CLINICAL STUDY

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Received: 4 November 2007

Accepted in revised form:

Published online: 6 June

707129 3730.

15 April 2008

2008

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Can the risk of retinal pigment epithelium tears after bevacizumab treatment be predicted? An optical coherence tomography study

Abstract

Background Retinal pigment epithelium (RPE) tears after bevacizumab treatment for neovascular age-related macular degeneration accompanied by a pigment epithelial detachment (PED) might be caused by stretching forces on the already weakened RPE. The purpose of this study was to evaluate whether simple measurements of optical coherence tomography (OCT) can predict the individual risk of an RPE tear in preoperative candidates. Methods A retrospective chart review study of 393 consecutive patients with neovascular agerelated macular degeneration evaluated OCT images (Stratus-OCT Zeiss, Jena, Germany). The height of the PED, the central retinal thickness, and the maximum retinal thickness were determined by two independent observers and retrospectively analysed.

Results Fifteen patients with an RPE tear had a significant higher PED than the remaining study population. In contrast, no correlation was seen with the central retinal thickness. In a linear regression model, the probability of an RPE tear exponentially increased in dependence of the extent of PED. *Conclusion* The risk of an RPE tear can be estimated by simple measurement of the height of the PED on OCT. *Eye* (2008) **22**, 1504–1507; doi:10.1038/eye.2008.145; published online 6 June 2008

Keywords: Bevazicumab; anti-VEGF; pigment epithelial tear; age-related macular degeneration; pigment epithelium detachment; optical coherence tomography M Leitritz, F Gelisken, W Inhoffen, M Voelker and F Ziemssen

Introduction

Retinal pigment epithelium (RPE) tears have been reported following intravitreous bevacizumab (Avastin) administration for neovascular age-related macular degeneration (AMD).^{1–4} Although the visual prognosis might be different in cases with spontaneous tears, where the choroidal neovascular membrane shows no regression, the rupture and displacement of the RPE might be a serious complication with the risk of visual damage. As serous pigment epithelial detachments (PED) associated with choroidal neovascularization (CNV) are often seen before an RPE tear, stretching forces on the weakened RPE were considered to play a causative role.^{5,6} Therefore, we investigated whether optical coherence tomography (OCT) could provide an estimate of the risk.

Materials and methods

A total of 393 consecutive patients with neovascular AMD were routinely monitored by OCT imaging (Stratus-OCT Zeiss, Software 4.0, Jena, Germany) before receiving 1.25 mg of bevacizumab. After dilation of the pupils (1% tropicamide and 2.5% phenylephrine), each patient was instructed to fixate an internal (or an external) target light. The scans were centred in the fovea. The study was continued until images were obtained with signal strength of five or higher, because reliable and accurate delineation of the retinal boundaries is crucial in measuring retinal thickness. Clinical characteristics of this cohort of patients are



described in detail by a paper recently published.⁷ Four of the prospective 397 patients were excluded because of missing or insufficient OCT images.

In the built-in image analysis programme, the analysed images often do not reflect the true retinal morphologies.

Applying normalized, Gaussian smoothing, and median smoothing scan protocols, alignment process of the images is known to modify the boundaries, in particular that of the RPE signal. To avoid inaccuracies due to various types of image artefacts produced during



Figure 1 Incidence of RPE tears in dependence on the OCT results. The box plots are showing the height of PED, central retinal thickness, and maximal retinal thickness (black circles: no RPE tears, grey boxes: RPE tears, lines: group mean), while adjacent normal quantile plots delineate the different distribution in both groups.

scanning or analysing process, the original scanned images were used. In the fast-macular thickness (128 scan points)/regular macular thickness (512 scan points) scanning protocols, a manual calliper-assisted measurement of the centre-point retinal thickness was taken in line with the A-scan by two observers certified for work in pharmaceutical company-sponsored clinical trials, who were blinded to the clinical course. After showing high inter-observer concordance (Pearson coefficient: 0.96), the mean of both measurements was used for statistic evaluation.

Manually measured central retinal thickness was the distance between the anterior boundary of the retinal nerve fibre layer and the posterior boundary of the photoreceptor layer. To determine the maximum retinal thickness, the highest peak within the scans was chosen. In locations where the baseline level of the RPE was disrupted or elevated, the height of the PED was defined as the distance between the anterior boundary of the RPE and the baseline RPE level traced from the unaffected area adjacent to the lesion. The PED showed domeshaped elevations of the highly reflective external bands, which corresponds to RPE with low reflectivity underlying it.

Only those cases with evidence of CNV using fluorescein angiography were included. Angiographic subtype of CNV and lesion characteristics (CNV size, total lesion size measured in disc area; DA) based on the modified definition of Macular Photocoagulation Study Group were analysed. Linear regression modelling was performed to detect the univariate influence of PED on the event of RPE tear (JMP 5.0.1.2). Values of P < 0.001 were considered statistically significant.

Results

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A total of 189 of 393 eyes showed no PED when evaluated by OCT (Figure 1). However, every one of the 15 patients with a subsequent RPE tear had a PED before. In this group, the mean height of the PED (714 μ m) was significantly higher than in the remaining group (146 μ m, P < 0.001, Wilcoxon signed-rank test). In contrast, no correlation was seen with the concomitant retinal oedema, reflected in central retinal thickness (P = 0.776) or maximum retinal thickness (P = 0.354).

Strong concordance was found between the height of the PED and the total lesion size (mean: 4.8 ± 4.9 DA; P < 0.001) as well as the CNV size (mean: 3.5 ± 3.6 DA; P < 0.001). The mean PED showed only non-significant differences between different lesion types (minimally classic: $124 \,\mu$ m, predominant classic: $125 \,\mu$ m, occult: $189 \,\mu$ m, and predominant haemorrhagic: $235 \,\mu$ m; P = 0.009).

Following a linear regression model, the probability of the tear incidence could be calculated in dependence of PED (Figure 2). The risk of an RPE tear exponentially increased from 0.5% (100 μ m) to 14.8% (600 μ m) with rising detachment of the RPE. In the absence of any PED, the probability was below 0.3%.

Discussion

Previous surveys have shown a significant influence of the PED size on the incidence of RPE tears after bevacizumab therapy.⁸ Although it is sometimes difficult and complex to determine the exact horizontal extension of the PED in a reproducible and standardized way, the measurement of its height by OCT is a fast and easy procedure. As most PEDs are characterized by the domeshaped, convex configuration of the detachment, the strong correlation between lesion size and PED height,⁹ also found in this study, justifies the consideration of PED height as a powerful predictor.

A limitation of this study is that OCT scans are centred by fixation. Thus, the maximum height of the PED might not have been determined correctly, if its apex was outside the fovea. It should also be taken into account that sometimes the exact localization of the RPE signal is technically limited. This might hinder the reliable evaluation of the PED height. Nevertheless, the direct influence of the PED height on the incidence of RPE tears points out that a simple OCT measures can be used for the calculation of a risk profile. In comparison to the retinal thickness at the fovea or the maximal retinal thickness, the extent of PED seems to determine



Figure 2 Following the linear regression model, the risk of an RPE tear can be predicted according to the height of PED assessed by OCT measurement. The single points represent the specified probability calculated for the individual patients of this study.

accurately the amount of the mechanical load and thus the high-risk cases for developing tears.^{6,7,10} Although other factors (eg, CNV and lesion size) should also be considered as potentially contributing factors, the OCT measurement seems to predict the individual risk of patients with neovascular AMD for developing RPE tears. In the case of an increased risk, detailed advice has to be given to the patient and alternative approaches should also be mentioned.

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