Restoration of Outer Retinal Layers After Aflibercept Therapy in Exudative AMD: Prognostic Value

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Purpose. To evaluate the outer retinal layer (ellipsoid zone [EZ] and external limiting membrane [ELM]) changes following intravitreal aflibercept injections in eyes with treatment-naïve exudative age-related macular degeneration (eAMD) and to correlate these changes with fluid response and visual improvement.

Methods. A retrospective case series of 50 treatment-naïve eAMD eyes followed-up for 18 months. All patients underwent regular comprehensive ophthalmic examinations. The presence of EZ disruption, ELM disruption, EZ swelling, subretinal hyper-reflective exudation (SHE), central macular thickness (CMT), cystoid spaces, subretinal fluid, and pigmented epithelium detachment were evaluated by two different retinal specialists at baseline and final visits, and correlated with best corrected visual acuity (BCVA) improvement.

Results. At 18 months, BCVA, EZ disruption, ELM disruption, EZ swelling and SHE improved significantly ($P = 0.001$) at 18 months. Improvement of BCVA showed a statistically significant correlation with ELM restoration ($P = 0.018$), but not with EZ restoration ($P = 0.581$). Swelling of the EZ decreased from 72% of the cases at baseline to 30% in 18 months while SHE decreased from 52% to 6% in 18 months ($P = 0.001$). We observed a statistically significant ($P = 0.001$) reduction between the baseline and final value of CMT.

Conclusions. Aflibercept is safe and effective in treating exudative AMD with the restoration of the outer retinal layers. Restoration of the EZ is not statistically correlated with the final BCVA, even though persistent EZ changes could be associated with irreversible decrease in vision. On the contrary, the final status of the ELM is directly correlated with final BCVA. Also, baseline changes in outer retinal layers, especially the ELM, appear to predict photoreceptor restoration and final BCVA, and must be comprehensively analyzed to enable and determine a future prognosis.

Keywords: aflibercept, age-related macular degeneration (AMD), anti-VEGF treatment, choroidal neovascularization (CNV), ellipsoid zone swelling, external limiting membrane (ELM), optical coherence tomography (OCT), pigmented epithelial detachment (PED), subretinal hyper-reflective exudation (SHE)

Exudative age-related macular degeneration (eAMD) is a major cause of legal blindness in elderly patients.[1,2] A correlation between the function and structures of the outer retinal layers, particularly the external limiting membrane (ELM) and the inner segment/outer segment junction called the ellipsoid zone (EZ), has been shown in AMD patients treated with either photodynamic therapy or anti-VEGF injections.[3–7] In addition, ELM status has been reported to be a good indicator for prognosis in eyes with AMD before and after anti-VEGF treatment.[8–10]

During the last decade, two anti-VEGF drugs (ranibizumab and bevacizumab, anti-VEGF in off-label use), have dramatically changed the management of patients with eAMD and have significantly improved the prognosis of the disease.[11,12] The comparison of age-related macular degeneration treatments trials (CATT study) showed that monthly intravitreal bevacizumab was noninferior to monthly intravitreal ranibizumab and that monthly injections resulted in better visual outcomes than PRN treatment.[13] Nevertheless, long-term studies have shown that eAMD patients remain at a substantially high risk of visual loss.[14]

Recently, VEGF trap (Aflibercept, Eylea, Bayer HealthCare, Berlin, Germany) was approved for the treatment of eAMD. This is a protein constructed by fusion of key domains of VEGFR1 and VEGFR2 receptors to the constant region (Fc) of human immunoglobulin G. Compared with bevacizumab and ranibizumab, VEGF trap has higher affinity to VEGF, and it has a longer half-life. Vascular endothelial growth factor trap binds to all VEGF-A and VEGF-B isoforms, as well as to the highly related placenta growth factor; VEGF trap has been shown to be equally effective to ranibizumab in improving BCVA and preventing visual loss.[15] The 2-year results of the VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD (VIEW)

