·Clinical Research·

Predictors of visual outcome in eyes with choroidal neovascularization secondary to age related macular degeneration treated with intravitreal bevacizumab monotherapy

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Abstract

• AIM: To evaluate the predictors of visual improvement in eyes with naive choroidal neovascularization secondary to age-related macular degeneration (CNV-AMD) treated with intravitreal bevacizumab (IVB) monotherapy.

• METHODS: Fifty eyes with naive CNV-AMD with pretreatment best-corrected visual acuity (BCVA) better than 20/200 and treated with IVB monotherapy were evaluated. Several variables including age, sex, pre-treatment BCVA, CNV type and lesion size on fluorescein angiogram as well as SD-OCT parameters including pre-treatment central macular thickness (CMT), inner-segment/outer-segment (IS/OS) junction integrity, and external limiting membrane (ELM) integrity were analyzed to predict visual outcome.

• RESULTS: On univariate regression, pretreatment ELM damage was associated with less visual improvement after treatment (P=0.0145). However, ELM damage predicted only 10% of the visual outcome. On multivariate regression, pretreatment BCVA, IS/OS junction, and ELM integrity on SD-OCT were the significant predictors for the treatment effect and together predicted 37% of visual improvement.

• CONCLUSION: Pretreatment BCVA, ELM and IS/OS junction integrity on SD-OCT are of significant value in predicting the visual improvement in naive wet AMD patients treated with IVB monotherapy.

• **KEYWORDS:** external limiting membrane; age-related macular degeneration; choroidal neovascularization; avastin

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INTRODUCTION

Age-related macular degeneration (AMD) is the leading cause of vision loss in the developed world [1,2]. Recent developments in treatment modalities for wet AMD have changed the visual outcome significantly. Treatment options include photodynamic therapy (PDT) [3] and anti-vascular endothelial growth factor (VEGF) drugs [4] alone or in combination [5].

Current therapies for wet AMD typically result in an incomplete visual recovery. It remains difficult to predict which patients will have a vision improvement after treatment. Before the widespread use of ocular coherence tomography (OCT), lesion size and location of the choroidal neovascularization (CNV) were considered to be the best predictive factors for visual improvement in eyes with CNV in AMD [6]. With the development of time-domain OCT, understanding of the disease has improved. Even so, time-domain OCT parameters do not correlate with the visual function and are not predictors for visual outcome [7-9].

With improved resolution of spectral domain optical coherence tomography (SD-OCT), visibility and interpretation of outer retinal structures such as the inner segment/outer segment (IS/OS) junction and external limiting membrane (ELM) have been facilitated. The association of these markers of photoreceptor layer integrity with vision has been reported in various retinal diseases [10-14]. Studies have shown a correlation of ELM with the final visual acuity in eyes with CNV secondary to AMD [15,16], but there are no studies evaluating the predictive ability of the integrity of these structures on visual outcome.

