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ORIGINAL ARTICLE

Exudative age-related macular degeneration lesion components predicting microperimetric retinal sensitivity during anti-vascular endothelial growth factor treatment

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Abstract

Purpose: To analyse the effect of exudative age-related macular degeneration (eAMD) lesion components on retinal sensitivity during anti-vascular endothelial growth factor treatment.

Methods: Visual acuity, fluorescein and indocyanine green (ICG) angiographies, autofluorescence images, microperimetries and optical coherence tomographies (OCTs) of 24 eyes of 24 patients were prospectively analysed in a 2-year study of pro-re-nata bevacizumab treatment for eAMD. Microperimetries were aligned with the OCTs, angiographies and autofluorescence images. Thicknesses of the neuroretina, pigment epithelial (RPE) elevation, neuroepithelial detachment (NED), subretinal tissue (SRT) and cystic intraretinal fluid were measured under each stimulus site, and areas of type 1 and type 2 macular neovascularizations (MNVs), ICG plaque, haemorrhage and RPE atrophy were identified. The effects and predictive values of lesion components on retinal sensitivity were analysed with multivariate mixed linear models for repeated measurements.

Results: The overall microperimetric retinal sensitivity increased during the first year (from 10.1 dB at baseline to 11.9 dB at 1 year; $p=0.021$, Wilcoxon signed ranks), but remained the same during the second year (11.5 dB, $p=0.301$). The baseline lesion components most strongly predicting deteriorated sensitivity at 1 year were RPE atrophy, the area of Type 2 MNV, intraretinal cysts, haemorrhage, Type 1 MNV and retinal thickening >350 µm. NED and RPE elevation had only small effects. At 2 years, the predictive values of the baseline lesion components remained quite unchanged.

Conclusion: The most powerful predictors of retinal sensitivity loss during 2 years of treatment were RPE atrophy, areas of haemorrhage, the area of MNVs, intraretinal cysts and SRT. RPE elevation and NED had lesser effects.

KEYWORDS
anti-VEFG treatment, exudative age-related macular degeneration, fluorescein angiography, microperimetry, optical coherence tomography, predictive factors, treatment response

1 | INTRODUCTION

The introduction of anti-vascular endothelial growth factor (VEGF) therapy brought a new dimension to the treatment of exudative age-related macular degeneration (eAMD) (Rosenfeld et al., 2006). Multiple studies have now proven the treatment effective in reducing visual loss, decreasing the activity of neovascularization as well as improving macular anatomy seen in optical coherence tomography (OCT) (Rofagha et al., 2013). The positive effect on function has been shown not only with the improvement of distance visual acuity (VA), but also with reading vision, reading speed and the quality of life (Munk et al., 2013). The exact mechanisms of functional improvement or deterioration, however, are not completely understood especially in the long-term perspective. Particularly intriguing is the role of subretinal, intraretinal and sub-retinal pigment epithelial (RPE)

fluid in VA changes, with the intraretinal fluid being associated with a worse outcome, whereas subretinal fluid may even be associated with a better VA. The effect of other morphological features of the macular area in exudative AMD, such as neovascular complexes, haemorrhage and atrophy has also been described (Sharma et al., 2016; Sulzbacher et al., 2014).

Microperimetry not only allows distinguishing VA from spatial sensitivity, but also enables a more accurate analysis of the effects of different macular changes on retinal sensitivity. Studies using microperimetry have shown a correlation between mean retinal sensitivities and VA (Parravano et al., 2010; Squirrell et al., 2010). The decline in retinal sensitivity in eAMD, however, is not homogenous. Overlaying the microperimetry grid with fundus images has shown the sensitivity to be especially decreased in areas with fibrosis, atrophy and haemorrhage (Tezel et al., 1996). However, microperimetry analysis based on fundus image overlays only gives restricted information on the relation of retinal sensitivity to the three-dimensional topography of an AMD lesion, whereas alignment with OCTs allows a more detailed analysis of the role of specific lesion components.

Using the Spectral OCT/SLO (OPKO/OTI) recording simultaneous microperimetry and aligned OCT, we have previously analysed recent wet AMD lesions and found the reduced sensitivity to be associated especially with areas of CNV, RPE-elevation and subretinal tissue (Hautamäki et al., 2014). Similar findings regarding RPE have also been reported by Sulzbacher et al. (2014).

