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SD-OCT morphological changes in wet age-related macular degeneration patients after bevacizumab treatment

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贝伐单抗治疗湿性年龄相关黄斑变性患者 SD-OCT 形态学变化

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摘要

目的:研究频域光学相干断层成像(spectral domain optical coherence tomography, SD-OCT)定量和定性检测指标在接受玻璃体腔内注射贝伐单抗的年龄相关性黄斑变性(age-related macular degeneration, AMD)患者人群中的变化,以评估这些指标是否可以用于预测治疗后视力情况。

方法:回顾性分析 66 眼 61 例未进行过 AMD 相关治疗的患者接受至少 3mo 玻璃体腔内注射贝伐单抗治疗的情况。治疗前后 SD-OCT 定量检测指标[中央视网膜厚度(central foveal thickness, CFT),外界膜(external limiting membrane, ELM)和椭圆区(ellipsoid zone, EZ)长度]和定性检测指标进行分析和比较。同时,分析这些指标和治疗前后的视力的相关性。

结果:平均视力(Log MAR)、CFT、ELM 和 EZ 长度治疗前为 0.62±0.41、419.3±110.0μm、378.2±377.2μm 和 156.4±253.7μm,治疗后为 0.53±0.44、325.8±117.9μm、547.1±421.5μm 和 173.1±207.1μm。治疗前视力和 CFT(rs=0.27)、ELM 长度(rs=-0.30)及 ELM 断裂(rs=0.43)有相关性。治疗后视力同样和治疗后 ELM 长度相关(rs=-0.40)。治疗后视力和治疗前视力(rs=0.66)、ELM 长度(rs=-0.35)和 ELM 断裂(rs=0.46)相关。

结论:研究显示:治疗前视力、ELM 长度和 ELM 断裂可以用于预测治疗后视力。

关键词:光学相干断层扫描;外界膜;椭圆区;年龄相关性黄斑变性

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Abstract

• AIM: To investigate the changes in spectral domain optical coherence tomography (SD-OCT) quantitative and qualitative parameters in a group of patients with age-related macular degeneration (AMD) that underwent bevacizumab intravitreal injections (IV). We assessed if one or more of these parameters can be used as prognostic factors of the post treatment visual acuity (VA).

• METHODS: Totally 66 eyes of 61 patients, with treatment naive AMD, that were treated with at least 3 monthly bevacizumab IV, were retrospectively studied. SD-OCT quantitative [central foveal thickness (CFT), external limiting membrane (ELM) and ellipsoid zone (EZ) lengths] and qualitative parameters were studied and compared before and after IV. We also tried to establish correlation between these parameters and before/after treatment VA.

• RESULTS: Mean VA(logMAR), CFT(μm), ELM length (μm) and EZ length(μm) changed from pre-IV values of 0.62±0.41, 419.3±110.0, 378.2±377.2 and 156.4±253.7 to post-IV values of 0.53±0.44, 325.8±117.9, 547.1±421.5 and 173.1±207.1. There was correlation between pre-IV VA and pre-IV CFT (rs=0.27), ELM length (rs=-0.30) and ELM disruption (rs=0.43). There was also correlation between post-IV VA and post-IV ELM length (rs=-0.40). Post-IV VA showed correlation with pre-IV VA (rs=0.66), ELM length (rs=-0.35) and ELM disruption (rs=0.46).

• CONCLUSION: In our study group pre-IV VA, ELM length and ELM disruption can be used as post-IV VA prognostic factors.

• KEYWORDS: optical coherence tomography; external limiting membrane; ellipsoid zone; age-related macular degeneration; visual acuity
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INTRODUCTION

Age-related macular degeneration (AMD) is an important chronic disease, being the major cause of important and irreversible vision loss, in developed countries, in individuals aged 50y or older[1-2]. The neovascular form of AMD, while accounting for only 20% of total AMD cases, is responsible for almost 90% of the serious vision loss associated with AMD[3]. Choroidal neovascularization (CNV) leading to hemorrhage, fluid and scar tissue formation is the cause for the vision loss associated with neovascular AMD.

