Original article

Oct parameters as predictive factors for the visual outcome after ranibizumab therapy in neovascular age related macular degeneration

A. Valverde-Megías a, *, J. Donate-López a, J. García-Gil-de-Bernabé b, A. Megías-Fresno c, J. García-Feijoo d

a Servicio de Oftalmología, Hospital Universitario Clínico San Carlos, Instituto de Investigación Sanitaria del Hospital Clínico San Carlos (IIdISSC), Madrid, Spain
b Servicio de Oftalmología, Hospital Universitario Rey Juan Carlos, Móstoles, Madrid, Spain
c Departamento de Bioquímica y Biología Molecular I, Facultad de Biología, Universidad Complutense, Madrid, Spain
d Servicio de Oftalmología, Hospital Universitario Clínico San Carlos, Instituto de Investigación Sanitaria del Hospital Clínico San Carlos (IIdISSC), Madrid, Spain; Instituto de Investigaciones Oftalmológicas Ramón Castroviejo, Universidad Complutense de Madrid, Spain; Red Temática de Investigación Cooperativa en Oftalmología (REITCS), Instituto de Salud Carlos III, Madrid, Spain

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ABSTRACT

Objective: To evaluate macular morphological parameters measured by spectral domain optical coherence tomography (SD-OCT) as predictive factors of visual outcome in patients with exudative age-related macular degeneration (AMD) treated with ranibizumab.

Methods: A retrospective study was conducted on 47 patients diagnosed with exudative AMD and treated with intravitreal ranibizumab for 12 months. Central retinal thickness (CRT), extension and thickness of modifications secondary to neovascular process, and status of the bands corresponding to the external limiting membrane (ELM) and to the ellipsoid region of the photoreceptors (ISe) were evaluated by means of SD-OCT. The relationship between these variables and visual acuity was analyzed by statistical methods.

Results: At the time of the diagnosis, preservation of ELM and ISe bands, and CRT were correlated with initial visual acuity. Twelve months later, CRT and visual acuity were independent parameters. Bivariate relationship analysis showed a correlation between final visual acuity and the following parameters: initial CRT, initial ISe and ELM status, and ISe and ELM integrity after loading dose. Multiple regression analysis indicated that initial visual acuity and ISe band status after loading dose have a predictive value for final visual acuity.


* Corresponding author.

E-mail address: alicia.valgreen@gmail.com (A. Valverde-Megías).

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Conclusions: The status of ISe and ELM bands after 12 months of treatment with ranibizumab was associated with visual outcome. Initial visual acuity and status of the ISe band after loading dose are prognostic factors of final visual acuity.

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Parámetros tomográficos como factores pronóstico del resultado visual tras terapia con ranibizumab en degeneración macular neovascular asociada a la edad

R E S U M E N

Objetivo: Evaluar parámetros morfológicos maculares determinados mediante tomografía de coherencia óptica de dominio espectral (SD-OCT) como factores predictivos de la respuesta funcional en pacientes con degeneración macular asociada a la edad (DMAE) de tipo exudativo tratados con ranibizumab.

Métodos: Estudio retrospectivo de 47 pacientes diagnosticados de DMAE exudativa y tratados con ranibizumab intravitreo durante 12 meses. Mediante SD-OCT se evaluaron el grosor retiniano central (CRT), la extensión y el grosor de las alteraciones secundarias al proceso neovascular, y el estado de las bandas correspondientes a la membrana limitante externa (MLE) y a la región elipsoidal de los fotorreceptores (ISe), analizándose por métodos estadísticos la relación entre estas variables y la agudeza visual.

Resultados: Al diagnóstico, la conservación de las bandas MLE e ISe y el CRT se correlaciona con la visión inicial. Doce meses después, el CRT y la visión final son parámetros independientes. Los análisis bivariante mostraron correlación entre la agudeza visual final y los siguientes parámetros: CRT inicial, estado inicial de las bandas ISe e MLE, y estado de estas tras la dosis de carga. El análisis de regresión lineal múltiple indica que la visión inicial y el estado de la banda ISe tras la fase de carga tienen valor predictivo de la visión final.

Conclusiones: El estado de conservación de las bandas ISe y MLE tras 12 meses de tratamiento con ranibizumab se correlaciona con el resultado visual. La agudeza visual inicial y el estado de la banda ISe tras la fase de carga son factores pronósticos de la agudeza visual final.