To our knowledge, only few studies have prospectively analysed the retinal sensitivity/OCT structure relationship during anti-VEGF treatment in treatment naïve eAMD eyes. Sulzbacher et al. analysed 22 patients with varying ranibizumab doses and fixed injection regimens for up to 12 months of treatment. Since current eAMD treatments are longstanding, and even in the most active treatment strategies the VA results tend to decrease with time, an analysis of data from a longer follow-up might offer further insight into the functional outcome of long-term anti-VEGF treatments. Thus, we analysed which eAMD lesion characteristics affect and predict the retinal sensitivity during a 2-year prospective follow-up on patients treated with bevacizumab using the PRN protocol and report our result here.

2 | METHODS

This report is based on our prospective 2-year study of bevacizumab treatment for recent, previously untreated eAMD on 50 patients between May 2008 and April 2012. The correlations between the retinal sensitivities and OCT and angiographic lesion characteristics at the baseline of this study have been reported earlier (Hautamäki et al., 2014), as well as the anterior chamber flare fluctuations and the genetic associations of short and long-term treatment responses (Hautamäki et al., 2016).

The inclusion criteria for this study were age >50 years, a newly diagnosed exudative AMD without prior treatment, a subfoveal or juxtafoveal CNV lesion and a visual acuity ≥20/200. The exclusion criteria were any other major eye disease than eAMD, the presence of Type 3 macular neovascularization (MNV), macular haemorrhage >2.5 disc diameters, or significant media opacities (described in detail in Hautamäki et al., 2014).

The patients received bevacizumab (Avastin®; Genentech Inc.) treatment at the first visit and were then examined monthly. During the first year, retreatment was given if any fluid intraretinally or subretinally in OCTs or a new haemorrhage was detected in the macular area. During the second year, the treatment was discontinued after 14 injections for stationary intraretinal cysts until progression was detected (Hautamäki et al., 2014).

The study protocol adhered to the tenets of the Declaration of Helsinki and was approved by the local ethics committee. A written informed consent was obtained from all participants before enrolment. The trial was included in the Australian New Zealand Clinical Trials Registry before beginning the enrolment (ACTR number 12608000223336).

The analysis of correlations between the microperimetric retinal sensitivities and the lesion characteristics detected in OCTs, angiographies and autofluorescence images is based on the results obtained at baseline, at 1 and at 2 years after the initiation of anti-VEGF treatment. Of the 50 patients enrolled, 47 completed the first and 43 the second year of follow-up. The three patients discontinuing the follow-up before the end of the first year completed seven, eight, and nine visits, respectively. These discontinuations were due to other medical problems, due to VA loss despite dry macula and due to severe uveitis of the study eye after the eighth bevacizumab injection. Four patients discontinued after completing the first year of follow-up because of the following reasons: one for retinal detachment after 12 visits, one for repeatedly rising eye pressure after mydriatic drops and need for cataract surgery after 13 visits, one for non-response to the treatment after 13 visits, and one for a dense cataract formation after 16 visits.

Of the 43 patients completing the 2-year follow-up, 24 had reliable microperimetries, good quality OCTs and angiographies available at baseline and at 1 and 2 years. The other patients were excluded because of unstable fixation, co-operational problems or missing data from certain visits due to software-related data loss.

In the main follow-up study, the monthly visit examinations included best corrected VA tested with the Early Treatment Diabetic Retinopathy Study (ETDRS) charts at 2 m, contrast sensitivity (CS) tested with the Pelli–Robson charts at 1 m, biomicroscopy as well as OCT and microperimetry recordings.