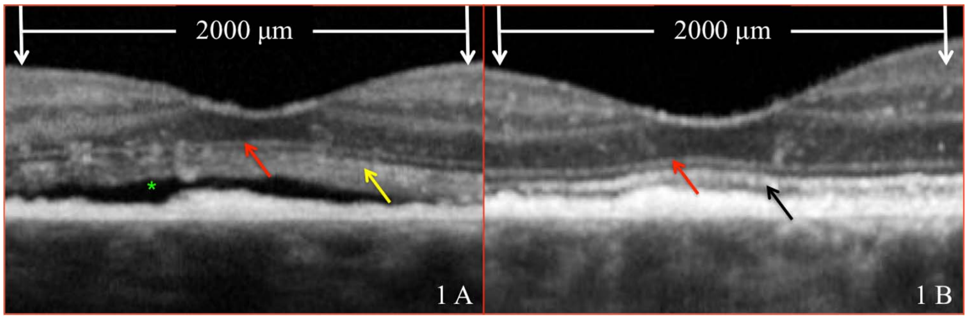

Figure 1. (**A**) Patient I: optical coherence tomography B-Scan of a treatment-naïve exudative AMD with type I choroidal new vessels at baseline. Normal visualization of subfoveal ELM (*red arrow*). Ellipsoid zone swelling (*yellow arrow*) shows change in reflectivity with increase in thickness, fragmentation, and hyper-reflective dots. Presence of subretinal fluid accumulation (*green star*). (**B**) Patient I at the 18-month visit. Clear visualization of subfoveal ELM (*red arrow*) with substantial regression of EZ swelling, detectable EZ layer, and complete regression of subretinal fluid.

trial showed similar visual outcomes between patients treated with 2q8 VEGF trap and patients treated with monthly ranibizumab during the first year and then as needed (pro re nata [PRN]) in both groups in the second year.[16]

In this study, we aimed to determine if the morphological status of the EZ and ELM (as defined in accordance with International Nomenclature for Optical Coherence Tomography Panel)[5] could be predictive factors for the efficacy of VEGF trap in routine clinical practice. We also analyzed the correlations between their status and functional and morphological outcomes in eAMD patients treated with aflibercept.

Materials and Methods

Study Design

Our study is a retrospective study conducted in two ophthalmological centers: Odeon Ophthalmology Center and Creteil University Hospital (Paris, France). This study was performed in accordance with the tenets of the Declaration of Helsinki after approval by the institutional ethics committee. Fully informed written consent was obtained from all study patients.

Population

This study evaluated 50 eyes of 49 consecutive patients treated with aflibercept for treatment-naïve active choroidal neovascularization (CNV) due to eAMD diagnosed between June and August 2013 (26 and 24 eyes in Odeon and Creteil Centers, respectively). The diagnosis of CNV secondary to eAMD was done by a retina specialist based on clinical examination, fluorescein angiography (FA), indocyanine green angiography (ICGA), and spectral-domain optical coherence tomography (SD-OCT).

Exclusion criteria were uncontrolled intraocular pressure (IOP) of more than 25 mm Hg; vitreous hemorrhage or inflammation; prior vitrectomy or AMD-related surgery or any intraocular surgery; previous photodynamic therapy (PDT); treatment with intravitreal triamcinolone; presence of significant subretinal fibrosis or atrophy; significant media opacities; and myocardial infarction, transient ischemic attack or cerebrovascular accident within the previous 90 days. All ocular exclusion criteria applied only to the study eye.

All patients included in this study received intravitreal aflibercept injections (IAI) as first-line treatment. A loading dose of 3 monthly IAIs was administered to all patients, followed by IAI every 2 months (from month 4). This fixed regimen was followed even if SD-OCT did not evidence morphologic recurrence or persistence of subretinal fluid associated with visual loss. All patients were followed for 18 months after the first IAI.

Initial baseline assessment included best-corrected visual acuity (BCVA) measured using ETDRS chart, fundus ophthalmoscopy, FA, ICGA, and SD-OCT of the macular area. Patients were followed monthly for 18 months. We performed FA and ICGA at baseline, and at the 4-, 6-, 12-, and 18-month visits; SD-OCT was performed at each visit using commercial equipment and software (Heidelberg Spectralis HRA-OCT with Heyex Software Version 5.7.0.6.; Heidelberg Engineering, Heidelberg, Germany). During consecutive follow-up visits, the OCT scans were acquired by using the "follow-up" mode of the eye-tracking-assisted system (AutoRescan, Heidelberg Spectralis).