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Introduction

Age-related macular degeneration (AMD) is the main cause of vision loss and legal blindness in patients over 50 years of age in developed countries, with growing incidence due to population aging.1 For precise diagnostic and follow-up of neovascular AMD, in addition to funduscopy fluorescein angiography is required as well as optic coherence tomography (OCT). The latter technology, developed by Huang et al.2 in 1991, is a fast and noninvasive imaging device that provides high-resolution tomographic images of biological tissue. In the last decade, OCT has revolutionized clinical practice in ophthalmology. The technological breakthroughs included in devices and software have provided detailed display of the retinal microstructure. Nowadays, OCT constitutes a fundamental tool for diagnosing and following up patients with choroidal neovascularization, to the extent that several multicenter studies for evaluating treatment protocols with antiangiogenics drugs has been designed including tomographic parameters obtained with OCT as the main or exclusive criterion for retreatment, above clinical and retinographic parameters.3-6 However, the relationship between baseline tomographic parameters and visual results obtained with antiangiogenics treatment for exudative ARMD has not been studied in depth. The excellent resolution of spectral domain OCT (SD-OCT) has facilitated visualization and interpretation of retinal structures. Accordingly, the conservation of photoreceptor reflectance strips in the inner segment ellipsoid (ISe) and external limiting membrane (ELM) are deemed to reflect the grade of integrity of photoreceptors in a number of retinal pathologies.7-9 Therefore, the evaluation of said parameters in neovascular ARMD can be useful to assess patient management in clinical practice. The objective of the present research is to identify by means of SD-OCT baseline tomographic parameters in exudative AMD with prognostic value for the visual results obtained after 1 year of treatment with intravitreal ranibizumab.

Subjects, material and methods

Subjects

All the procedures were carried out in accordance with the principles of the Helsinki declaration and the study was
approved by the Ethics and Clinical Research Committee of the
San Carlos Clinic Hospital of Madrid. A retrospective review
of the clinical records of patients diagnosed with exudative
AMD was made in the Macular Unit of the Ophthalmology
Department of the San Carlos Clinic Hospital from June 2010
up to December 2012. The study included patients fulfilling
the following criteria: (a) absence of any treatment before intravit-
real ranibizumab established in our hospital; (b) a minimum
follow-up period of 12 months, and (c) evaluation in the initial
visits and in all the scheduled visits throughout the follow-up
period with SD-OCT. The study excluded patients intervened
for cataracts within 6 months prior to the choroidal neovas-
cularization diagnostic, as well as those exhibiting coexistent
disorders of the retina or optic nerve in the eye being studied.
Finally, the sample comprised 47 patients, who signed an
informed consent for the utilization of their clinical data.

Antiangiogenic treatment

For treating choroidal neovascularization secondary to exudative
AMD, antiangiogenics therapy was applied exclusively
with intravitreal injections of ranibizumab (Lucentis®; Novart-
tsis Pharma AG, Basel, Switzerland) at a dose of 0.5 mg/0.05 ml.
The follow-up was carried out for at least 12 months in ac-
cordance with the guidelines approved by the Retina and Vitreous
Society of Spain10 utilizing in all cases the same protocol,
which consisted in three consecutive monthly injections as
a loading dose and additional injections “on-demand” when
any of the following changes were observed in the monthly
evaluation visits: (1) persistence of fluid in OCT in the visit
after the injection; (2) CRT increase of at least 100 microns;
(3) qualitative changes in tomographies indicating the pres-
ence of recurring fluid: appearance of retinal cysts, subretinal
fluid, growth of pigment epithelium detachment; (4) new mac-
ular hemorrhage or new classic neovascularization area, and
(5) visual acuity (VA) loss exceeding five or more letters of the
Early Treatment Diabetic Retinopathy Study (ETDRS), with evi-
dence of macular fluid by means of OCT. These criteria were
utilized during the second year of the PrONTO study.4,5

Optic coherence tomography and spectral domain

A Spectralis HRA-OCT device (Heidelberg Engineering Inc. Hei-
delberg, Germany) with software version 5.4 was used for
capturing images. The tomographic examinations were car-
ried out under midriasis after administering 0.5% tropicamide
eyedrops, adapting the adjustment of the axial scan position
and optimizing focus to obtain high-quality images. The pre-
ferential analysis pattern was six sections centered on the
fovea. Patient examinations were carried out with a “follow-
up” proprietary image acquisition mode of the device which,
after establishing a reference image, carries out a comparison
of successive and subsequent images, taking retinal vessels
as reference for an exact image overlap. Automatic segmen-
tation errors were detected in 6% of the tomographic images,
which were manually segmented and corrected. The follow-
ing parameters were established: (a) CRT; (b) width of retinal
alterations secondary to the neovascular process, measured
at the level of the baseline of healthy retina pigment epite-
lium (RPE); (c) height of the retinal alterations secondary to the