2.1 | Fluorescein and indocyanine green angiographies

Fluorescein (FA) and indocyanide green angiographies (ICGA) were performed at baseline and 1 and 2 years. The Topcon Imagenet (Topcon Inc.) or Heidelberg retinal angiograph (Heidelberg Engineering) systems were used in the angiographies. The areas of Type 1 and Type 2 MNVs, haemorrhages and serous RPE detachments (PEDs) were determined at baseline, but at 1 and 2 years a

single lesion area type was defined, containing all MNV subtypes, scar tissue and serous PED. The boundaries of the lesions in the angiographies were drawn manually and aligned with the OCT images. The neovascular lesions were identified as macular neovascularization type 1 or type 2 lesions according to the criteria in Consensus on Neovascular Age-Related Macular Degeneration Nomenclature Study Group (Spaide et al., 2020). In addition, late fluorescing plaques in ICG angiographies were recorded and measured. The fundus autofluorescence images were analysed and the areas were classified either as atrophic or non-atrophic.

2.2 | OCT and microperimetry

We used the Spectral domain OCT/SLO models B (13 baseline visits) and E (all other 59 visits) because of technical problems with the model B unit. The device captures 28 000 A-scans per second with an axial resolution of 6 µm. The system uses a scan of 64 lines, 256 A-scans or 512 A-scans per line, both high-speed capture reconstructing a 9-by-9 m 3D map of the macula. The one with less artefacts was the one used in alignment.

The Polar 3 pattern microperimetry program of Spectral OCT/SLO with 200 ms stimulus, size Goldman III, interval 2 s, step size 1 dB, a cross as fixation target, threshold strategy 4–2 and background illumination of 10 cd/m^2 was used. The microperimetry autotracks retinal landmarks before each stimulus to enact a reproducible position. The central 11 degrees of the visual field was analysed with 28 points organized as follows: one central circle with four points, one middle circle with 12 points and one outer circle with 12 points (Figure 1).

The patients were thoroughly familiarized with the procedure before performing the examinations. The microperimetry was performed in a dim room with time reserved for the patient to adapt to this illumination as described earlier (Hautamäki et al., 2014).

We considered the fixation stable if 75% of the fixations were within a 2 degrees circle and the number of false positives was less than 10%, using the criteria described previously (Fujii et al., 2002). In the two models of the Spectral-domain OCT/SLO used the ranges of threshold values in microperimetry were <4–20 dB (model B) and <0–20 dB (Model E). In the multivariate data analysis, the model used (B or E) had no effect on the final results.

2.3 | Microperimetry and OCT alignment

The microperimetries were automatically aligned with the OCTs and manually aligned with the angiographies and autofluorescence images by aligning the major vessels. Under each stimulus site of the microperimetry the thicknesses of the neuroretina, RPE, neuroepithelial detachment (NED), subretinal tissue (SRT) and cystoid spaces were identified and manually measured. In the subretinal space, hyperreflective areas were considered to be subretinal tissue and hyporeflective to be subretinal fluid (NED). Neuroretinal thickness was further divided into three categories: <150 µm, 151–320 µm and over 320 µm to better analyse the effect of retinal atrophy during a longer treatment.

The areas of MNV type I and II in FA, ICG plaque, haemorrhage and RPE atrophy were identified using the aligned angiographies and autofluorescence images.

2.4 | Statistical analysis

Multivariate mixed linear model analysis (LMM) of IBM SPSS STATISTICS version 24 (IBM Corp.) designed for repeated measurements and correcting for interindividual differences in the measurement levels were used to estimate the effects of lesion components on retinal sensitivity during the PRN treatment. The analysis included 28 repeated measurements of retinal sensitivity for 24 patients at baseline, 1 and 2 years. The baseline lesion components were also used as predictors of retinal sensitivity at 1 and 2 years, and 1-year lesion components were used as predictors at 2 years. The models were built using a scaled identity matrix as the repeated covariance type and including an individual-level random intercept. Wilcoxon signed-rank test was used to compare the changes observed in VA and retinal sensitivity during the follow-up. A two-tailed p-value <0.05 was considered statistically significant.

3 | RESULTS

Demographics of the patients and lesion characteristics are presented in Table 1.

The mean retinal sensitivity increased during the first year (median, baseline, 10.1 dB, range 3.7–14.0 dB; to 11.9 dB at 1 year, range 2.8–14.3 dB, $p=0.021$, Wilcoxon signed ranks), but remained the same during the second year (median 11.5 dB, range 2.0–14.7 dB, $p=0.301$). Similarly, the mean VA increased only during the first year (median, baseline, 72.0 ETDRS letters, range 45–85; to 77.5 letters at 1 year, range 65–85, $p=0.006$). At 2 years the mean VA was 77.0 letters (range 64–85, $p=0.808$). Figure 2 shows the means of retinal sensitivity, visual acuity and contrast sensitivity at 0, 1 and 2 years.

