen in any of the eyes. All intraocular pressures were in the normal range. All data for BCVA, central foveal thickness (CFT), Visual Field (VF), and mf-ERG of test groups are summarized in Table 2.

The mean BCVA at baseline was 0.14 ± 0.27 (decimal), which improved to 0.34 ± 0.13 at 3 months.

After three ranibizumab injections, all measurements of the CFT were decreased. We could find significant decreases in the average CFT from baseline (376.16 ± 66.23 months) to 261.58 ± 37.55 months at 3 months. However, no significant differences were found among the postoperative records (P = 0.609, respectively; Fig. 4).

In mfERG, the amplitude of P1 at baseline was 20.41 ± 3.42 nV/deg^2 in the central ring. After 3 months of follow-up, the increases in the average P1 amplitude of the central ring at all examinations when compared with baseline were significant.

Compared with the baseline (11.38 ± 2.98), the difference was significant (for each, P = 0.000; Fig. 4).

Table 2: Preinjection and postinjection changes in best corrected visual acuity, optical coherence tomography, multifocal electroretinogram, and VF

	Baseline	After 4 months
Best corrected visual acuity (logMAR)	0.80±0.27	0.31±0.13
Central foveal thickness (μ)	362.25±56.39	266.89±27.77
P1 amplitude (nv/deg^2)	20.39±3.96	23.98±3.87
P1 implicit time (ms)	41.60±3.84	40.41±3.82
MD in 10-2 perimetry (dB)	−5.03±0.65	−3.27±0.62
Pattern SD (PSD) in 10-2 perimetry (dB)	3.68±0.46	2.02±0.43

After treatment, the visual acuity of 25 eyes showed improvement; whereas five eyes showed stabilization of visual acuity with the same central foveal thickness on optical coherence tomography.

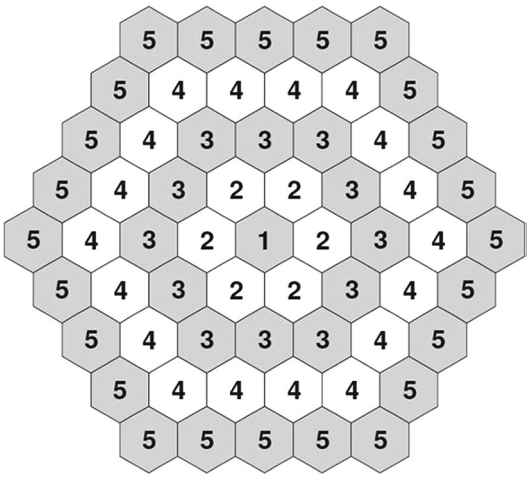

Figure 1: Multifocal electroretinogram ring topography showing the five concentric rings consisting of 61 hexagonal patterns used in the analyses.

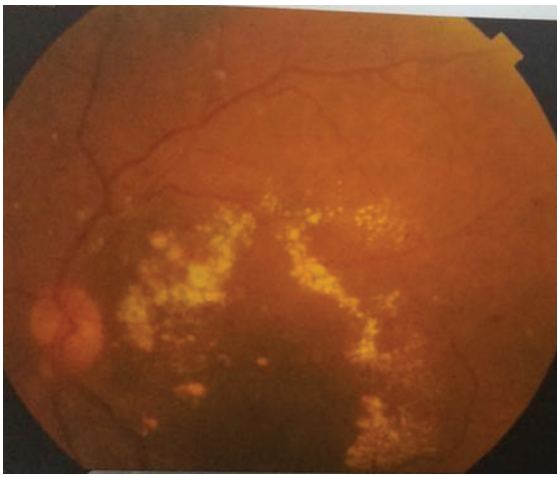

Figure 2: Fundus photograph of the left eye showing clinically significant macular edema.