Morphologic Measures

The status of the two hyper-reflective EZ-ELM layers were individually analyzed within the central 2000 μm (1000 μm nasally and 1000 μm temporally to the fovea) in a horizontal B-scan passing through the center of the foveal depression (30°, 100 frames/scan). The evaluation, performed on a 2-mm diameter section, was based on the diameter of the physiologic fovea, which is 1.85 mm.[8]

The disruption of the ELM and EZ (length in μm), defined as the absence of clear visibility of these layers, was measured using the caliper provided by the manufactured software (Heidelberg Engineering) at baseline and the final study visit at 18 months. The ellipsoid zone was defined as the second hyper-reflective band above the RPE (the first hyper-reflective band above the RPE is considered the interdigitation zone). The external limiting membrane was defined as a discrete hyper-reflective band at the outermost border of the outer nuclear layer, located above the EZ.[5,10]

Ellipsoid zone swelling was defined as a localized change in reflectivity due to an increase in thickness and/or presence of focal fragmentation and/or presence of hyper-reflective dots, and was qualitatively evaluated. This swelling of the EZ may be associated with local disruptions of the ELM and sometimes with an extensive subretinal hyper-reflective material corresponding to a relatively homogeneous "grey band" (between the RPE and remnants of the EZ),[17–19] also described as subretinal hyper-reflective exudation (SHE[20]; Figs. 1–3).

The provided software automatically measured the central macular thickness (CMT), defined as the distance between the outer limit of Bruch's membrane and the internal limiting membrane.

The height of the macular pigment epithelial detachment (defined as the distance between the outer limit of the Bruch's membrane and the inner limit of the RPE layer, at the fovea) was manually measured. The presence of subretinal fluid or

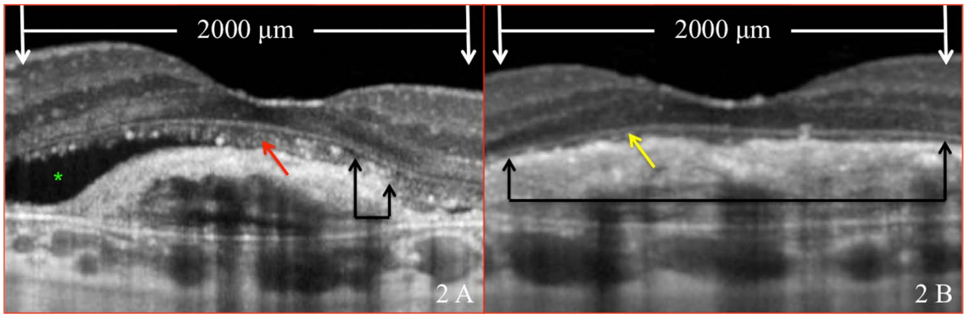

FIGURE 2. (A) Patient II: optical coherence tomography B-Scan of a treatment-naïve exudative AMD with type I choroidal new vessels at baseline. Evidence of EZ swelling (*red arrow*) and EZ disruption/nonvisualization (distance in between the *black arrows*). Presence of subretinal fluid accumulation (*green star*). (B) Patient II at the 18-month visit. Complete regression of subretinal fluid. Clear visualization of ELM (*yellow arrow*), but absence/nonvisualization of EZ layer in the entire subfoveal area (distance between the *black arrows*).

intraretinal cystoid spaces (CS) was detected on a 19 B-scans volume protocol (30 frames per scan on a 20 × 15° area). An enhanced-depth imaging optical coherence tomography (EDI-OCT) method was used to better explore PED features and changes and to measure CMT. All evaluations were made by two retinal specialists (FC, MS) who were masked to each other and graded the OCT B-scans independently at different time points in different orders. These results were then compared and, in case of discordance higher than 15% for quantitative measures, were further analyzed by a senior retinal specialist (ES, GC).

Outcome Measures

Functional outcomes included BCVA measurement at baseline and at the final 18-month visit. Changes of BCVA from baseline (ETDRS scale) to the final visit were also evaluated.

Morphological outcomes included the lengths of EZ and ELM disruption, the percentage of focal or diffuse swelling of the EZ, presence of SHE, CMT, PED height, percentage of patients with subretinal fluid (SRF), and the percentage of patients having cystoid spaces, at baseline and at 18 months. The difference between the baseline and final value of ELM (or EZ) disruption, defined as ELM (or EZ) restoration, was also calculated.

Patients were divided into two groups: those who gained less than five ETDRS letters and those who gained five or more at the final evaluation. This was done in order to find a possible correlation between morphological and functional outcome at 18 months.