At baseline, the lesion components affecting most the retinal sensitivity were RPE atrophy [LMM, effect size (ES) 6.1, $p<0.0001$], presence of haemorrhage (ES 4.4, $p<0.0001$), Type 2 MNV (ES2.9, $p<0.0001$), intraretinal cysts (ES 2.5, $p<0.0001$) and subretinal tissue (ES 2.4, $p<0.0001$). The presence of RPE elevation (ES 1.5, $p<0.0001$), Type 1 MNV (ES 1.4, $p<0.0001$) and NED (ES 1.1, $p<0.0001$) had moderate effects, whereas the effect of retinal thickening (>320 µm, ES 0.8, $p<0.0001$) was less prominent. Figure 3a shows the retinal sensitivities over each lesion component.

At 1 year, the CNV subtypes were not distinguishable in FA and the areas of type 1 and type 2 MNVs were grouped together with fibrosis and PEDs to form a single angiographic lesion area. None of the analysed sites had any haemorrhage present. The lesion components having the most pronounced effects on retinal sensitivities were RPE atrophy (ES 9.1, $p<0.0001$), neuroretinal thinning (<150 µm, ES 3.3, $p=0.004$) and subretinal tissue (ES

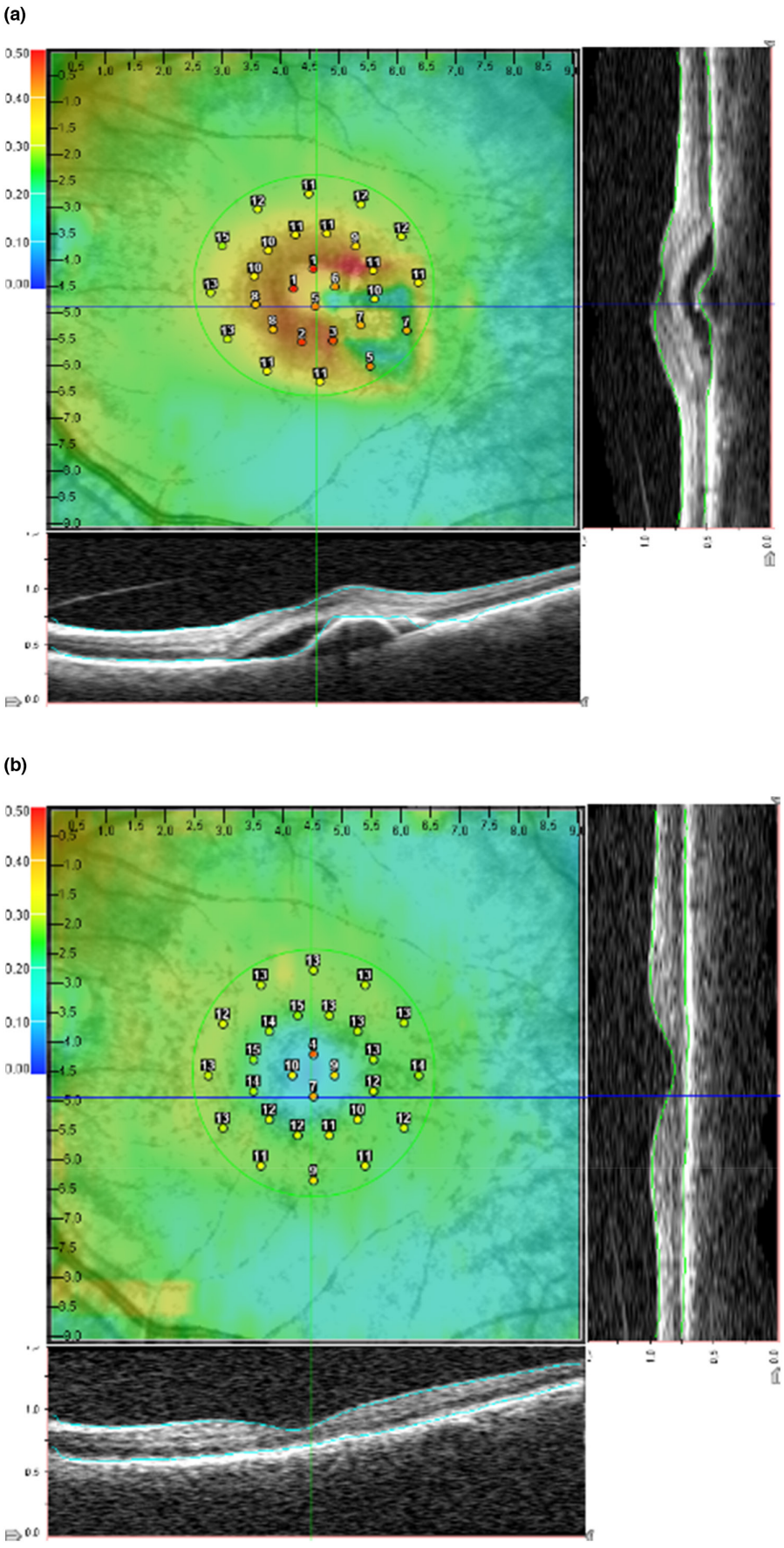

FIGURE 1 Microperimetry aligned with a three-dimensional OCT topography map. The OCT corresponding to the microperimetry stimulus site can be seen. (a) From baseline, (b) from the same patient at 1 year. OCT, optical coherence tomography.

2.5, $p<0.0001$). The effect of lesion in FA was moderate (ES 1.7, $p<0.0001$), whereas the effect of RPE elevation was less prominent (ES 0.8, $p=0.008$). The presence of NED was not a significant factor. Also, the presence of cysts remained non-significant, probably due to the small number of analysed sites with cystic changes ($n=6$).

However, if the thickness of cystic fluid was taken into account, the effect became significant despite the scarcity of the affected sites ($p=0.011$). Figure 3b shows the retinal sensitivities over each lesion component.