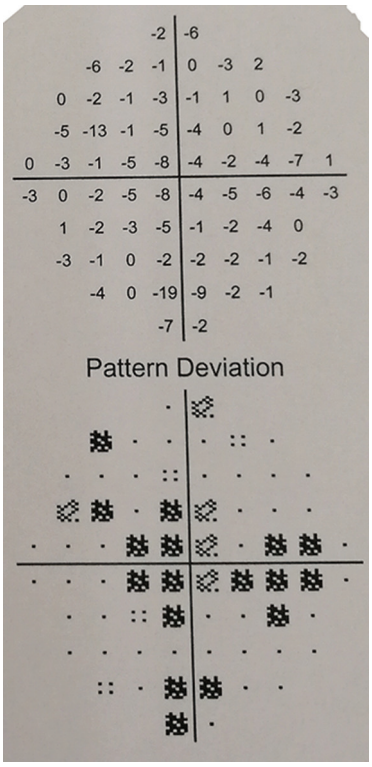

Figure 3: A 45-year-old patient with type 1 diabetes: visual field defects in white-on-white perimetry (b), gray-scale representations are based on differential light sensitivity values expressed in dB.

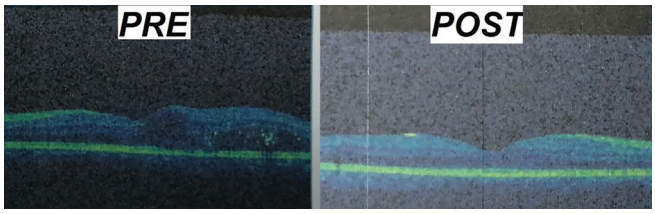

Figure 4: Images obtained from optical coherence tomography of a 52-years-old patient before (up) and after (down) IVI of Ranibizumab.

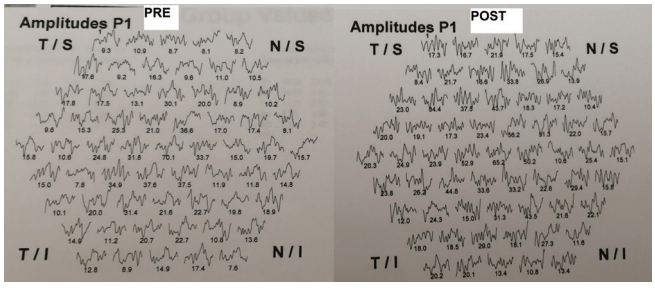

Figure 5: A 60-year-old patient with long-standing type II diabetes mellitus, treated with IVI of Ranibizumab.

All changes in the mean BCVA, CFT, P1 amplitude, and implicit time are shown in relation to the time after IVR in Fig. 5.

At baseline, the association between BCVA as a dependent variable and the P1 amplitude of the central ring was significant ($P = 0.008$). The association between BCVA and P1 implicit time in the central retina was not significant ($P = 0.766$, 0.512, respectively), but the association between BCVA and CFT was significant ($P = 0.041$) at baseline.

Discussion

DME is a complicated process associated with some factors; the pathogenesis is thought to be due to altered permeability of the blood–retinal barrier, resulting in fluid accumulation at the macula [2]. The previous treatment standard of DME was laser photocoagulation, but there are different degrees of complication, including lack of an obvious increase in visual acuity (VA) and intraocular pressure rise. A quantity of randomized multicenter studies have proven that repeated IVR have superior outcomes on patients with DME when compared with laser treatment alone [3].

Intravitreal ranibizumab, a monoclonal antibody fragment targeted against Vascular Endothelial Growth Factor (VEGF-A), has been shown to decrease macular edema and improve vision in patients with DME and is approved for this indication in several regions, including Europe [5] and the USA [6].

In comparison with laser photocoagulation, anti-VEGF therapy can achieve better corrected VA and less visual field defect in addition to lower incidence of center-involved macular edema and vitreous hemorrhage reported in the anti-VEGF group than in the laser photocoagulation group [7]. Nguyen *et al.* [4] assumed that anti-VEGF treatment by IVR should be the first-line treatment for DME.