Statistical Analysis

Statistical analysis was performed using commercial software (SPSS for Windows software version 17.0; SPSS, Inc., Chicago, IL, USA). Descriptive analyses are reported as means and standard deviation for continuous variables and as percentage for qualitative variables. For continuous variables evaluated manually (loss of continuity of EZ and ELM, CMT, PED height), interobserver correlation was evaluated using the Pearson's correlation coefficient. Baseline and final (18-month) evaluations were compared using the paired *t*-test and McNemar test. The Mann-Whitney and χ^2 tests were used to compare subgroups of patients while Pearson's correlation coefficient was used to correlate continuous variables. A 2-tailed probability of 0.05 or less was considered statistically significant.

RESULTS

Baseline Data

We included 50 eyes of 49 patients with treatment-naïve active CNVs secondary to AMD and treated with IAI. All eyes completed 18-months of follow up. The mean age was 77.1 ± 7.5 years; 39 patients (80.0%) were female. Occult or minimally classic CNV was diagnosed in 31 eyes (62%), classic or predominantly classic in 12 eyes (24%), retinal angiomatous proliferation in three eyes (6%), and polypoidal choroidal vasculopathy in four eyes (8%). All patients were treated with monthly IAI for 3 months followed by IAI every 2 months (from month 4 after treatment initiation). All eyes had received an average of 10.4 injections (range, 10–11) at 18

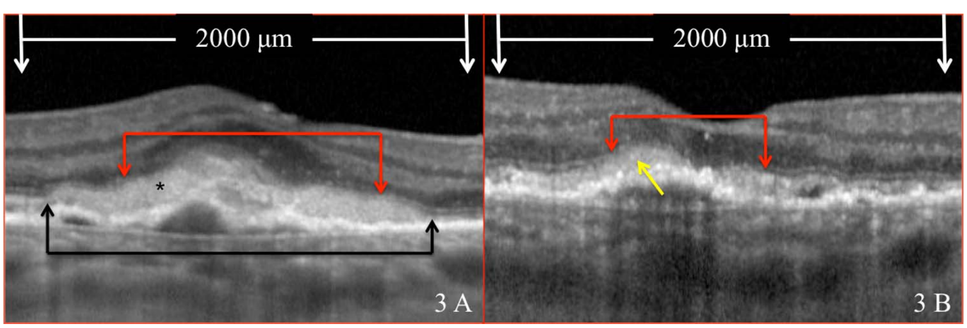

FIGURE 3. (A) Patient III: optical coherence tomography B-Scan of a treatment-naïve exudative AMD with type I choroidal new vessels at baseline. Presence of extensive SHE as a relative homogenous "gray band" (*black star*) between the retinal pigmented epithelium and remnants of outer retinal layers. Reduced or no visibility of EZ (distance between the *black arrows*) or ELM (distance between the *red arrows*) in the subfoveal area affected by SHE. (B) Patient III at the 18-month visit. Substantial regression of SHE, with slight persistence of EZ swelling (*yellow arrow*) associated with ELM disruption (distance between the *red arrows*).

TABLE 1. Functional and Morphological Changes During Study Period

Parameters	Baseline	Final Visit	*P* Value
BCVA, ETDRS letters	60.3 ± 12.9	66.1 ± 11.9	0.001
CMT, μm	382.4 ± 11.9	290.6 ± 69.5	0.001
ELM disruption, length in μm	404.7 ± 368.8	191.6 ± 251.1	0.001
EZ disruption, length in μm	767.4 ± 317.4	377.9 ± 318.7	0.001
PED height, μm	171.7 ± 135	105.8 ± 114.2	0.001
EZ swelling, focal/diffuse	72	30	0.001
SRF, %	80	22	0.001
Cystoid spaces, %	42	12	0.001
SHE, %	52	6	0.001

months. We observed no ocular side effects such as endophthalmitis, noninfectious endophthalmitis, vitreous hemorrhage, retinal tear, retinal detachment, or elevation in intraocular pressure.

Best Corrected Visual Acuity

Best corrected visual acuity improved significantly from 60.3 ± 12.9 ETDRS letters to 66.1 ± 11.9 ETDRS letters ($P = 0.001$; Table 1). At 18 months, the BCVA significantly ($P = 0.001$) compared with baseline. The improvement in BCVA showed a statistically significant correlation with ELM restoration ($P = 0.018$), but not with EZ restoration ($P = 0.581$). At the final visit, 58% of the patients had gained less than five ETDRS letters while 42% had gained five or more ETDRS letters (Table 2). Comparing the two groups with different grades of visual improvement, we observed a statistically significant difference in BCVA ($P = 0.001$); CMT ($P = 0.019$), and ELM disruption ($P = 0.002$) at baseline, and in ELM restoration ($P = 0.001$; Table 2).

