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Research Article

Association Between Biomarkers in Optical Coherence Tomography and Visual Acuity in Patients with Edema Diabetic Macular Treated with Antiangiogenics

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Abstract

Purpose: To evaluate the association between the main bio- markers of Diabetic Macular Edema (DME) and the Visual Acuity (VA), and determine its importance as a prognostic tool at time to start an antiangiogenic treatment in each patient.

Methods: Retrospective, observational and longitudinal cohort study. 25 OCT scans of 23 patients with diabetic macular edema (DME) were analyzed, and the Best Corrected Visual Acuity (BCVA) at baseline and at 3, 6 and 9 months of treatment was registered. Baseline images were evaluated for predominant type of macular edema (cystoid, spongiform, with subfoveal serous detachment, or tractional compromise); presence of outer retinal damage (ORD, considered as any discontinuity in Limiting Extern Membrane, Ellipsoid Zone, and/or Interdigitation Zone); presence of disorganization of the Inner Retinal Layers (DRIL), and Hyperreflective Focus (HF) quantity, as well as Central Macular Thickness (CMT). Correlations between each OCT biomarker and visual acuity gain were analyzed using longitudinal mixed-effects models.

Results: Twenty five eyes with NAIVE DME were included. Baseline best-corrected visual acuity (BCVA) was between 0.3 and 1.3 on a logarithm of minimum angle of resolution visual chart (logMAR). Type of macular edema, DRIL presence, and CMT presented a statistically significant effect on the VA modification along the time ($p < 0,001$ in all cases). Patients with DRIL showed worse VA in logMAR terms at 9 months than patients without DRIL, being the difference statistically different ($p = 0,026$), and showed less improvement in VA along the nine months treatment (interaction effect $p = 0,007$). Eyes with subfoveal serous detachment and eyes with tractional component gained less vision than patients with only cystoid macular edema. There were no statistically significant differences between presence of hyperreflective focus, extern retinal layers alteration and VA along the treatment time.

Conclusion: This study showed that it is useful to assess the initial CMT but not in isolation, and above all the presence of DRIL, which proved to be the tomographic biomarker with the greatest potential as a predictor of clinical response in terms of VA.

Keywords: *Diabetic Macular Edema; OCT; Biomarkers; DRIL*

Introduction

Diabetic Macular Edema (DME) represents an accumulation of fluid within the central portion of the retina, which arises as a result of the failure of the hematoretinal barrier and remains an important cause. of visual loss in patients with diabetes mellitus [1]. The classification of DME is important to establish the severity of the pathology, as well as to select the most appropriate treatment for the patient. Different patterns of macular edema have been described to date: spongiform edema is present in 88% to 96% of all DME. It is a leakage of fluid in the outermost layers of the retina, and if it occurs in isolation, it has a good response to treatment. Cystoid type is present in 47% to 57% of all DME; are intraretinal cystic changes and represent more severe forms of leakage associated with worse VA; laser treatment in these cases is less effective, but they have a good response to pharmacological treatment. Tractional macular edema occurs in 15% of all DME, does not respond to laser therapy or isolated pharmacological treatment, and requires vitrectomy [2,3].

On the other hand, subfoveal serous detachment (DSS) has an incidence of 11% to 15% in DME; laser therapy has been shown to be ineffective in these cases and the existence of an associated inflammatory component has been proposed that could explain a better response to steroids [3,4]. However, despite these associations, in recent years, advances in OCT technology have made it possible to expand the study of DME to focus on other biomarkers that often accompany it. It has been shown that these are related in different measures with the structure and functional therapeutic response. The most studied include: alterations of the external ca- pas of the retina, disorganization of the internal layers of the same (sign known in recent years as "DRIL"), the presence of hyperreflective points (PH) in the inner or external layers of the retina, and also the central macular thickness (EMC), being one of the first to be studied in relation to visual acuity, showing contradictory results, which led to the need to find more reliable parameters when talking to the patient about a visual prognosis.

The biomarkers found in OCT help us identify ultrastructural alterations in early stages of the disease. Their presence has been linked to the severity of diabetic retinopathy, which makes them useful for raising a prognosis and assessing response to therapy.