In this study, we observed that IVR significantly improved BCVA from baseline, which was due to the reduction in CFT. Our findings correlate with previous study results concerning the relationship between central retina thickness and VA after IVR [4]. At the same time, we also found that, in five eyes, macular thickness decreased significantly as observed by OCT but the VA did not significantly improve; a decrease in macular thickness without any improvement in vision shows a discrepancy between OCT findings and visual function [8]. Browning *et al.* [9] mentioned that although there was correlation between BCVA and CFT, there was a great change in VA at any given retinal thickness, and OCT measurement solely would not be a nice replacement for VA as a main result in researches on DME. OCT can only record the degree of edema; the duration of edema, and the damage to cells cannot be evaluated.

In contrast, mf-ERG is a technique that through simultaneous stimulation of different regions of the retina [10], retinal function now can be mapped in the posterior pole. It has been used for recording local electrophysiological responses of different retinal parts. Yamamoto *et al.* [11] showed that mf-ERG readings from the macular area were a good objective indicator of macular function in patients with DME and were strongly correlated with morphologic changes in the macula.

Our study focused on P1 of the central ring, including amplitude and implicit times. The results have shown that, in addition to improvement in BCVA and reduction in CFT, intravitreal injections of ranibizumab improved macular function as assessed by mf-ERG in diabetic patients. The increases were significant in the average central ring response of P1 at all examinations, compared with baseline, after IVI.

Hood *et al.* [12] reported that P1 was generated by Muller and bipolar cells, and N1 was generated by photoreceptors, so a decrease in P1 amplitude mainly reflects functional damage to the inner retina, and a decrease in N1 amplitude shows that the function of the outer retina is compromised.

The results showed that DME causes damage to the inner and outer layers of the macular retina, but the inner damage was more than that to the outer layer.

This showed that IVR is not only able to reduce macular edema, but also can aid in the recovery of inner retina cell function.

Significant correlations between BCVA and mf-ERG amplitude have been reported in previous studies of maculopathies [13]. We also found a significant correlation of BCVA, as a dependent variable, with P1 and N1 amplitudes in the central ring at baseline and after 3 months of treatment.

Previous studies have reported [14] that implicit times were just increased reasonably or still within normal ranges, in spite of amplitudes diminished and severe vision loss, implying that the decrease in VA is not necessarily related to the change in implicit time.

Holm *et al.* [14] found that BCVA and CFT were improved after IVR treatment, but there was no difference in mf-ERG results when compared with baseline.

Most researchers believe that the regimen of 3 consecutive Injections followed by PRN (pro re nata) is the best scheme for IVR (intravitreal ranibizumab)[13].

DME can be divided into three types on the basis of results of OCT [15]: diffuse retinal thickening, cystoid macular edema, and serous retinal detachment. After patients with the three different OCT types of DME had received IVR, differences in macular edema and VA were obvious, and the effect on diffuse retinal thickening was the best [16].

All patients had no complications during the follow-up period, and their fasting blood glucose levels were stable. Although it is reported that fasting blood glucose levels may affect mf-ERG outcomes [17], no differences in fasting blood glucose were found between the examinations in our study.

In summary, improvements in VA and mf-ERG parameters, and decreases in CFT were all maintained for 4 months of follow-up in our patients with DME.

Eyes with DME have significantly abnormal mf-ERG responses. VA was closely correlated with P1 amplitude in the central ring, based on mf-ERG, showing a greater correlation than with CFT based on OCT. It is important to improve our understanding of DME in order to produce more elaborate suggestions regarding when to begin therapy and when not. This indicates that the functional changes in the retina of patients with diabetes mellitus assessed by mf-ERGcan complement OCT findings. Long-term researches and bigger sample sizes are required for better documentation.

Conclusion

VA correlates closely with CFT and P1 amplitude in the central ring of the mf-ERG, where P1 amplitude shows higher sensitivity than with CFT based on OCT.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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