At 2 years, RPE atrophy (ES 6.7, $p<0.0001$), subretinal tissue (ES 3.9, $p<0.0001$) and intraretinal cysts (ES 2.6, $p=0.003$) were the most important determinants of retinal sensitivity. The effects of lesion in FA (ES 1.2, $p<0.0001$), RPE elevation (ES 1.2, $p<0.0001$) and NED (ES 1.1, $p=0.028$) were moderate. Figure 3c shows the retinal sensitivities over each lesion component.

TABLE 1 Patient characteristics.

Patient characteristics	
Sex	
Female, *n*	19
Male, *n*	5
Age, median, at baseline (range)	74 (63–87)
Visual acuity	
ETDRS score, median (range)	76.5 (45–85)
LogMAR, median (range)	0.63 (0.16–1.0)
Lesion type	
Type 1 MNV, *n*	18
Type 2 MNV, *n*	5
Nondefined (serous pigment epithelial detachment covering >50% of lesion area), *n*	1
CNV location	
Subfoveal, *n*	17
Juxtafoveal, *n*	5
Extrafoveal, *n*	2

Abbreviations: CNV, choroidal neovascularization; ETDRS, Early Treatment of Diabetic Retinopathy Study chart; MNV, macular neovascularization.

The baseline characteristics predicting deteriorated sensitivity at 1 year were RPE atrophy, the area of type 2 MNV, intraretinal cysts, haemorrhage, occult CNV and retinal thickening >350 μm. Older age predicted less increase in function. NED and RPE elevation had small effects (Table 2a). At 2 years, the predictive values of the baseline lesion components remained quite unchanged, but the ICG plaque also had some effect (Table 2b).

The lesion components detected after 1 year of treatment predicting worse function at 2 years (Table 2c) were quite similar. The combined area of CNV lesion in FA at 1 year remained a significant predictor, haemorrhage was not present in any of the study eyes at this point of treatment and, in contrast to the baseline characteristics, SRT became a somewhat significant predictor of further deterioration.