It is important to note that new biomarkers are being studied, such as the rate of choroidal vascularization in OCT, peripheral vascular anomalies in broad-field angiography, or in OCT angiography, where the foveal avascular zone is evaluated (FAZ) or the fractal dimension. The usefulness of these techniques is that they could detect subclinical diseases and vascular changes of the retina even before clinically detectable changes or the development of symptoms occur visual [8].

Materials and Methods

The study was designated as cohort, retrospective, observational and longitudinal. Twenty-three patients (25 eyes) affected by DME referred to the Retina Department of the Instituto de Alta Complexity Oftalmos, from November 2018 to July 2019, were considered for the study. To be included in the analysis, patients had to meet the following criteria: (1) age between 24 and 84 years; (2) type 1 or 2 diabetes mellitus; (3) and naïve DME, which causes visual loss (clinically defined macular edema, and by a central macular spesor EMC > 250 microns, as well as intra- or subretinal fluid in the SD-OCT).

All patients received monthly treatment with an intravitreal antiangiogenic within nine months. For patients receiving bilateral treatment, both eyes were included (two patients).

The exclusion criteria were: any other ophthalmological pathology that causes significant opacity, such as a dense cataract or vitreous hemorrhage, poor OCT imaging quality, patient inability to collaborate with OCT examination or imaging, as well as any previous therapy received for the EMD.

Twenty-five OCT scans of 23 patients with DME and their Best Corregida (AVMC) at baseline and at 3, 6 and 9 months of treatment.

The patients' baseline CMVA was between 0.3 and 1.3 in logMAR units.

Baseline images were evaluated to determine the predominant type of macular edema (cystoid, spongiform, with sub-foveal or tractional serous detachment), as well as the presence of biomarkers such as alterations in the retina external (including here those with discontinuity of the external limiting membrane, the ellipsoid zone and/or the interdigitation zone in the macular area), the presence of DRIL, and the amount of PH, as well as the EMC (Figure 1). The correlation between each biomarker and visual acuity gain was analyzed using mixed-effect length models. Each patient underwent to an ophthalmological examination, which included the AVMC measured in logMAR units, biomicroscopy with slit lamp and spectral domain OCT (SD-OCT; HRA Heidelberg, Germany).

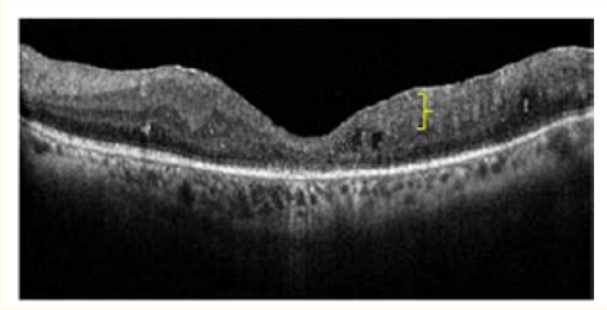

Figure 1: *Concomitant presence of DRIL and alteration of the external retina in the subfoveal area in a patient with Spongiform-predominant DME (DRIL: yellow key).*

Statistical analysis

To represent the distribution of cmVA of the 25 eyes at the four measurement moments, according to the type of edema and the presence or absence of the biomarkers under study, diabox grasses and whiskers. To evaluate the possible difference in mean AVMC between the groups at each measurement time, an ANOVA analysis was performed.

To analyze the temporal evolution of CMVA according to the type of edema and the presence or absence of biomarkers, univariate longitudinal models with mixed effects were adjusted, considering as fixed effects the treatment time, the covariate to be studied and the interaction between them and, as nested random effects, patients and eyes. To evaluate the significance of the fixed effects, the probability associated with the Wald type II test was calculated and the coefficients of the model were estimated. The value of the reporting criterion was calculated.

Subsequently, a longitudinal model of multivariate mixed effects, including all biomarkers, adjusted for edema type, was adjusted. The backward elimination algorithm according to the AIC value was used to obtain a set of covariates explaining the time evolution of the AVMC.

In all cases, an associated probability p less than 0.05 was considered significant. The analysis was carried out with the software R v.3.6.2 and RStudio v. 1.2.5033.

Results

Type of edema

When comparing the mean AVMC at each moment of measurement, according to the type of diabetic macular edema, no statistically significant differences were found at any of these times (Figure 2).