Fig. 1 – Various ISe line alteration grades (white arrows)
in patients of the study. The integrity of this line was
assessed in vertical and horizontal sections along
1000 microns in each direction of the fovea. Assigning
the value of “0” (undamaged along the entire length), “1”
(defects not exceeding 200 microns) or “2” (larger defects).
Top: intact ISe line, grade 0; centre: ISe line with alterations
corresponding to grade 1; bottom: ISe line with a deep
grade 2 alteration.

neovascular process, measured from the baseline of healthy
RPE up to the neurosensory retina, and (d) integrity of the ISe
and ELM lines. Said integrity was assessed in accordance with
the procedure described by Maheshwary et al.9 as explained
below. Starting from image acquisition of six sections, the ver-
tical section was taken and the ISe line was assessed at a
distance of 1000 microns in each direction of the fovea. Alter-
ations in said line through said 2000 microns were graded as
0, 1 and 2 according to the following criterion: “0” was given
if the ISe line exhibited no defects throughout said length,
“1” if any defects did not exceed 200 microns, and “2” if said
defects were larger. The same assessment was made for the
horizontal section, 1000 microns toward the nasal side and
1000 to the temporal side. Adding up both scores gives a con-
tinuous scale ranging from 0 (full integrity) up to 4 (mostly
altered). Fig. 1 shows an example of three categories of the ISe
line in the patients of the present study. ELM was assessed
applying the same method to the line that represents said
structure.

Statistical analysis

The statistical analyses were carried out with the Centu-
rium XVI application by Statgraphics. All the values were
expressed as mean ± standard deviation (SD). For establishing
the relationship between VA and quantitative tomographic parameters, Pearson’s correlation coefficient or Spearman’s Rho coefficient were applied depending on whether normality conditions were fulfilled or not. For comparing more than two median values, as in the case of the various conditions of the ELM and ISe lines, the ANOVA test and Fisher’s LSD method were used for subsequent comparisons. When the normality or homosedasticity was not fulfilled (value of p in the Shapiro–Wilk test or the Levene test below 0.05), the Kruskal–Wallis and Dunn tests were utilized for subsequent comparisons. Prognostic factors were identified with multiple linear regression analysis, applying indicator variables (dummies) and including possible confusion factors in the model to discard any possible detected effect bias for tomographic parameters. Considering all factors, the maximum model was established, subsequently removing the variables which were not significant by means of the backwards procedure. For all tests, the value of p<0.05 was taken for statistical significance.

**Results**

The demographic and clinical characteristics of the patients who participated in the study are shown in Table 1. After 12 months follow-up, the mean VA was of 66.6 ETDRS letters (SD = 13.8) and the mean number ± SD of ranibizumab injections received by the patients was of 5.9 ± 1.9.

**Table 1** – Demographic and clinical characteristics of patients with exudative AMD who participated in the study.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age</td>
<td>81.9 ± 7.3</td>
</tr>
<tr>
<td>Sex</td>
<td>65–94</td>
</tr>
<tr>
<td>Involvement</td>
<td>38.3%</td>
</tr>
<tr>
<td>Studied eye</td>
<td>40.4%</td>
</tr>
<tr>
<td>Smoking habit</td>
<td>59.6%</td>
</tr>
<tr>
<td>Ophthalmological antecedents</td>
<td>53.2%</td>
</tr>
<tr>
<td>Without previous neovascularization treatment</td>
<td>100%</td>
</tr>
<tr>
<td>Type of lesion</td>
<td>46.8%</td>
</tr>
<tr>
<td>Hidden</td>
<td>59.6%</td>
</tr>
<tr>
<td>Minimally classic</td>
<td>6.4%</td>
</tr>
<tr>
<td>Classic group</td>
<td>19.1%</td>
</tr>
<tr>
<td>RAP</td>
<td>30.6%</td>
</tr>
<tr>
<td>CPV</td>
<td>4.3%</td>
</tr>
<tr>
<td>Location of the lesion</td>
<td>80.9%</td>
</tr>
<tr>
<td>Subfoveal</td>
<td>19.1%</td>
</tr>
<tr>
<td>Juxtapfoveal</td>
<td>17.8%</td>
</tr>
</tbody>
</table>

Table 2 – Correlations between VA and tomographic parameters determined in spectral domain OCT images at diagnostic, after the ranibizumab loading phase and at 12 months follow-up.