4 | DISCUSSION

In this 2-year follow-up study, we found that decreased focal retinal sensitivity occurred primarily in the loci of RPE atrophy, subretinal tissue, haemorrhage, intraretinal fluid, type 2 and type 1 MNV and neuroretinal thinning;

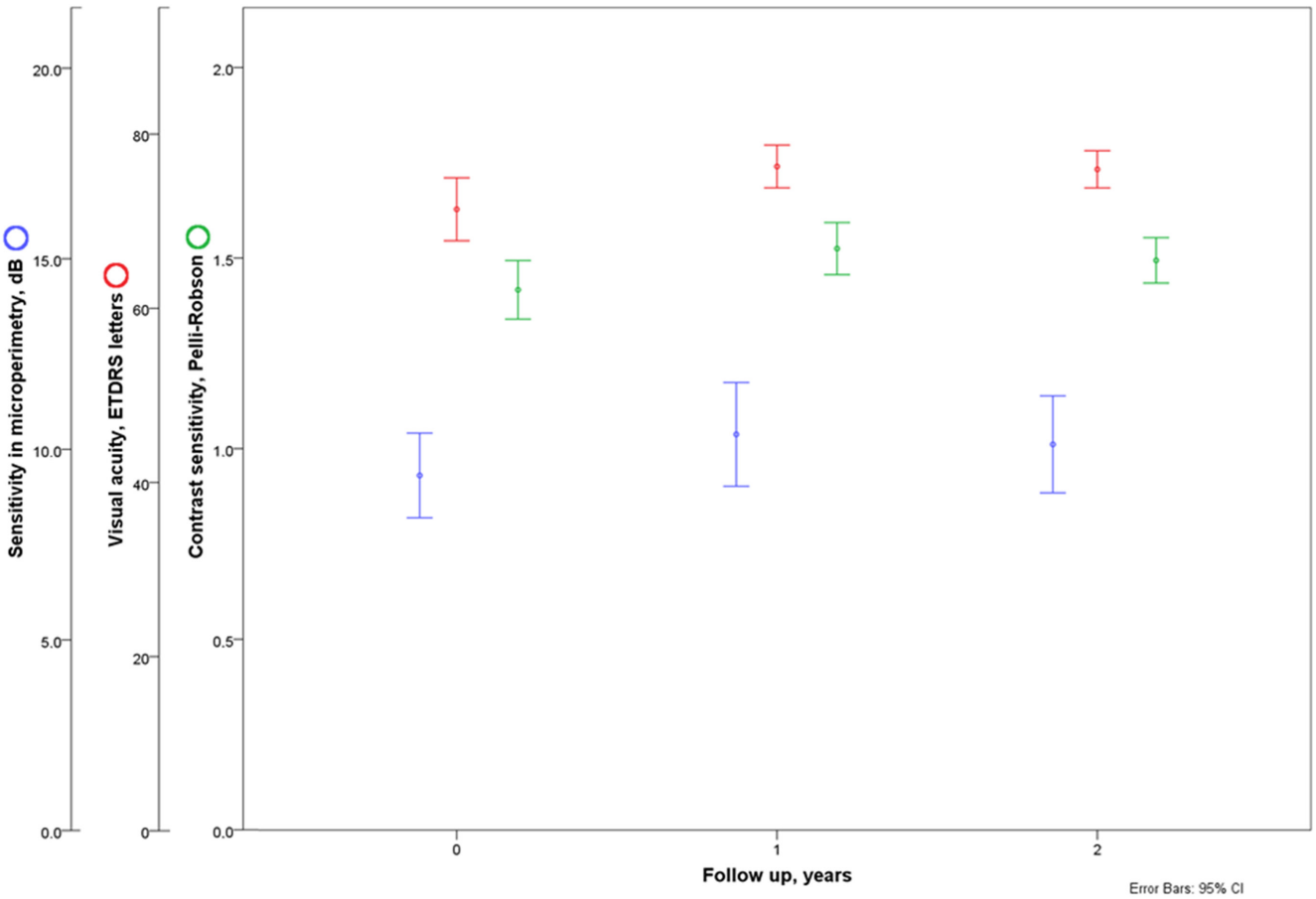

FIGURE 2 Mean retinal sensitivity, VA and contrast sensitivity at baseline, 1 and 2 years. ETDRS, Early Treatment of Diabetic Retinopathy Study chart; VA, visual acuity.