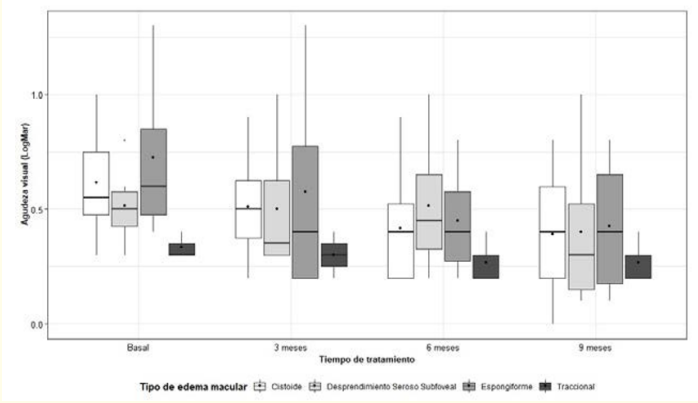

Figure 2: *Distribution of VA (logMar) according to the measurement time and type of edema.*

DRILL

Mean visual acuity was not statistically different according to the presence or absence of DRIL in the first three measurements. However, a significant difference was found when comparing both groups at 9 months (p = 0.026), given that cases with the presence of DRIL showed a mean Value of LogMar higher than those with absence of DRIL (Figure 3).

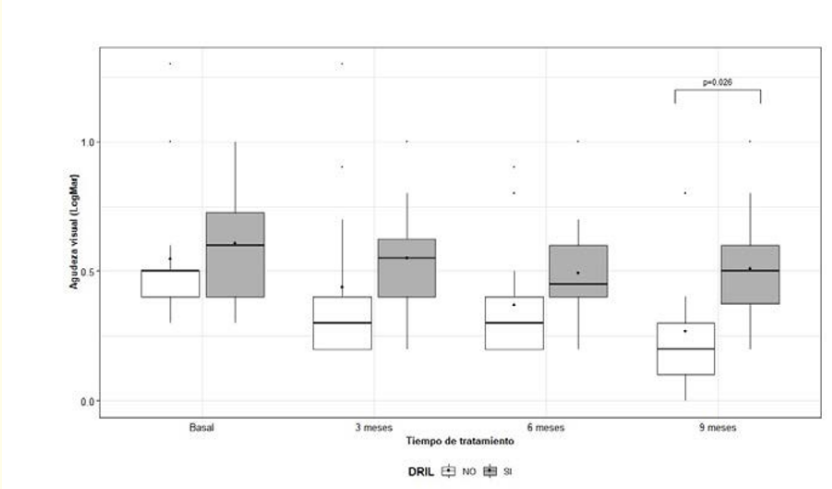

Figure 3: *Distribution of the VA (LogMar) according to the measurement time and presence of DRIL.*

When considering the longitudinal modification of visual acuity, it was found that it was significant in terms of time ($p < 0.001$) and the presence of DRIL (interaction effect: $p = 0.007$). Cases with ELDR showed a smaller decrease in visual acuity than cases without DRIL (Table 1).

Alteration of the external retina

Mean visual acuity was statistically different between cases with altered external retina and cases without, when measured at 6 months of treatment ($p = 0.035$) (Figure 4). No significant differences were found at the other measurement times (Figure 5). When analyzing the behavior of visual acuity, according to the LogMar scale, longitudinally, it was found that it presented a statistical decrease initially significant depending on the treatment time ($p < 0.001$), without differing according to the presence or absence of alterations in the external retina (interaction effect: $p = 0.912$) (Table 1).

Number of hyperreflective points (PH)

Mean visual acuity, compared according to PH number, showed no statistically significant differences at any of the measurement moments (Figure 6).

When analyzing the behavior of visual acuity, according to the LogMar scale, in a longitudinal way, it was found that it presented a statistically significant decrease in function of the treatment time ($p < 0.001$), without differing according to the number of hyperreflective points (interaction effect: $p = 0.082$) (Table 1).

