Photoreceptor integrity following treatment of diabetic macular edema: a prospective OCT study

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Abstract

PURPOSE: To describe changes of the foveal photoreceptor layer using optical coherence tomography (OCT) in diabetic macular edema (DME) treated with argon laser photocoagulation (ALP) or intravitreal triamcinolone (IVTA) and correlate these changes with visual outcome.

DESIGN: Analysis of OCT images from a prospective randomised controlled trial of ALP versus IVTA for DME.

METHODS: We studied the final OCT images of 71 eyes with diabetic macular edema. The tomographic finding of the foveal third hyper-reflective band (HRB) was classified into 2 groups: intact HRB and disrupted or absent HRB. The final visual outcome in these groups were compared in both the laser group and the IVTA group.

RESULTS: The presence of the third HRB at the fovea was associated with better visual outcome in both treatment groups with the laser group showing statistically significant correlation.

CONCLUSION: Intact foveal third HRB is a reliable indicator of favourable final visual outcome following treatment of DME.

Introduction

Macular edema is the main cause of visual impairment in diabetic patients 1. Timely macular (focal or grid) laser photocoagulation remains the principal therapy for sight-threatening diabetic macular edema (DME) and it reduces the risk of moderate visual loss by 50 % 2. Due to the limitations of current treatment for DME, new pharmacological therapies such as intravitreal triamcinolone (IVTA) have been tried 3-6.

The long-term effects of IVTA can be unpredictable mainly due to the limited half-life of the drug and photoreceptor atrophy associated with advanced disease. Optical coherence tomography (OCT) allows objective, quantifiable, and reproducible measurements of the retinal layers. Evaluation of the reflectance of the posterior retinal structures have demonstrated two well-defined, linear hyper-reflective bands (HRBs) at the level of the outer retina in the macular region of healthy subjects 7. The inner HRB (third HRB) is thinner and is believed to correspond to the junction between the inner and outer photoreceptor segments while the outer HRB corresponds to the retinal pigment epithelium-choriocapillaris commonly visualised in the first generations of OCT. The presence or absence...
of the 3rd HRB is thought to correlate with visual function.

In this study, we carried out an analysis of the OCT images obtained during a recently completed prospective RCT comparing macular laser with IVTA in the treatment of DME. The aim was to assess the influence of third HRB on the final visual outcome in patients with DME and compare those who were treated with macular laser or IVTA.

Methods

The study protocol adhered to the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board of Moorfields Eye Hospital. Patients were recruited from the Medical Retina clinics in the Hospital. Each eligible patient gave written, informed consent before entering in the study.

Patient Eligibility and Evaluation

Patients were included if they had refractory diffuse DME (defined as biomicroscopic and fluorescein angiographic evidence of clinically significant DME that is unresponsive to focal laser photocoagulation performed at least 3 months before evaluation). Each patient received a detailed ophthalmologic examination, including measurement of best corrected visual acuity (BCVA) according to a standardised refraction protocol using modified ETDRS charts 1, 2, and R, applanation tonometry, and slit lamp biomicroscopic examination every 4 months for 12 months. Investigations including digital colour fundus photography, fluorescein angiography and OCT were also performed at baseline, 4, 8 and 12 months.

Triamcinolone acetonide injection

Four milligrams (total volume, 0.1ml) of IVTA (Kenacort, Bristol-Myers Squibb, Paris, France) was injected into the vitreous under sterile conditions. The injection was performed under subconjunctival anesthesia with a 30-gauge needle. Repeat IVTA was performed at 4 monthly intervals if there was angiographic and OCT evidence of persistent DME.

Grid laser photocoagulation

Patients randomized to the laser arm underwent further macular grid photocoagulation according to the ETDRS guidelines. Treatment was repeated at 4 monthly intervals if there was angiographic and tomographic evidence of persistent DME.

Optical coherent tomography

We used high-resolution optical coherence tomography (Stratus model 3000; Carl Zeiss Meditec, Dublin, CA) with software version 3.0 to measure retinal thickness and assess retinal structure. With this third-generation instrument (OCT3) we recorded from each eye six 6-mm (~20°) line scans in a radial spoke pattern intersecting at fixation. Each tomogram consisted of 512 A-scans, each A-scan comprising 1024 data points spanning a 2-mm depth. The examiner (FI) asked each study participant to look at the internal fixation spot, which was kept in its central location, and confirmed that the image of the macula appeared to be approximately centred with respect to the spot’s image on the fundus monitor. The OCT software was used to position on the screen a vertical line that designated the centre of the scan image. During each scan, the examiner checked whether the fovea in the scan image was centred with respect to the vertical line.

The vertical retinal sections of the OCT images at the final follow-up were converted into greyscale raw images. These images were graded for third HRB by two graders (SS and PP) masked to the treatment assignment. The foveal third HRB was classified into two groups: (i) intact or (ii) disrupted or absent so as to be able to assess whether visual acuity varied with the configuration of the third HRB. Patients with absent 3rd HRB band in the non-foveal area were excluded to avoid methodological artefact.

Statistical Analyses

The visual outcome was determined by the change in the number of ETDRS letters read at the final visit compared to baseline. The visual outcome was determined in three categories: all patients irrespective of treatment, post laser group and post IVTA group. The patients were classified into two groups. Group 1 were patients with intact third HRB. Group 2 consisted of patients with absent or disrupted third HRB at the fovea. The data were processed on computer (SPSS version 11.5; SPSS Sciences, Chicago, IL). Paired t-test was used to compare the visual outcome in patients in...
group 1 and 2. P<0.05 was considered statistically significant. The inter-grader and intra-grader reliability were calculated using the kappa statistics.