Intravitreal anti-vascular endothelial growth factor (VEGF) injections are considered the first-line treatment option, slowing down and stabilizing most forms of neovascular AMD[4].

Spectral domain optical coherence tomography (SD-OCT) allows the detailed study of the microstructural changes that occur in the retinal layers with neovascular AMD. Photoreceptor lesion and disruption can be seen in the high-resolution SD-OCT images as loss of integrity of the external retinal layers: external limiting membrane (ELM), ellipsoid zone (EZ) and interdigitation zone[5-7].

Several studies show that in neovascular AMD patients, treated with anti-VEGF injections or with photodynamic therapy, the integrity and length of the ELM and EZ correlate to a greater or lesser degree with before/after treatment visual acuity (VA)[8-9]. In neovascular AMD patients submitted to intravitreal anti-VEGF injections, the integrity and length of the ELM and EZ can also be used as prognostic factors for the post treatment VA[10-11].

The purpose of this study was to investigate the changes in SD-OCT quantitative and qualitative parameters in a group of patients with neovascular AMD that underwent bevacizumab intravitreal injections (IV). We assessed if one or more of these parameters can be used as prognostic factors of the post treatment VA.

SUBJECTS AND METHODS

Retrospective study of 66 eyes of 61 patients with neovascular AMD diagnosis (treatment naive) that underwent 3 or more (4 maximum) consecutive, monthly bevacizumab IV (Avastin®, Genentech, South San Francisco, CA, USA) -1.25mg per injection. The treatment of each patient was done in the Ophthalmology Department of Central Lisbon Hospital Center between Jan. 2013 and Jan. 2015. All patients were submitted to a complete ophthalmological evaluation (including best corrected VA, intraocular pressure measurements and fundoscopy assessment) and fluorescein angiography, SD-OCT exams before and after treatment with bevacizumab IV. Mean follow-up between treatment and SD-OCT was 6±2mo.

Neovascular AMD diagnosis was made with fundoscopy, fluorescein angiography and SD-OCT. The decision was made to exclude from the study eyes that had other retinal diseases (diabetic retinopathy, epiretinal membrane, myopic degeneration, venous and arterial occlusion), optic neuropathy (glaucomatous, ischemic, compressive) and eyes that had previous vitreo-retinal surgery, IVs, laser photocoagulation or photodynamic therapy.

SD-OCT images were obtained with Spectralis (5.1.3.0 version, Heidelberg, Germany) with Heidelberg Eye Explorer software (1.7.1.0 version, Heidelberg, Germany). For each eye horizontal macular scans were made. Active eye tracking automatic software assured that scan positions were correct and that they didn't change with treatment. Foveal center was determined manually. Eyes for which the SD-OCT images were poor in quality and/or quantity (poor fixation or medium opacity) were excluded from the study.

SD-OCT quantitative [central foveal thickness (CFT), ELM and EZ lengths] and qualitative [ELM and EZ disruption, sub-retinal fluid, intra-retinal fluid, sub-retinal fibrosis and retinal pigment epithelium (RPE) detachment] parameters were studied and compared before and after bevacizumab IV. Taking into consideration that the foveal physiologic diameter is 1.50mm[12], all of these parameters were studied and measured 1mm (1000μm) nasal and 1mm (1000μm) temporal to the foveal center, in an area including 2mm (2000μm) total diameter (Figure 1). Mean CFT was obtained by SD-OCT automatic measurement.

ELM and EZ lengths were determined by manual measurement, with the caliper tool of the Heidelberg Eye Explorer software, of the intact, without disruption ELM and EZ zones. These measurements were made by two independent observers. The final ELM and EZ length values were obtained by the mean of these two measurements.

Disruption was considered to be present when more than 50% of ELM and EZ continuity was affected.

Best corrected VA was evaluated before and after treatment. It was measured with Snellen chart and converted to logarithm of the minimum angle of resolution (logMAR) equivalent for statistical study.