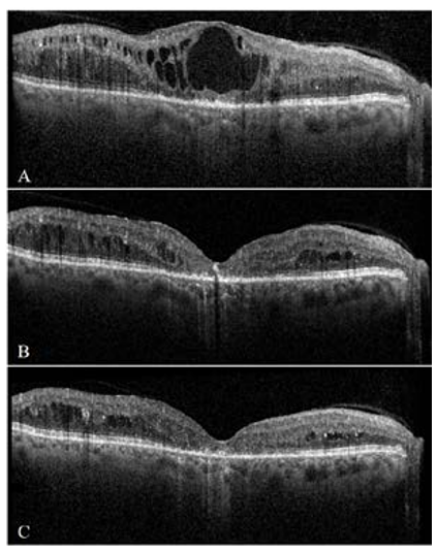

Figure 4: *Optical coherence tomography: signs in presence of DME. Cystoid DME with alteration in the layers of the outer retina and poor AV gain despite a marked reduction in MS at nine months of treatment. AVMC: A) Baseline: LogMAR 0.9 (Eq. Snellen: 20/160); B) Mes 3: LogMAR 0,7 (Eq. Snellen: 20/100); C) Mes 6: Log- MAR 0,7 (Eq. Snellen: 20/100).*

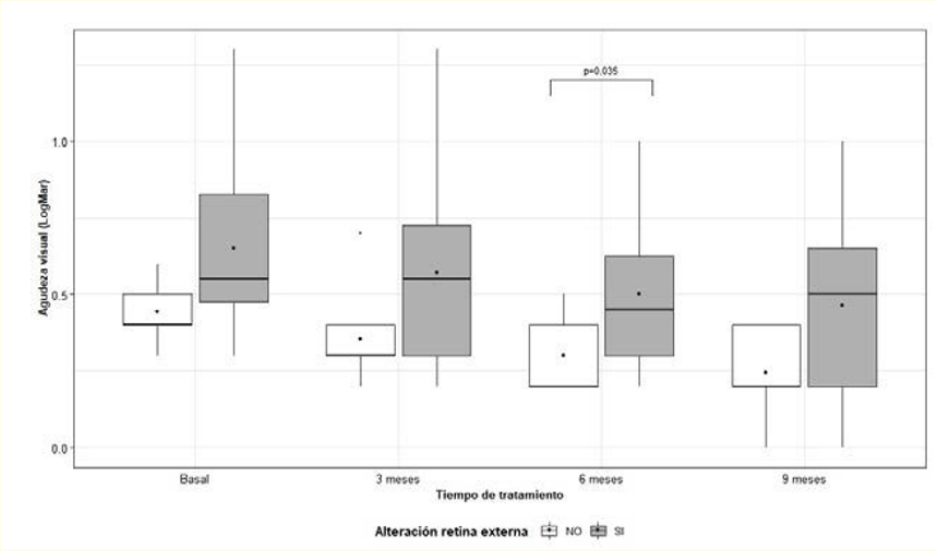

Figure 5: *Distribution of AV (LogMar) according to the time of measurement and alteration of the external retina.*

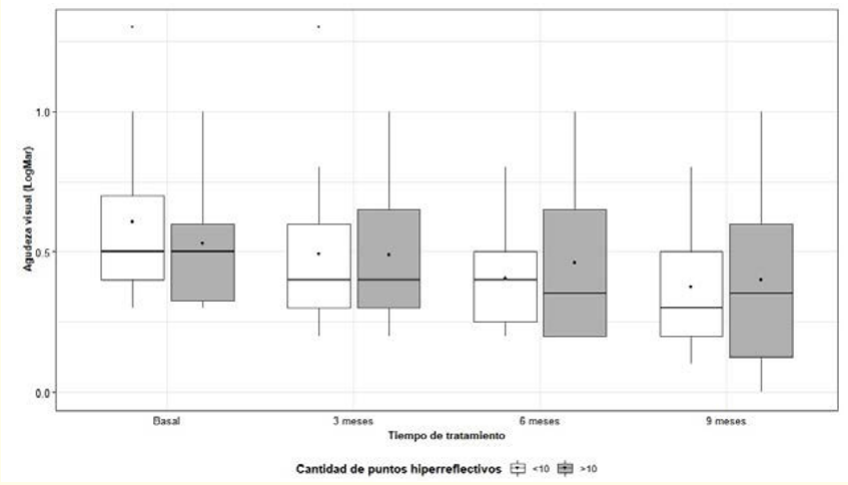

Figure 6: *Distribution of AV (LogMar) according to the measurement time and the number of hyperreflective points.*

Espesor macular central (EMC)

The correlation between visual acuity and central macular thickness was not statistically different from zero at any of the measurement times (Figure 7). However, it was found that the visual acuity over time differed depending on the central macular thickness, with less decrease in the LogMar value at higher central macular thickness (interaction effect: p = 0.005) (Table 1).