<table>
<thead>
<tr>
<th>Tomographic parameter</th>
<th>VA</th>
<th>r</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At diagnostic</td>
<td>Baseline</td>
<td>−0.45</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>At 12 months</td>
<td>Final</td>
<td>−0.27</td>
<td>0.07</td>
</tr>
<tr>
<td>At diagnostic</td>
<td>Final</td>
<td>−0.51</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>At diagnostic</td>
<td>Final</td>
<td>−0.18</td>
<td>0.22</td>
</tr>
<tr>
<td>After loading</td>
<td>Final</td>
<td>−0.53</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ISe line</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At diagnostic</td>
<td>Initial</td>
<td>−0.37</td>
<td>0.008</td>
</tr>
<tr>
<td>At 12 months</td>
<td>Final</td>
<td>−0.58</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>At diagnostic</td>
<td>Final</td>
<td>−0.44</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>At diagnostic</td>
<td>Final</td>
<td>−0.53</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>After loading</td>
<td>Final</td>
<td>−0.53</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ELM line</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At diagnostic</td>
<td>Initial</td>
<td>−0.28</td>
<td>0.06</td>
</tr>
<tr>
<td>At 12 months</td>
<td>Final</td>
<td>−0.54</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>At diagnostic</td>
<td>Final</td>
<td>−0.49</td>
<td>0.0004</td>
</tr>
<tr>
<td>After loading</td>
<td>Final</td>
<td>−0.46</td>
<td>0.001</td>
</tr>
</tbody>
</table>

VA: visual acuity; CRT: central retinal thickness; ISe line: the line representing the ellipsoid region of internal photoreceptor segments in tomographs obtained with spectral domain OCT; ELM line: external limiting membrane line; OCT: optic coherence tomograph.
no correlation between both parameters and the gain in ETDRS letters with respect to CRT reduction, which did not match a linear model (data not shown). This indicates that other factors were influencing the visual response. It is noteworthy to observe a statistically significant correlation between foveal thickness at diagnostic and VA at the end of the 12 months, as this indicates that a high or baseline CRT is a predictive factor for poorer visual results.

Fig. 3 shows the evolution of the mean values of length (Fig. 3A) and height (Fig. 3B) of the retinal alterations secondary to the neovascular process. At diagnostic, these values were of 3.087.8 ± 1.083.9 microns (interval: 5.173–413) and 294 ± 191.2 microns (interval: 942–67), respectively. The evolution of both parameters followed a similar pattern with the treatment: after the loading dose, a significant reduction was observed (p < 0.05) against baseline and at 12 months, the values remained below baseline even though the differences did not achieve statistical significance. No correlation was found between the length or height of the lesion and VA, neither at baseline (Pearson correlations, r = −0.12; p = 0.43 and r = −0.23; p = 0.11, respectively), after the loading phase (r = −0.10; p = 0.51 and r = −0.14; p = 0.31, respectively), nor after the end of the 1st year (r = −0.15; p = 0.31 and r = −0.07; p = 0.6 respectively).

Fig. 4 – Visual acuity based on the condition of the ISe line. ISe+: patients exhibiting some degree of conservation of this line in SD-OCT images; ISe−: patients with total de-structuring of said line in tomographs. * p < 0.01; ** p < 0.001.

Similarly, at diagnostic none of the two parameters exhibited a significant correlation with the final VA (r = −0.16; p = 0.28 and r = −0.18; p = 0.196 respectively), and therefore lack predictive value for the visual result.