Patient gender, age and CNV angiographic pattern (classic or occult) were also assessed.

Statistical analysis was made with IBM SPSS Statistics for Windows, version 23.0.0.0. (IBM Corp., Armonk, N.Y., USA) statistical software. Descriptive analysis of the quantitative results are expressed in mean ± standard deviation and the qualitative results in percentages unless otherwise noted. Wilcoxon signed-rank test was used to compare the values of each variable before and after treatment. Correlation between the variables was made with Spearman rank-order correlationtest. All values of P less than 0.05 were considered to be statistically significant.

RESULTS

Mean age was 79.0±6.5y, gender was 77% female and 23% male (51 eyes female and 15 eyes male). CNV angiographic pattern was classified as classic in 68% (45 eyes) and as occult in 32% (21 eyes) of the eyes (Table 1).

Mean VA (Log MAR), CFT (μm), ELM length (μm) and EZ length (μm) changed from pre-IV values of 0.62±0.41; 419.3±110.0; 378.2±377.2 and 156.4±253.7 to post-IV values of 0.53±0.44; 325.8±117.9; 547.1±421.5 and

Table 1 General parameters

General parameters	
Eyes (Number)	66
Gender	
F	51(77%)
M	15(23%)
Age(a)	79.0 ± 6.5
CNV	
Classic	45(68%)
Occult	21(32%)

CNV: Choroidal neovascularization.

173.1±207.1 with P values of 0.02, <0.01, <0.01 and 0.07 respectively (Table 2). There was significant improvement of the best corrected VA with treatment. CFT was reduced significantly (22% reduction) and ELM length recovered significantly (45% recovery) (Figure 2 and 3). EZ length recovery was not statistically significant.

Qualitative parameter changes with treatment are shown in Table 3. There were significant reductions with treatment in ELM disruption, sub-retinal fluid, intra-retinal fluid and RPE detachment. Sub-retinal fibrosis increased significantly with treatment. There were no statistically significant changes with treatment in EZ disruption.

When studying the correlation results between VA and the pre and post treatment parameters there were correlations between pre-IV VA and pre-IV CFT (rs=0.27), ELM length (rs=-0.30) and ELM disruption (rs=0.43). There was also correlation between post-IV VA and post-IV ELM length (rs=-0.40) (Table 4 and Figure 4).

Post-IV VA showed correlation with pre-IV VA (rs=0.66), ELM length (rs=-0.35) and ELM disruption (rs=0.46) (Table 5 and Figure 5).

Of the total of the eyes studied (66 eyes), 35 eyes improved, 15 eyes maintained and 16 eyes worsened the VA with treatment. In the group of the eyes that had improved VA (35 eyes) post-IV VA also showed correlation with pre-IV VA (rs=0.68), ELM length (rs=-0.41) and ELM disruption (rs=0.56) (Table 6 and Figure 6).

DISCUSSION

In our study bevacizumab anti-VEGF treatment seems to lead to an increase in ELM length and decreased ELM disruption. There wasn't significant EZ length recovery or reduced EZ disruption with treatment. These results suggest that in our patients ELM suffersstructural recovery and that this recovery does not occur in the EZ. Loss of the integrity of the external retinal layers occurring first in the EZ layer and only after in the ELM, as shown previously in retinitis pigmentosa[6,13], can be one possible explanation for these results. However, it has also been shown that after macular hole surgery anatomical recovery of these retinal layers follows an inverted order, with first ELM followed by EZ being reestablished[14-15] and that this process can take up to 12mo[14]. The EZ recovery also occurs only where there is intact ELM[16]. While obtained in

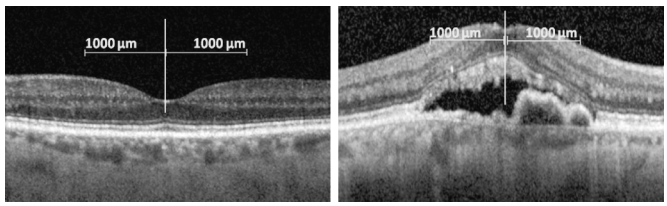

Figure 1 SD-OCT macular study area All of the parameters were studied and measured 1mm (1000μm) nasal and 1mm (1000μm) temporal to the foveal center.