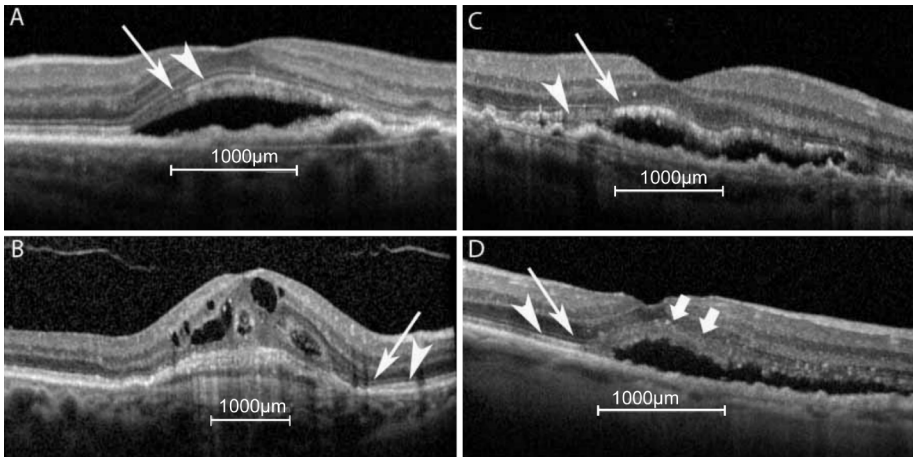

Figure 1 Assessment of external limiting membrane (ELM) (arrow) and inner segment / outer segment (IS/OS) junction integrity in eyes with choroidal neovascularization prior to treatment using spectral-domain optical coherence tomography (SD-OCT) A: ELM (arrow) and IS/OS (arrow-head) are preserved in the central 1 000 microns over a fibrovascular pigment epithelium detachment (PED) with subretinal fluid (SRF); B: Preserved ELM (arrow) but completely disrupted IS/OS (arrow-head) in the central 1 000 microns with small PED and thickened retinal pigment epithelium (RPE) complex; C: Disruption of both ELM (arrow) and IS/OS junction (arrow-head) in the central 1 000 microns with thickened retina and intraretinal fluid with fibrovascular PED; D: Minimal disruption (10%) (Thick arrows) of ELM (arrow) with complete disruption of IS/OS junction (arrow-head) in the central 1 000 microns with subretinal fluid and bumpy retinal pigment epithelium.

Knowledge of predictors for visual outcome would be of value for patient management and for designing clinical trials. For these reasons, we were interested in determining the predictors of vision improvement in eyes with choroidal neovascularization secondary to AMD. We studied the ability of various factors including age, sex, pre-treatment best corrected visual acuity (BCVA), CNV type and lesion size on fluorescein angiogram (FA) as well as SD-OCT parameters including pre-treatment central macular thickness (CMT), IS/OS junction integrity, and ELM integrity to predict visual outcome in eyes with CNV secondary to wet AMD treated with intravitreal bevacizumab monotherapy.

SUBJECTS AND METHODS

Subjects We evaluated the integrity of IS/OS, ELM, and CMT as predictors for visual outcome in a retrospective study between April 2008 through December 2009 in patients with CNV secondary to AMD (number of eyes=50, patients=47) by using SD-OCT and fluorescein angiography. Informed consent was obtained from all participants. All procedures conformed to the Declaration of Helsinki for research involving human subjects and the study was approved by the Institutional Review Board of the University of California, San Diego, USA. All patients underwent a complete baseline ophthalmologic examination including FA and SD-OCT that was repeated every two months through the last follow-up. BCVA was recorded using Early Treatment Diabetic Retinopathy Study (ETDRS) charts at four meters under the standard protocol. Inclusion criteria included new onset (2-3 months) subfoveal CNV secondary to AMD, no prior treatment for exudative AMD in the study eye, baseline visual acuity better than 15 letters (20/200), and followed monthly for at least six months. Eyes with prior photodynamic therapy or anti-VEGF therapy in the treated eye, patients who were followed up less than six months, or eyes with co-existing ocular disease were excluded.

Methods

Anti-VEGF treatment All the patients received intravitreal Bevacizumab (IVB) (1.25mg) every four weeks under standard sterile protocol performed by a single clinician (WRF). These injections were repeated until the resolution of fluid on SD-OCT or the absence of active leakage on FA was confirmed. Persistent fluid on SD-OCT or persistent leakage on FA was the re-treatment criteria.

SD-OCT images (Spectralis OCT, Heidelberg Engineering, Vista, CA, USA) of the fovea, along the vertical and horizontal meridians, were evaluated in a masked fashion by two retina specialists (JC, JK). SD-OCT images were evaluated at baseline and at one month after complete resolution of fluid. Complete resolution of fluid was defined as no intraretinal or subretinal fluid on SD-OCT or leakage on FA for a minimum of three consecutive months.