Table 3 indicates the grade of conservation of the ISe line in the patients of the study throughout the follow-up period. A high percentage of patients (76.5%) exhibited at baseline severe or total de-structuring of the ISe line. Treatment with ranibizumab induced improvements in the overall sample, as shown in the mean score reduction. The condition of the ISe line seemed to have a significant influence on the visual function. As observed in Fig. 4, patients with some degree of preservation of the ISe line at baseline exhibited an average VA of 18 letters above that of patients with total de-structuring thereof (mean values of 70 and 51.6 ETDRS letters, respectively; Kruskal–Wallis; p < 0.001). The situation was same after the loading phase (71.6 and 58.7 ETDRS letters; p < 0.001) and at 12 months follow-up (75.6 and 56 ETDRS letters; p < 0.0001). The relationship between ISe line status and VA is clearly shown in Fig. 5, which depicts a very similar but inverted evolution of these parameters. The correlation coefficient between said two variables (Table 2) indicates that the
condition of the ISe at diagnostic and after the loading phase does have a predictive value for final vision.

In what concerns the condition of the ELM line, the mean score ± SD at diagnostic for the overall sample was of 1.76 ± 1.76, which illustrates a better preservation than that of the ISe line. At that point, the greater integrity of the ELM line was not related to better vision, contrary to the association of the ISe line. Accordingly, patients with the structured ELM lines exhibited a mean division of 55 ETDRS letters, while that of patients with greater preservation was of 59.6 (ANOVA, p = 0.4). The variation of this tomographic parameter was very small throughout the follow-up period. At the end of the loading phase, the mean score was of 1.29 ± 1.53, while 14.9% of sample (7 patients) exhibited a severe ELM damage and differences in vision vis-à-vis other patients with better preservation of said line (48.7 vs 68.5 ETDRS letters; p < 0.001). After 12 months, the mean score was of 1.63 ± 1.58, without statistically significant differences against the baseline value. Here again the authors found a significant difference between the vision of the group with total de-structuring and the rest of patients (56.1 vs 68.9 ETDRS letters; p = 0.01). These results indicate that the preservation of the ELM is also an important factor for the visual function. In fact, none of the patients who exhibited improvements in the ISe line after the loading phase against the situation at diagnostic (15 patients, 32% of the sample) exhibited at the time a de-structuring of the ELM line, and in 60% of these the preservation of this line was perfect. On the contrary, none of the seven patients who exhibited said via ELM line de-structuring at the end of the loading phase were able to improve the ISe line (all had a score of 4). A statistically significant correlation was found between the condition of the ELM at baseline or after the loading dose and the final VA (Table 2). Consequently, both the baseline condition of the ISe line as well as the ELM line appear to have a predictive value for the final vision.

Identification of prognostic factors for visual function

A multiple linear regression analysis was carried out to assess the contribution made to final VA by each of the factors initially identified in the bivariate analysis. As the number of patients is relatively small, the amount of variables to be included in said analysis has been limited. VA was assessed at diagnostic, CRT at baseline, while the condition of the ISe and ELM lines was assessed at diagnostic and after the loading phase. The variables were removed from the model in order of significance. At the end of this analysis, the definitive model ($R^2 = 0.53; p < 0.0001$) for the dependent variable (VA change at one year) only included VA at diagnostic ($p < 0.0001$) and the condition of the ISe line at the end of the loading phase ($p < 0.001$).

Discussion

The main finding of the present study is that the preservation of the ISe line at the end of the loading phase has a prognostic value for visual outcome after 12 months of treatment with ranibizumab. The importance of the condition of the ISe line for visual function is indicated by the fact that, at all stages of the study, the average VA of patients with some degree of preservation thereof was higher than that of patients with a totally destructured ISe line. Even though the final VA exhibited a correlation with the degree of integrity of said line at diagnostic and after the loading dose, the multivariate analysis has shown that only the latter parameter is a prognostic factor for final vision. This result is explained taking into account that the initial condition of the ISe line is susceptible to improve during this first phase of the treatment, including totally de-structured cases, while the condition achieved after the loading dose does not change substantially during the subsequent follow-up period.

The protocol followed in this study (loading dose “on-demand”) proved efficient for improving the condition of retinal structures and the average vision of patients in the sample. The mean visual gain was of +8.3 ETDRS letters, comparable with the gains described in reference clinical trials applying similar protocols.

However, individual response was variable, with no improvements in VA in some cases even though macular edema was resolved. Correlation coefficients between VA and CRT indicated that this tomographic parameter is not necessarily related to visual function. A negative correlation existed between both variables at diagnostic, as would be expected considering that the presence of fluid distorts macular morphology, which is highly likely to affect photoreceptor function. As with similar studies, the authors have not identified a correlation between VA and foveal thickness in the final visit. This indicates that macular edema resolution is a necessary but not sufficient condition for restoring vision, as this will depend on the final condition of photoreceptors. In addition, normalized CRT values do not imply integrity thereof. However, final VA does exhibit a negative correlation...
with baseline CRT, so that a higher value of this parameter is associated to a poorer visual result. Probably, higher CRT values at diagnostic are a consequence of a longer evolution of the pathological process and/or greater aggressiveness thereof, which would translate into increased photoreceptor damage.