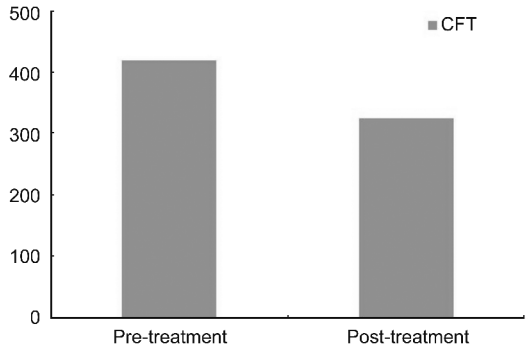

Figure 2 CFT variation.

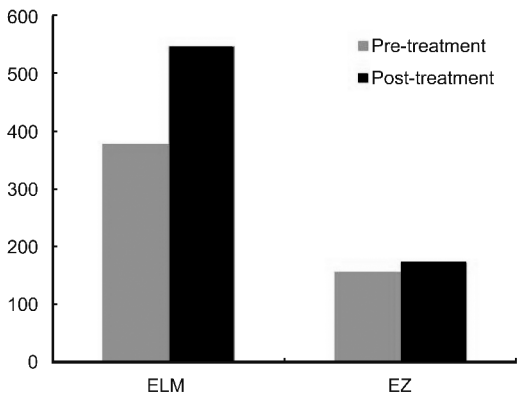

Figure 3 ELM and EZ length variation.

Table 2 Quantitative parameters

Parameters	Pre-treatment	Post-treatment	P
VA (logMAR)	0.62±0.41	0.53±0.44	0.02
CFT (μm)	419.3±110.0	325.8±117.9	<0.01
ELM length (μm)	378.2±377.2	547.1±421.5	<0.01
EZ length (μm)	156.4±253.7	173.1±207.1	0.07

VA: Visual acuity; CFT: Central foveal thickness; ELM: External limiting membrane; EZ: Ellipsoid zone.

Table 3 Qualitative parameters n(%)

Parameters	Pre-treatment	Post-treatment	P
ELM disruption	42/66 (63.6)	17/66 (25.8)	<0.01
EZ disruption	56/66 (84.8)	51/66 (77.3)	0.06
Intra-retinal fluid	37/66 (56.1)	14/66 (21.2)	<0.01
Sub-retinal fluid	39/66 (59.1)	14/66 (21.2)	<0.01
Sub-retinal fibrosis	25/66 (37.9)	43/66 (65.2)	<0.01
RPE detachment	22/66 (33.3)	15/66 (22.7)	0.01

ELM: External limiting membrane; EZ: Ellipsoid zone; RPE: retinal pigment epithelium.