Morphological Results

There was high correlation ($r > 0.8$; $P < 0.05$) between the examiners for all manually evaluated continuous variables.

ELM and EZ Disruption/Restoration (Length in μm)

The disruption of EZ and ELM improved significantly ($P = 0.001$) from a baseline value of 767.4 ± 317.4 μm and 404.7 ± 368.8 μm, respectively, to 377.9 ± 318.7 μm and 191.6 ± 251.1 μm at the final visit (Table 1). The disruption of disruption was more accentuated than ELM disruption at baseline and at 18 months (Table 1). The disruption of ELM at baseline was correlated with its value at the final evaluation ($P = 0.001$), but the EZ disruption at baseline had no such correlation ($P = 0.272$). There was also a statistically significant ($P = 0.035$) correlation between restoration of the EZ and ELM.

EZ Swelling

At baseline, in the 2000-μm subfoveal B-scan, a focal or diffuse EZ swelling was evident in 72% of eyes. At 18 months, only 30% of the eyes showed such swelling ($P = 0.001$).

Subretinal Hyper-Reflective Exudation

Considering the 2000-μm subfoveal B-scan, SHE was present in 52% of eyes at baseline; at 18 months, only 6% of eyes showed this type of lesion ($P = 0.001$).

TABLE 2. Correlation Between Different Morphological Parameters and BCVA Gain

Parameters	Gain <5 ETDRS Letters, *n* = 29, 58%	Gain ≥5 ETDRS Letters, *n* = 21, 42%	*P* Value
BCVA at baseline, ETDRS letters	66.7 ± 12.5	55.8 ± 11.3	**0.001**
CMT at baseline, μm	343 ± 64	410 ± 103	**0.019**
CMT at 18 mo, μm	272 ± 52	304 ± 78	0.154
CMT change, μm	71 ± 82	107 ± 87	0.118
ELM disruption at baseline, length in μm	251 ± 363	516 ± 336	**0.002**
ELM disruption at 18 mo, length in μm	182 ± 274	198 ± 237	0.585
ELM restoration, length in μm	69 ± 210	317 ± 284	**0.001**
EZ disruption at baseline, length in μm	755 ± 361	776 ± 289	0.835
EZ disruption at 18 mo, length in μm	333 ± 336	410 ± 307	0.361
EZ restoration, length in μm	422 ± 440	366 ± 398	0.687
EZ swelling at baseline, focal/diffuse	71	72	0.94
EZ swelling at 18 mo, focal/diffuse	38	24	0.356
SRF at baseline, %	80	79	0.887
SRF at 18 mo, %	24	21	0.999
Cystoid spaces at baseline, %	38	44	0.637
Cystoid spaces at 18 mo, %	19	7	0.223
SHE at baseline, %	57	48	0.540
SHE at 18 mo, %	0	10	0.254

Gain measured as <5 or ≥5 ETDRS letters.

Central Macular Thickness

The mean CMT improved significantly at 18 months ($P = 0.001$) reducing from a baseline value of 382.4 ± 11.9 μm to 290.6 ± 69.5 μm (Table 1). We observed a statistically significant ($P = 0.001$) correlation between the baseline and the final CMT value. Also, the CMT reduction was correlated to ELM restoration ($P = 0.009$), but not to EZ restoration or BCVA improvement ($P = 0.252$ and $P = 0.320$, respectively).

Additional Data

The presence of SRF, CS, and PED had statistically significant changes between the baseline and final evaluations. These are summarized in Table 1.

DISCUSSION

Different qualitative and quantitative parameters usually aid the treatment decision of an active eAMD lesion: BCVA loss, increase in retinal thickness, presence of macular hemorrhage, angiographic evidence of type II choroidal neovascular membrane, and evidence of fluid accumulation (i.e., retinal cystoid spaces and subretinal fluid).[13,19,21] The present study focused on the microstructural changes in the foveal area of

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treatment-naïve neovascular AMD, at baseline and at 18 months, after aflibercept therapy; these changes were then correlated with visual function.