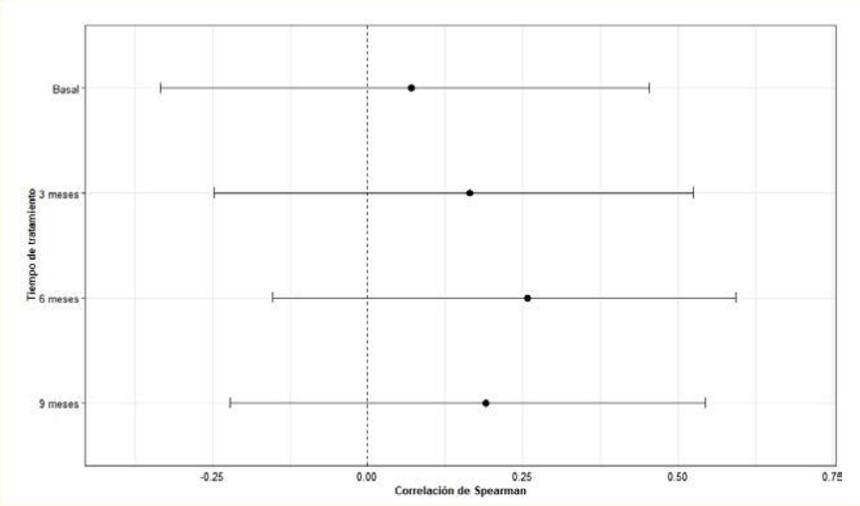

Figure 7: *Distribution of AV (LogMar) according to measurement time and central macular thickness.*

According to the univariates longitudinal analyses. According to the AIC values, a better fit of the data is obtained when the prevalence or absence of DRIL is considered as a predictive factor (Table 1).

Variable	Effect on baseline		Effect on the change over time		AIC
	Dear (EE)	p	Dear (EE)	p	
Type of macular oedema (ref.: Cystoide)					
Subfoveal Serous Detachment	-0.215 (0.103)	0.039	0.014 (0.008)	0.079	
Spongiform	0.034 (0.208)	0.871	-0.009 (0.009)	0.362	-43.452
Tractional	-0.427 (0.234)	0.083	0.018 (0.010)	0.094	
DRILL (YES vs. No)	0.188 (0.141)	0.090	0.018 (0.007)	0.009	-50.964
Alteration of the external retina (Yes vs. No)	0.166 (0.148)	0.276	0.001 (0.007)	0.913	-41.847
Number of hyperreflective points (>10 vs. <=10)	-0.114 (0.158)	0.477	0.012 (0.007)	0.087	-43.614
Central macular thickness (Standardized)	-0.066 (0.079)	0.417	0.009 (0.003)	0.007	-48.034

Table 1: *Result of the univariate models according to the effect of each predictive factor on the measurement of VA at baseline and over time.*

EE= Standard Error.

Finally, a mixed longitudinal model was proposed considering all the biomarkers under study, adjusted for the type of macular edema. Table 2 shows the results obtained after the backward elimination process (backward). The type of macular edema, the presence of DRIL and central macular thickness were the factors that remained in the final model, showing a statistically significant effect on the modification of visual acuity over the treatment time (effect of the interactions: $p < 0.001$ in all cases).