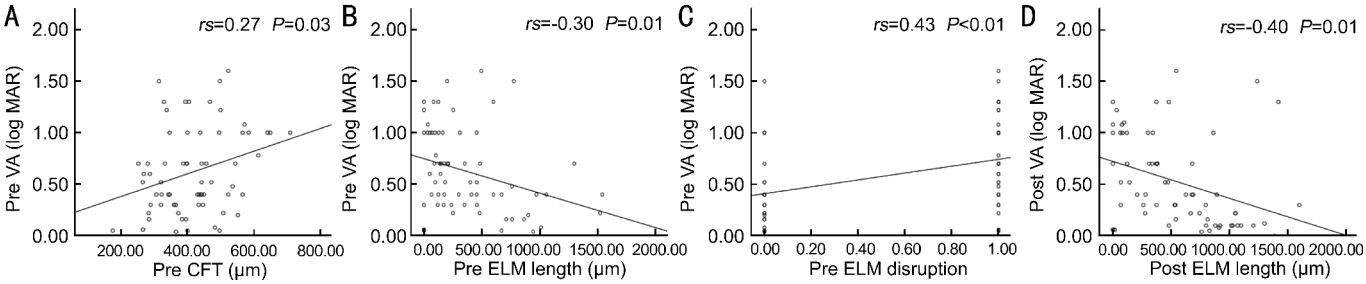

Figure 4 Pre and post-treatment correlations Dispersion graphs of the correlations between A) pre-treatment VA and pre-treatment CFT, B) pre-treatment VA and pre-treatment ELM length, C) pre-treatment VA and pre-treatment ELM Disruption, D: Post-treatment VA and post-treatment ELM Length. VA: Visual acuity; CFT: Central foveal thickness; ELM: External limiting membrane; *rs*: Correlation coefficient.

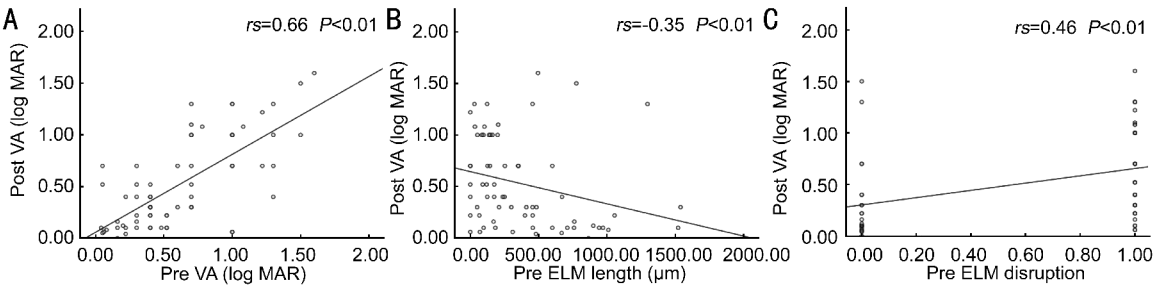

Figure 5 Post-treatment VA with pre-treatment parameterscorrelations Dispersion graphs of the correlations between A) post-treatment VA and pre-treatment VA, B) post-treatment VA and pre-treatment ELM length, C) post-treatment VA and pre-treatment ELM disruption. VA: Visual acuity; ELM: External limiting membrane; *rs*: Correlation coefficient.

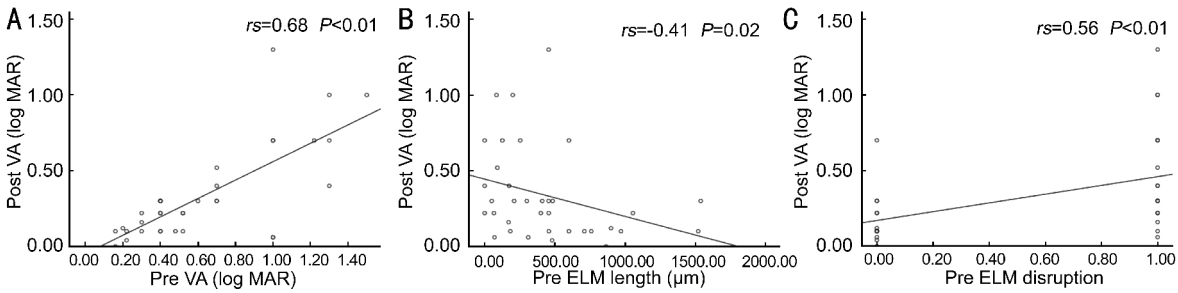

Figure 6 Correlations in the group with improved post AV Dispersion graphs of the correlations in the group with improved AV between A) post-treatment VA and pre-treatment VA, B) post-treatment VA and pre-treatment ELM length, C) post-treatment VA and pre-treatment ELM disruption. VA: Visual acuity; ELM: External limiting membrane; *rs*: Correlation Coefficient.