Integrity of the IS/OS and ELM was evaluated in the central 1 000 microns centered on the fovea. A disruption in the IS/OS or ELM was defined as the loss of the back-reflection line on a good quality SD-OCT scan. Analysis of the retinal structures was done as our previous publications described [13]. The IS/OS junction and ELM damage was measured as a percentage of disruption along the IS/OS and ELM backlines in 500 microns section in either direction from the foveal center (Figure 1). The percentage disruption was averaged to generate a number between 0% (no disruption) and 100% (total loss of the layer in both horizontal and vertical scans)

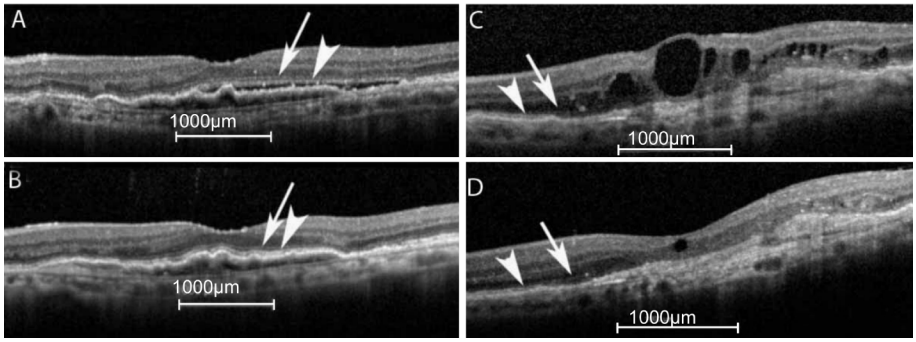

Figure 2 A and B: Case 1: Intact ELM and IS/OS at baseline. Eighty-one year old female with pretreatment BCVA of 44 ETDRS letters ($20/63^{-1}$) presented with intact ELM (arrow) and IS/OS (arrow-head) junction in the central 1000 microns as seen on spectral-domain optical coherence tomography (SD-OCT) (A) BCVA improved to 67 letters ($20/25^{-2}$) following four monthly intravitreal Bevacizumab injections (B): C and D: Case 2: Completely disrupted ELM and IS/OS at baseline. Eighty-year old female with pretreatment BCVA of 29 ETDRS letters ($20/125^{-1}$) presented with completely disrupted ELM (arrow) and IS/OS (arrow-head) junction in the central 1000 microns seen on spectral-domain optical coherence tomography (SD-OCT) (C) BCVA improved to 35 letters (20/100) following seven monthly intravitreal Bevacizumab injections (D).

(Figure 1). For assessment of percentage disruption concordance between the two masked observers was high (κ statistics value of 0.91).

CMT was defined as the distance between the internal limiting membrane (ILM) and the inner border of the choriocapillaris, including subretinal fluid collection and any observable CNV complex. Lesion size was determined in square millimeters using the digital software of the Heidelberg Spectralis.

Statistical Analysis An initial univariate regression was performed using visual outcome as a response and array of pre-treatment parameters as predictors including age, sex, lesion size and CNV type on FA, BCVA, CMT, IS/OS damage and ELM damage. To further establish an optimized model, a multivariable regression was performed using these variables along with two interaction terms of baseline BCVA_IS/OS damage and baseline BCVA_ELM damage. The optimized model was selected based on the minimum Bayesian Information Criterion. All analysis was performed using JMP software version 9.0.2.

RESULTS

This study included 50 eyes of 47 patients (41 women) with an average age of 81 years (range 56-94 years). All the patients presented with recent vision loss (2-3 months) due to subfoveal CNV secondary to wet AMD and had a visual acuity better than 15 letters (20/200). The patients had also been treated with intravitreal bevacizumab monotherapy (Figure 2). Classic CNV was present in 26 eyes (52.0%), minimally classic CNV in five eyes (10%), and occult CNV in 19 eyes (38%).Clinical characteristics are shown in Table 1.

A univariate regression analysis revealed that the extent of pretreatment ELM damage was the only significant predictor for visual improvement after treatment (Table 2).

Eyes with more ELM damage at the baseline when measured on SD-OCT manifested poorer visual improvement than the eyes that with less ELM damage (P=0.0145, Figure 3).