	Variable Effect on baseline		Effect on the change over time	
	Dear (EE)	p	Dear (EE)	p
Type of macular oedema (ref.: Cystoide)				
Subfoveal serous detachment	-0.249 (0.089)	0.006	0.018 (0.007)	0.011
Spongiform	-0.135 (0.242)	0.583	0.012 (0.009)	0.200
Tractional	0.540 (0.250)	0.042	0.037 (0.009)	< 0.001
DRIL (Yes vs. No)	0.129 (0.150)	0.402	0.024 (0.006)	< 0.001
Central macular thickness (standardized)	-0.108 (0.098)	0.281	0.013 (0.003)	< 0.001
EE = Standard Error				

Table 2: *Results of the multivariate model that evaluates the effect of each predictive factor on Log-Mar AV measurements at baseline and over time (backward elimination result).*

For fixed values of DRIL and central macular thickness, present serous detachment of the retina instead of cystoid macular edema it produces a small decrease in the LogMar measurement, as it happens if tractional involvement occurs instead of cystoid macular edema. The change in visual acuity does not differ between the types of cystoid and spongiform edema.

For fixed values of edema type and central macular thickness, the presence of DRIL is associated with a smaller decrease in the LogMar measurement.

Finally, a greater central macular thickness is related to a lower decrease in the measurement of LogMar, considering the type of macular edema and the presence of DRIL fixed.

Discussion

DRILL

As is known, the internal, internal nuclear and external plexiform layers of the retina contain anatomical structures critical for the transmission of visual data from photoreceptors to ganglion cells. The inability to distinguish the boundaries between these layers, recently described as DRIL, probably suggests a disorganization of some axons and nuclei of amacrine, bipolar and/or cells. horizontal located in these areas, and leads to poor visual results, as can be seen in this and other studies. It has also been hypothesized that disorganization occurs when bipolar axons rupture after their elastic limit has been exceeded due to edema [2,9-12].

This study consistently demonstrated that in DME there is a correlation between the presence of DRIL at baseline and subsequent VA even after emD resolution. The final VA was significantly lower compared to cases that did not present DRIL at the start of antiangiogenic therapy. Cases with the presence of DRIL showed a mean LogMar value at 9 months higher than those without DRIL. Also the longitudinal modification of VA was significant as a function of time and the presence of this biomarker. Sun., *et al*. described the disorganization of the inner layers of the retina finding a negative correlation with VA in eyes with current DME and, what is more importantly, also in eyes where the DME has already been resolved; this phenomenon was also observed in our study. It also showed that a greater extension of the DRIL at the baseline correlates with a worse VA at the baseline; on average, within the central foveal zone of 1 mm, a tempran increase in DRIL of 300 µ m was associated with a worsening of VA in 1 line during the 12-month follow-up period [2].

In 2015, Salma H. Radwan., *et al*. also screened four DRIL resolution patterns in patients with DME, showing that early and late resolution of DRIL showed a greater positive reduction in AV deficiency at 8 months, compared to those without resolved, which showed a

negative reduction. The best vision outcomes at 8 months were seen in eyes without baseline DRIL throughout the 9 months of treatment, even in patients in whom macular edema was not resolved in full, in line with our study [10].

Although in the present work the modifications in the extension of the DRIL over time were not considered, it is clear that its presence at the beginning of retinopathy is an important predictor of poor visual prognosis beyond treatment and should be taken into account when discussing visual expectations with the patient.

Types of diabetic macular edema

Several studies to date have reported different morphological categories of DME based on OCT. Otani., *et al*. reported three morphological types: spongy, cystoid and macular serous detachment, while Kim., *et al*. also considered the presence of tractional-type DME.

Panozzo., *et al*. identified three main morphological patterns: a "simple" thickening in the macular area, the cystoid subtype, and that of "neuroepithelial detachment", and classified traction. epiretinal in four types [3,4,13].

In contrast to that reported by the studies carried out by Yamamoto and Otani, in which the spongiform subtype was the most frequently found pattern (88% and 60% respectively, vs. 47% and 40% respectively for the cystoid type), in the present study the predominance was of the pattern cystoid (48% vs. 20% spongiform). However, it should not be considered clinically significant as a consequence of the small population studied [4,14].

The longitudinal behavior of the VA according to the LogMAR scale showed a significant decrease as a function of time for all types of edema, without notable differences between them. In a study by Kim., *et al*. mean VA varied between different subgroups of DME, although only significantly for the cystoid type, which was associated with worse visual outcomes [3].