Table 4 Pre and Post-treatment correlations

Correlations	*rs*	*P*
Pre VA/Pre CFT	0.27	0.03
Pre VA /Pre ELM length	−0.30	0.01
Pre VA /Pre ELM disruption	0.43	<0.01
Post VA /Post ELM length	−0.40	0.01

VA: Visual acuity; CFT: Central foveal thickness; ELM: Externallimiting membrane; *rs*: Correlation coefficient.

Table 5 Post-treatment VA with pre-treatment parameters correlations

Correlations	*rs*	*P*
Post VA/Pre VA	0.66	0.01
Post VA / Pre ELM length	−0.35	<0.01
Post VA / Pre ELM disruption	0.46	<0.01

VA: Visual acuity; ELM: External limiting membrane; *rs*: Correlation coefficient.

Table 6 Correlations in the group with improved AV

Correlations	*Rs*	*P*
Post VA/Pre VA	0.68	<0.01
Post VA / Pre ELM length	−0.41	0.02
Post VA / Pre ELM disruption	0.56	<0.01

VA: Visual acuity; ELM: External limiting membrane; *rs*: Correlation coefficient.

different diseases these results may be one possible explanation for the differences in ELM and EZ structural recovery that we observed. It can be that in our patients the structural damage of the ELM wasn't serious enough (less likely if we consider the initial ELM mean length and disruption) or that the period of time following treatment wasn't long enough to allow for sufficient EZ structural recovery. It can also be the case that in neovascular AMD (mainly in advanced disease), EZ damage is more serious that in other retinal diseases, not allowing for significant future structural recovery.

In another study[11] that included patients with neovascular AMD submitted to ranibizumab treatment, the results were different than ours: ELM length didn't differ significantly after treatment and EZ length showed significant length recovery. Mean ELM initial length in that study was 1312.4±660.3μm and in our study it was 378.2±377.2μm. These differences

may signify greater before treatment ELM structural damage in our patients, with more recovery potential.

In our study pre-treatment VA was mildly correlated with CFT and moderately correlated with ELM length and ELM disruption. Post-treatment VA was moderately correlated with ELM length.

Retinal external layer lesion or disruption is a sign of photoreceptor damage or dysfunction in several retinal diseases[17-19].

Disruption or integrity loss of the retinal external layers (in our study ELM) seems to negatively influence pre and post-treatment VA. Our results seem to follow other previous studies where neovascular AMD patients VA was better or worse according to better or worse retinal external layer structural integrity[8,11,20].

In our study, post-treatment VA was strongly correlated with pre-treatment VA and moderately correlated with pre-treatment MLE length and disruption. These correlation results were similar in the group of patients that had improved VA with treatment. As also seen in previous studies[11], the most important factor for visual prognosis was pre-treatment VA. However, ELM length and disruption (although less consistently so) also seem to predict the after treatment VA recovery potential. These SD-OCT structural integrity parameters may eventually be used as VA recovery prognostic factors, but presently pre-treatment VA seems to be the most important factor in our study.

This study had several limitations: 1) it was a retrospective study and not prospective, randomized or controlled; 2) SD-OCT and fluorescein angiography exams made after treatment were not at the same defined time for each patient; 3) SD-OCT precise ELM and EZ length measurements were difficult in some eyes that had too much macular distortion, abundant sub-retinal fluidor fibrosis and RPE detachment; 4) MLE and EZ length recovery in some cases may only reflect better visualization of these layers because of less intra/sub-retinal fluid and not real structural integrity recovery.

Our study suggests that in neovascular AMD patients submitted to bevacizumab treatment ELM has potential for structural integrity recovery. We also conclude that certain SD-OCT structural changes before starting treatment (ELM length and disruption) can be used as predictors for the VA recovery that occurs with treatment. However, the most important prognostic factor seems to be pre-treatment VA. More studies are needed to clarify if there is a direct causal association between SD-OCT structural parameters and post bevacizumab treatment VA.

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