The present study demonstrates that after 12 months of therapy with ranibizumab, VA exhibits a correlation with the condition of the ISe and ELM lines. The first of the hyper-reflective strips has been attributed to the signal produced by the junction area between external and internal photoreceptor segments, known as IS/OS line. However, recent studies have concluded that this strip is aligned with the mitochondria-rich ellipsoid region of the internal segments,14,15 for which reason it is known as the ISe line. Above this line, the ELM line identifies the area between the myoid region of the internal segments, juxtaposed to the Müller cell adherent zonules and the nuclear external layer which comprises photoreceptor cellular bodies. ELM functions as a barrier that prevents the diffusion of proteins, maintains osmotic pressure and plays an important role in photoreceptor function and retinal physiology.16

In the present cohort of patients, ranibizumab therapy produced an overall improvement of the ISe line and therefore the condition of photoreceptors. As is the case with VA, a substantial improvement was observed after the loading dose. It has been demonstrated in animal models that cone degeneration begins with the loss of external segments, whereas cellular death occurs much later.17 Accordingly, the initial de-structuring of the ISe line probably indicates damages in the mitochondria and external segments of photoreceptors, which could be regenerated if the cellular body is preserved. Under physiological conditions, the completed renewal of external segments is completed in about 10 days18 so that the period of the loading phase could be sufficient to enable the structural recovery of photoreceptors once the macular edema has been resolved. The restoration of the ISe line explains the VA gain achieved after this phase because of the external segments account for phototransduction and the mitochondria provides the energy required by this process. The patients who do not exhibit improvements in a totally de-structured baseline ISe line after the first three injections would have few probabilities of obtaining said improvements in the subsequent period (in the present study, only 3 out of 21, i.e., 14%). In contrast, an ISe in good condition after the loading dose is a prognostic factor for good final vision.

In what concerns the ELM line, the mean preservation at diagnostic in the overall sample was better than that of the ISe line. It is likely that its de-structuring indicates severe photoreceptor damage and perhaps complete degeneration. Accordingly, its plasticity is lower than that of the ISe line as the recovery of its integrity is difficult or impossible. The preservation of the ELM line seems to be a precondition for the improvement of the ISe line. In addition, in the cases in which the former was not visualized, the latter was not either. It is worthy of note that in contrast with the ISe line, no correlation was found between the condition of the ELM at diagnostic and VA at that time. A possible explanation is that other factors, such as the presence of exudative changes and/or the de-structuring of the ISe line at baseline could negatively affect vision, regardless of the ELM condition.

Other studies with patients affected by exudative AMD also found a correlation between the final VA and the preservation of the ISe and ELM lines after photodynamic therapy or antiangiogenic treatment.12,13,19–21 However, the relationship between the condition of the foveal layers in the final visit and VA has not proved useful for predicting the visual response of patients to treatment. Recent studies have endeavored to find baseline tomographic parameters with a prognostic value for the visual outcome, but results are inconsistent and the only clearly identified predictive factor for final VA has been baseline VA.22–26 In the present research not only the baseline OCT images but also those obtained at the end of the loading dose have been examined, considering that in general the most relevant changes in VA occur in this period. On the basis of this approach, the multivariate analysis has been applied to establish that the preservation of the ISe line after the loading phase is a prognostic factor for final VA. Accordingly, said tomographic parameter can be useful in clinical practice to assess the effectiveness of ranibizumab after the loading dose and to ponder the convenience of continuing with the treatment.

The main limitations of this study include its retrospective nature, the small number of patients and the absence of a standardized protocol for assessing SD-OCT images. Another point to be taken into account is that the final predictive modeling in the multivariate analysis does not entirely explain VA variability, which indicates the presence of other factors related to the final visual outcome. Studying the function carried out by a range of neurotrophic factors in the regeneration processes of damaged retinal structures in AMD and the assessment of their levels in patient cohorts could provide useful supplementary information for prognosticating individual response to antiangiogenics therapy.

Conflict of interest

No conflict of interests was declared by the authors.

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