**Results**

There were 45 patients in the IVTA arm and 43 patients in the laser arm of the study. Nine patients in the IVTA group and eight patients in the laser group were excluded from analysis because they were either lost to follow-up or the third HRB was not gradeable. Therefore, 36 patients in the IVTA group and 35 patients from the laser group were included in the analysis. There were no significant differences in baseline clinical characteristics of the patients studied (Table 1). The mean number of IVTA injections was 1.8 (range 1 to 3) while the mean number of further grid laser sessions was 2.1 (range 1 to 3) in this group of patients.

**Table 1: Baseline characteristics of patients randomized to the two treatment groups**

<table>
<thead>
<tr>
<th></th>
<th>IVTA group</th>
<th>Grid laser group</th>
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</thead>
<tbody>
<tr>
<td>No. of eyes</td>
<td>36</td>
<td>35</td>
</tr>
<tr>
<td>Mean age in years</td>
<td>60.82</td>
<td>62.43</td>
</tr>
<tr>
<td>Duration of diabetes in years</td>
<td>15.15 years</td>
<td>14.96 years</td>
</tr>
<tr>
<td>Mean previous laser</td>
<td>3.2</td>
<td>3.1</td>
</tr>
<tr>
<td>Proliferative diabetic retinopathy</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Mean HbA1C</td>
<td>7.31</td>
<td>7.58</td>
</tr>
<tr>
<td>Baseline visual acuity (ETDRS letters) mean ± SD</td>
<td>51.60 ± 11.31</td>
<td>53.12 ± 10.84</td>
</tr>
<tr>
<td>Baseline CMT mean ± SD (μm)</td>
<td>438 ± 105</td>
<td>441 ± 98</td>
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There were also no significant differences in baseline clinical characteristics of the patients categorised depending on the presence of the foveal third HRB (Table 2).

**Table 2: Baseline characteristics dependent on the presence of third HRB**

<table>
<thead>
<tr>
<th></th>
<th>Third HRB intact</th>
<th>Third HRB not intact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean ± SD) ETDRS letters at baseline (mean ± SD)</td>
<td>61.29 ± 3.2</td>
<td>60.92 ± 2.7</td>
</tr>
<tr>
<td>Mean foveal thickness (μm) at baseline</td>
<td>52.31 ± 14.28</td>
<td>53.12 ± 15.32</td>
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Intact 3rd HRB was associated with better final visual outcome (Table 3). This was statistically significant in the laser group although the IVTA group also suggested a similar trend.

**Table 3: Mean change in visual acuity at 12 months follow-up**

<table>
<thead>
<tr>
<th></th>
<th>Third HRB intact</th>
<th>Third HRB not intact</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>+4.2 (n=36)</td>
<td>-2.68 (n=35)</td>
<td>0.007</td>
</tr>
<tr>
<td>Patients in the laser group</td>
<td>+6.16 (n=18)</td>
<td>-1.05 (n=18)</td>
<td>0.04</td>
</tr>
<tr>
<td>Patients in the IVTA group</td>
<td>+2.27 (n=18)</td>
<td>-4.14 (n=17)</td>
<td>0.08</td>
</tr>
</tbody>
</table>

+ indicates gain in ETDRS letters; - indicates loss in ETDRS letters

The mean change in central macular thickness in the two treatment groups at 12 months follow-up were not statistically different (p=0.2). Change in central macular thickness were also not significantly different in the two third HRB groups (p=0.09).

**Discussion**

This study shows that the presence of an intact third HRB is an important determinant of final visual prognosis following treatment of diabetic macular edema. Macular edema can affect all layers of the retina and may even cause a serous macular detachment. However, good visual recovery is independent of the location of the macular edema or the central macular thickness.

The 3rd HRB has been evaluated in many conditions such as retinitis pigmentosa, resolved central serous retinopathy and following the management of macular edema secondary to branch retinal vein occlusion with intravitreal tissue plasminogen activator. In all these conditions, the presence of intact third HRB was associated with better visual prognosis. Our study complements these studies and indicates that an intact 3rd HRB may be a better surrogate marker of visual acuity than the reduction in central macular thickness following treatment for DME.

The higher resolution of the new ultrahigh-resolution OCT (UHR OCT) system confirmed that the third HRB detected by Stratus OCT3 represents the junction between the inner and outer segments of the photoreceptors. Damage of photoreceptors may occur...
as a consequence of the macular edema and the treatment and may be responsible for the reduced visual acuity seen in patients despite return to normal macular thickness.

Macular edema, especially long-standing cases and those associated with ischaemia may be more prone to photoreceptor dysfunction and atrophy. The exact mechanisms underlying the beneficial effects of laser photocoagulation are poorly understood but it is thought that laser causes loss of photoreceptors thereby decreasing the oxygen consumption of the outer retina and reducing production and release of angiogenic stimuli. Similarly, animal studies have shown that IVTA produces dose-dependent toxic effects on the retinal photoreceptors and pigment epithelium. Although the edema and the treatments may cause photoreceptor atrophy, it is unclear why the loss of the third HRB is noted in some and not in others.

Further studies are required to determine the factors that cause the loss or disruption of the 3rd HRB.

References