All the features related to the exudative activity of eAMD disease—such as cystoid spaces, SRF, PED, or EZ swelling—were substantially reduced ($P = 0.001$) in our study following IAI. These results are consistent with previous studies concerning anti-VEGF treatment outcomes in eAMD.[15,16,19]

Recently, many authors have focused their attention on the presence of SHE, defining it on the basis of treatment response to anti-VEGF, as a phenomenon of inflammatory origin.[19,20,22,23] Ores et al.[19] demonstrated a total or partial regression of the "gray hyper-reflective subretinal lesion" in 93% of the cases 2 months after ranibizumab intravitreal treatment. These results are in accordance with another study,[23] which highlighted that subretinal tissue volume (measured by time-domain OCT) was significantly reduced after intravitreal ranibizumab, by an average of 0.07 mm^3 per month. In our study, SHE underwent a substantial reduction ($P = 0.001$) from 52% at baseline to 6% at 18 months. This, in our opinion, could be in favor of the exudative nature of SHE.

In the present study, a decrease in CMT from baseline to 18 months, although statistically significant, was not associated with improved visual function ($P = 0.320$). This was in accordance with recent findings,[10,24] and highlights the necessity of additional morphologic features that help estimate the visual prognosis of patients undergoing anti-VEFG treatment.

In our quantitative assessment of the subfoveal outer retinal layers, both the ELM and the EZ disruptions underwent a statistically significant improvement ($P = 0.001$) from baseline to 18 months. However, only the ELM disruption at 18 months was proportional to its baseline value ($P = 0.001$). The restoration in the ELM and EZ were correlated ($P = 0.035$), but only the ELM restoration had a direct impact on BCVA improvement at 18 months ($P = 0.018$). Several quantitative and nonquantitative analyses have reported that the ELM condition was the most important factor influencing visual function at baseline.[6–9,25–28] Roberts et al.[10] reported that ELM alterations had a significant impact on visual acuity at baseline, and at 12 and 24 months. Oishi et al.[8] showed that ELM status was more highly correlated with BCVA than was the IS/OS junction possibly because the IS/OS status reflects visual acuity loss only in those with mild photoreceptor damage. Changes of IS/OS may be too sensitive to evaluate diseases, such as AMD, that cause severe retinal damage.

The comparison analysis focused on different OCT findings and BCVA improvement, in which patients were divided into two groups on the basis of their visual improvement ($<$ or ≥ 5 ETDRS letters) at 18 months, highlighted a statistically significant difference between the two groups only in the case of ELM disruption at baseline ($P = 0.002$); ELM restoration ($P = 0.001$); and CMT at baseline ($P = 0.019$). Interestingly, lower CMT values or ELM disruption at baseline were associated with a lesser degree of BCVA improvement after treatment. Thus, an initially better CMT did not guarantee significantly greater visual improvement, as the BCVA gain was not necessarily associated with higher visual acuity.[24] Therefore, one possible hypothesis could be that initial conditions of greater damage, characterized by higher values of CMT and ELM disruption and associated with lower visual acuity, might undergo substantial improvement, even if they remained at a lower level of BCVA.[24]

Our results demonstrate the main role of ELM in determining the visual outcome of eAMD patients after IAI. A recent study,[29] which did not evaluate the length of disruption, reported that the presence of ELM in the foveal area could determine a better outcome at 12 months after IAI. The external limiting membrane represents the junction-zone between Müller cells and photoreceptors and could be a hallmark for photoreceptor function. Therefore, its integrity might be related to the visual function after treatment.[8,10,28–32] Many authors have hypothesized different roles for ELM in visual function: it could work as an osmotic or mechanic barrier for macromolecules[33,34] or provide structural support to Müller cells in order to maintain the correct refractive indices of the different retinal layers.[35] A recent study pointed out that the condition of ELM reflects the integrity of photoreceptor cell bodies, while the EZ line might represent the integrity of the outer segments; this could explain the reason for the functional link between ELM and photoreceptor integrity.[31,36]

We are aware of the limits of the present study, mainly due to its retrospective nature, the limited number of patients, the evaluation of only one single horizontal B-scan, and the qualitative evaluation of the outer retinal layers which, although conducted in a masked fashion, could suffer from the subjective nature of the assessment.

In conclusion, our study demonstrated the safety and efficacy of intravitreal Aflibercept injection, administered as a fixed regimen, in treating exudative AMD. We also highlight the importance of comprehensive evaluation of the outer retinal layers, both for treatment decision and functional prognosis. In common clinical practice, the management decision of a patient affected by eAMD generally depends on the presence of exudative phenomena (i.e., subretinal fluid, cystoid spaces). However, the evaluation of the ELM status, as a marker of photoreceptor integrity, should be an integral part of the diagnostic process to enable the determination of future prognosis.

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