Table 1 Clinical characteristics of the patients

Characteristics	Values
Number of eyes	50
Mean age (a)	81
Gender	M=6, F=41
Mean Pretreatment BCVA (ETDRS letters)	50.92±11(SD)
Mean Pretreatment CMT (mm)	310.06±108.6(SD)
Mean Pretreatment IS/OS damage (%)	50.31±38.6(SD)
Mean Pretreatment ELM damage (%)	19.4±29.1(SD)
Mean number of injections	5.14
Mean follow up duration	11.2
Mean Post-treatment BCVA (ETDRS letters)	52.9±13.87(SD)
Mean change in BCVA (ETDRS letters)	1.98

Table 2 Results of univariate regression analysis

Predictive factor	*P*
Pre-treatment BCVA	0.21
Pre-treatment CMT	0.82
CNV type	0.49
Lesion size	0.23
Pre-treatment IS/OS junction damage	0.085
Pre-treatment ELM damage	0.0145

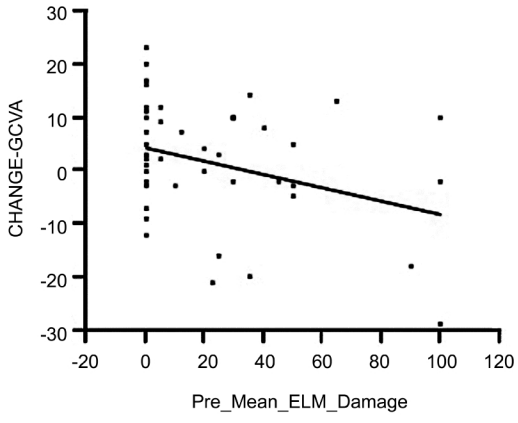

Figure 3 Graph showing association of ELM damage (in percentage) with change in BCVA (in ETDRS letters) after treatment (ELM = External limiting membrane, BCVA=Best corrected visual acuity).

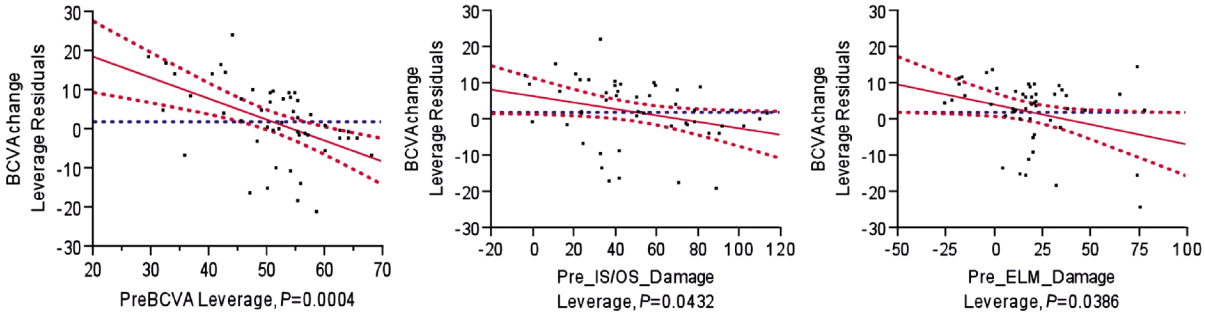

Figure 4 Graphs showing statistical analysis of predictive factors for visual outcome in multivariate regression analysis (Red dotted lines are 95% confidence interval of the regression line, blue dotted line is the line of mean of all data points).

However, with this simple model, only 10% of the variation of visual acuity changes from the treatment was explained. In univariate regression analysis, other pretreatment parameters were not of predictive value for visual improvement from the treatment.

A multivariable regression analysis revealed that pretreatment BCVA, pretreatment IS/OS integrity on OCT, pretreatment ELM integrity on OCT, and the interaction term of preBCVA*preIS/OS were all significant predictors.