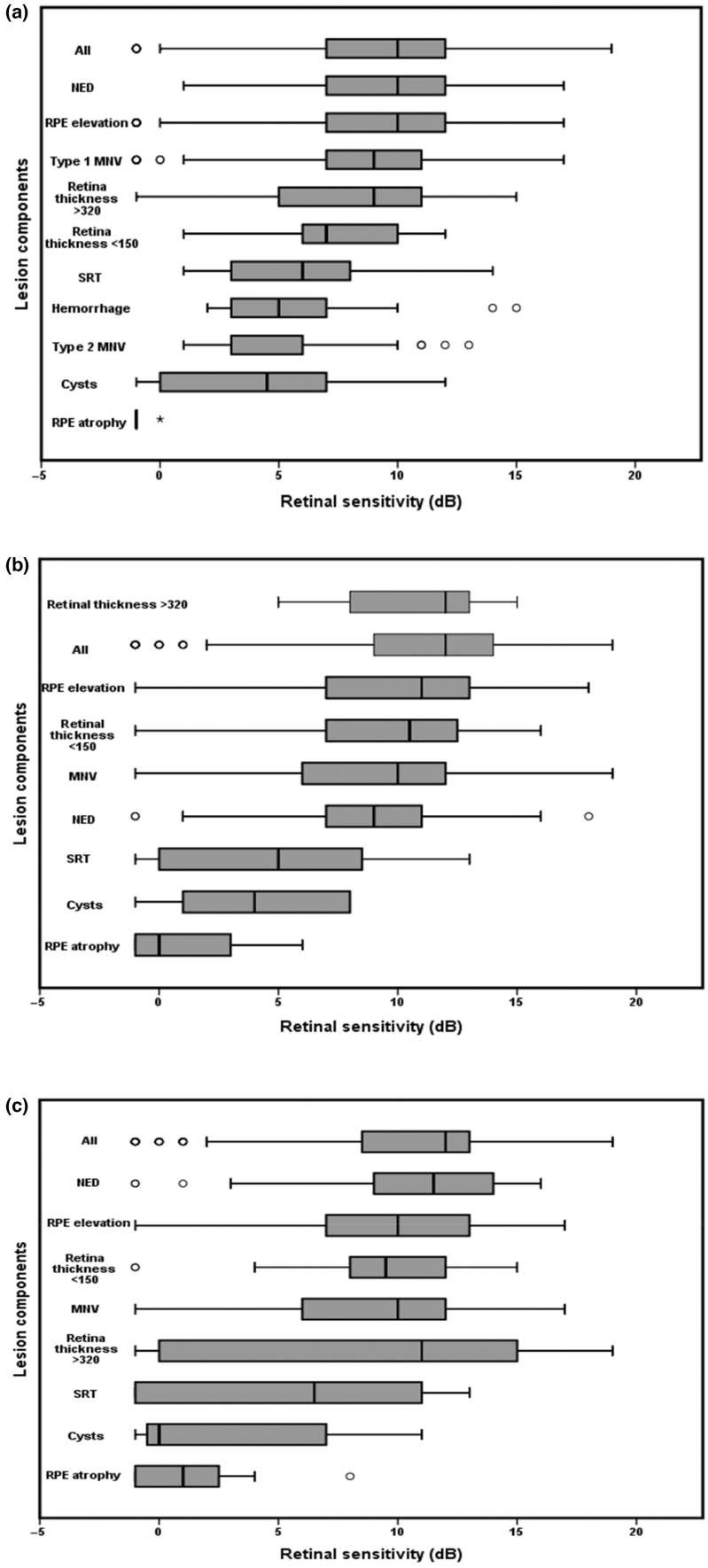

FIGURE 3 Retinal sensitivity at (a) baseline, (b) 1 year and (c) 2 years. MNV, macular neovascularization; NED, neuroepithelial detachment; RPE, retinal pigment epithelium; SRT, subretinal tissue.

the same components shown to be associated with decreased VA in earlier studies (Jaffe et al., 2013; Waldstein et al., 2016).