This study showed that both DME associated with a vitreo-macular tractional component, as well as the presence of subfoveal serous edema (which is visible in the OCT as a hyporeflexive area below the neuroretina), have a statistically significant effect on the modification of VA along long as 9 months of treatment. In the tractional component, the indication of vitrectomy to release traction becomes imperative, while the DSS has had a controversial role as a predictor of AV and final anatomical changes and are still unclear.

The prevalence of DSS is approximately 15 - 30% in eyes with DME, and it has been studied that it has an important inflammatory component, which will lead to consider intravitreal corticosteroids as a very good option [15].

A study in patients with DME and DSS treated with antiangiogenics for 12 months, showed that there were no differences in VA compared to the group without DSS, however, other studies have shown that the presence of this biomarker is associated with good AV gain and recovery of the anatomy of the macula. The findings of the RESTORE study and the post hoc analysis of the RISE/RIDE study showed a protective role of the SSD, evidencing that the presence of the SSD in the baseline was associated with better visual results after one year [16,17].

Hyperreflective points (PH)

Hyperreflective points are defined as "discrete lesions, well circumscribed, with equal or greater reflectivity than the band of the pigmentary epithelium of the retina" [18].

Also described as hyperreflective spots or foci, PHs occur in diabetic eyes even when retinopathy is clinically undetectable; their number increases with the progress of retinopathy, and they show migration from the inner retina to the outer retina. A well-accepted hypothesis, based on some histopathological studies, is that of the activation of microglial cells with the consequent secretion of inflammatory molecules at the level of the retina, associated with neuronal and endothelial death [15,19].

In the present study, the mean VA, compared according to the number of PH, showed no statistically significant differences in any of the measurement points. Likewise, a reduction in the number of PH was observed to the extent that the edema decreased, being marked in those whose edema resolved completely. This is in line with the study conducted by Carsten Framme., *et al*. which showed good response to the antiangiogenic treatment in anatomical terms with disappearance of the PH, but not necessarily with good visual results [20]. Sun., *et al*. found no relationship between the presence of PH and AV [2].

The exact nature of the relationship between PH and AV is still unknown. Some studies such as those carried out by Schreur., *et al*. most random contradictory results: while in 2018 the presence of PH was linked to poor results in VA (despite it being unclear whether the decrease in VA was secondary to the presence of edema or not), in a study conducted in 2020 a potential clinical relevance of PH as predictors of good response to anti-VEGF treatment or corticosteroid therapy in DME. Our study did not demonstrate a good relation between PH and VA, so we consider that they should be taken into account in combination with biomarkers of greater reliability to predict the final VA [7,21].

Alterations in the layers of the external retina

Spaide., *et al*. performed a correlation of the bands observed in the external retina by OCT, identifying four: 1) External Limiting Membrane (MLE), 2) junction between the inner segment (SI) and external (SE) photoreceptors (SE/SI), 3) Verhoeff membrane (defined as a hyperrefringent line below the SE/SI), and 4) RPE, possibly including the Bruch membrane and choriocapillaris [22].

In recent stages of DME, rupture of the hematorretinian barrier may occur, resulting in an accumulation of plasma proteins, lipids, and extracellular fluid in the macula. This process could be related to damage to MLE and SI/SE. The integrity of the layers of the retina is a direct indicator of the health of photoreceptors and RPE [22].

Several studies indicate that a lack of integration of the same in the OCT is related to a worse VA post treatment, as well as a greater gain of final VA has been found in those with an IF/SE unharmed. Also an increase in the visibility of the segment tip of the cones (also called in English cost: “cone outer segment tips”) through the Time was associated with better Avs [2,23-25].

With the help of the OCT, Shinichiro Ito., *et al*. he also described a directly proportional relationship between VA and MLE status, SE/SI, and external segments of the cones, concluding that it should be used as a biomarker predictor of VA [23].

Despite this, in our study VA showed a statistically significant improvement depending on the treatment, without differing according to the presence or absence of alterations in the external retina. However, a statistically significant relationship was found at month 6, where vision gain was lower in the group with elevation of some of the outer layers (Figure 1). For their part, Sun., *et al*. also did not find a consistent relationship between VA and reflective alterations or changes at the level of MLE or ZE, in contrast to the results they obtained for DRIL, in line with our study [2].