The regression equation can be expressed as follows:

BCVA change=38-0.5×preBCVALogMAR-0.09×preIS/ OSdamage -0.11×preELMdamage+0.01×(preBCVALogMAR× preIS/OS)

With this optimized model, the variation of BCVA change from the treatment can be explained by 37%. In this model, both pretreatment IS/OS and ELM integrity were negatively associated with visual response (P=0.043 and P=0.039, respectively). Pretreatment BCVA was also negatively associated with visual response to treatment (P=0.0004). However, the size of the effect of pretreatment BCVA on visual response to treatment was different at the different levels of pretreatment IS/OS integrity (P=0.0072). The effect of pretreatment BCVA on visual response to the treatment decreases with pretreatment IS/OS damage increase (Figure 4).

DISCUSSION

In the present era of anti-VEGF drugs, the improvement of visual acuity is variable in eyes with CNV secondary to wet AMD. In the present study, we analyzed all the information about the patient including age, sex, pretreatment BCVA, pretreatment lesion size, CNV type on FA, pretreatment SD-OCT factors including CMT, IS/OS junction and ELM integrity to find the most important predictive factor for visual outcome. Prior knowledge of predictive factors of visual outcome would prove to be useful for patient counseling and clinical trial planning.

Before the development of the OCT, pre-treatment BCVA, location of the lesion and lesion size were considered to be the best predictive factors for the treatment response [6,17,18]. Subsequently, OCT thickness was proposed to provide a better prediction. However, many studies failed to define the relationship between the time-domain OCT parameters with the visual outcome due to limited resolution [8,19].

SD-OCT allows better visualization of the IS/OS junction and ELM and these structures have been suggested to be associated with the visual acuity in various macular diseases [11-14,20] including CNV [15,16,21].

ELM, the line above the IS/OS junction line, is clearly seen on ultrahigh resolution optical coherence tomography (UHR-OCT) and SD-OCT images. It represents the border between the outermost aspect of the outer nuclear layer composed of photoreceptor cell bodies and the photoreceptor inner segment myoid portion. ELM acts as a diffusion barrier to maintain osmotic pressure and protein gradients. ELM plays an important role in photoreceptor function and retinal physiology [22]. Recently ELM has been shown to have a correlation with the visual acuity in macular disease and after retinal detachment repair surgery [11], macular hole surgery [23] DME [12], and wet AMD [15].

In the present study, we did a longitudinal evaluation of pretreatment factors as predictor of visual improvement. We found that the pretreatment BCVA, IS/OS junction, and ELM integrity on SD-OCT together predict 37% of visual improvement. Interestingly, with increasing damage of IS/OS junction, the predictive value of pretreatment BCVA decreases. In univariate analysis, ELM was a better predictor of visual improvement than IS/OS junction/pretreatment BCVA, but only 10% of visual outcome could be predicted by ELM integrity. Therefore, knowledge of pretreatment BCVA and status of the outer retinal structures together are the best predictors for visual outcome.

There are no studies that have evaluated IS/OS and ELM as a predictive factor for treatment response in eyes with wet AMD. Our study clearly shows that both ELM and IS/OS are good predictive factors for treatment response. We excluded eyes that had any previous treatment like PDT/Laser. These treatment modalities cause damage to outer retina and may cover the disease process. We excluded eyes with visual acuity worse than 20/200 (15 ETDRS letters) to avoid very advanced cases, which will not respond to any type of

treatment. Therefore, our study results could not be useful for eyes with advanced CNV disease secondary to wet AMD.

One of the limitations of our study is that we did not include psychophysical tests to check AMD progression. Dimitrov *et al* [24] showed that psychophysical assessment included steady state thresholds using 4- and 14-Hz flicker and red and blue color; and dynamic tests such as photostress recovery and dark adaptation could be useful to monitor progression of early AMD and assessing the efficacy of interventions.

We conclude that pretreatment BCVA, ELM and IS/OS junction together are useful predictive factors for 37% of visual outcome in eyes with CNV secondary to wet AMD.

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