Therefore, we believe that the integrity of the ca- pas of the external retina should be taken into account as a complementary tool for the prognosis of the patient’s vision at the start of treatment.

Espesor macular central (EMC)

Retinal thickness was determined as the distance between the inner surface of the retina, defined as the interface between the dark vitreous and the glossy reflection of the inner limiting membrane, and the superiphery of the outer retina [27].

The relationship between this and reduced VA is well known and has been the focus of attention and study in recent decades, becoming a useful clinical tool. Other biomarkers have also been gaining ground in tandem with the evolution of OCT technology. Although it has

been studied that an increased CME would be associated with a decrease in VA, and that those treatments that reduce it would improve vision, the quantitative evaluation of this relationship proved to be controversial, and other biomarkers currently have more prominence.

It has also been shown that the response of VA to focal laser treatment by decreasing macular thickness after treatment is paradoxical by up to 26% of the treated eyes, with a relationship no more than moderate between the two, and stating that although retinal thickness measurements with OCT represent an important instrument, they could not reliably replace VA against the various therapeutic options [28].

Ito., *et al*. demonstrated that patients with a mayor CME at 250 μm present are a negative correlation with VA, predisposing to a lower final VA despite antiangiogenic treatment. But they also noted that thickening the EMC may not have an immediate effect on VA. In fact, it was observed that some patients maintained a good VA with an increased macular thickness and an intact outer retinal layer in early stages of DME. Otani and associates also demonstrated that CMVA is moderately correlated with CME, regardless of tomographic characteristics, whether patients with or without DME [23,28].

In the present study, EMC also demonstrated a significant association with changes in VA. Throughout treatment, those with an above-average increase in CMO did not show great improvements in VA compared to those with lower-than-average initial CMO.

The EMC should be considered an accurate and important tool that can help us predict a response, although not without associating and considering the presence of other biomarkers that, in this one, and in studies with a greater number of participants demonstrated a greater association with VA than EMC.

Conclusion

It is important to carry out a detailed clinical evaluation and a thorough diagnostic and prognostic analysis using the OCT, through the visualization of the different biomarkers studied to date.

The study showed that when providing a visual prognosis to the patient in the context of initiating an antiangiogenic treatment, it is certainly useful to evaluate the central macular thickness, even if not in isolation; and, above all, to evaluate the presence or absence of DRIL, which proved to be the tomographic biomarker with the greatest potential to determine a poor gain of final AV to despite anti-angiogenic treatment and resolution of CME. This makes it an excellent tool for prospectively determining which patients might have a favorable or unfavorable response, would aid therapeutic selection, and would reduce the number of patients who were given. subject to invasive and prolonged and ineffective treatments. More studies are needed to incorporate the analysis of the different biomarkers together, including that of new technologies such as OCT angiography with biomarkers such as capillary density, vas-reshaping, etching. The study of the foveal avascular zone, which, as well as DRIL, seem promising as biomarkers in diabetic macular edema.

Ethics Approval Statements

This study was approved by the IRB of the Institute of High Complexity Oftalmos, Buenos Aires, Argentina.

Consent to Publication

Not applicable.

Availability of Data and Materials

The datasets used and/or analyzed during the present study are available at the request of the corresponding author.

Conflicts of Interest

CID, SP, ALC, LC, GD, PC and FDR declare to have opposing interests. AAA has served on advisory boards of Roche, Alcon, Bayer and Novartis.

Financing Support

Not applicable.

Authorship

CID Conception of the project, design of the study, data acquisition, writing of the article, approval of the final version.

SP Writing of the article, intellectual critical review, approval of the final version.

ALC Analysis and interpretation of data, drafting of the study, and final approval of the final version.

LC Design of the study, statistical analysis and interpretation of the data, final approval of the final version.

GD Study design, critical review of the intellectual content, final approval of the version. PC Analysis and interpretation of the data, critical review of the intellectual content, definitive approval of the final version.

FDR OCT image acquisition, critical review of intellectual content, final approval of the final version.

AAA Study design, critical review of the intellectual content, final approval of the final version.

All authors undertake to respond personally to their own contributions and to ensure that questions related to the accuracy or completeness of any part of the work, including those in which the author has not personally participated, are properly investigated and resolved, and the resolution is documented - mind in the bibliography.

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