Visual acuity is an overall measure of function but does not give an exact insight into the tissue changes contributing to decreased function. Various studies have

TABLE 2 Baseline components associated with decreased retinal sensitivity at (a) 1 year, (b) 2 years and (c) lesion components at 1 year associated with decreased retinal sensitivity at 2 years.

Lesion components	Estimate	Std.er	Sig.	95% CI
(a)				
RPE atrophy vs. no RPE atrophy	−6.59	1.29	<0.001	−9.12 to −4.06
Haemorrhage vs. no haemorrhage	−5.30	0.81	<0.001	−6.90 to −3.70
Type 2 MNV vs. no Type 2 MNV	−4.99	0.67	<0.001	−6.31 to −3.67
Intraretinal cysts vs. no cysts	−3.14	0.80	<0.001	−4.70 to −1.58
Type 1 MNV vs. no Type 1 MNV	−1.64	0.33	<0.001	−2.29 to −1.00
PED vs. no PED	−1.19	0.33	<0.001	−1.85 to −0.55
Neuroretinal thickening (>320 μm) vs. normal neuroretina	1.67	0.40	<0.001	0.89 to 2.45
Neuroretinal thinning (<150 μm) vs. normal neuroretina	−1.31	1.30	0.314	−3.86 to 1.2
Middle circle vs. outer circle of stimuli	−0.70	0.32	0.028	−1.32 to −0.08
Inner circle vs. outer circle of stimuli	0.40	0.47	0.390	−0.52 to 1.32
Intercept	10.03	1.69	<0.001	6.71 to 13.25
(b)				
RPE atrophy vs. no RPE atrophy	−6.49	1.02	<0.001	−8.49 to −4.48
Type 2 MNV vs. no Type 2 MNV	−2.89	0.62	<0.001	−4.12 to −1.67
Haemorrhage vs. no haemorrhage	−1.91	0.73	0.009	−3.34 to −0.48
Intraretinal cysts vs. no cysts	−1.78	0.63	0.005	−3.02 to −0.55
Type 1 MNV vs. no Type 1 MNV	−1.28	0.32	<0.001	−1.92 to −0.65
ICG plaque vs. no ICG plaque	−1.14	0.33	0.001	−1.79 to −0.50
NED vs. no NED	−0.87	0.33	0.009	−1.52 to −0.21
Thickness of PED (μm)	0.005	0.0009	<0.001	0.007 to 0.03
Age (year)	0.16	0.07	0.048	0.002 to 0.31
Neuroretinal thinning (<150 μm) vs. normal neuroretina	0.10	0.95	0.296	−0.88 to 2.87
Neuroretinal thickening (>320 μm) vs. normal neuroretina	0.87	0.34	0.011	0.20 to 1.54
Inner circle vs. outer circle of stimuli	−0.24	0.34	0.490	−0.91 to 0.44
Middle circle vs. outer circle of stimuli	−1.06	0.23	<0.001	−1.52 to −0.60
Intercept	−7.64	5.86	0.204	−19.7 to 4.43
(c)				
RPE atrophy vs. no RPE atrophy	−4.52	1.86	<0.001	−8.17 to −0.87
SRT vs. no SRT	−4.35	0.78	<0.001	−5.89 to −2.81
Intraretinal cysts vs. no cysts	−2.92	1.52	0.056	−5.91 to 0.07
ICG vs. no ICG	−2.13	0.40	<0.001	−2.91 to −1.34
PED vs. no PED	−1.17	0.39	0.003	−1.94 to −0.41
Lesion vs. no lesion in FA	−1.10	0.39	0.005	−1.86 to −0.33
Thickness of NED (μm)	0.032	0.01	0.003	0.01 to 0.05
Inner circle vs. outer circle of stimuli	−0.73	0.45	0.230	−1.62 to 0.16
Middle circle vs. outer circle of stimuli	−1.26	0.32	<0.001	−1.89 to −0.64
Intercept	4.10	1.94	<0.035	0.29 to 7.91

Abbreviations: CI, confidence interval; FA, fluorescein angiography; ICG, indocyanine green angiography; MNV, macular neovascularization; NED, neuroepithelial detachment; PED, pigment epithelial detachment; RPE, retinal pigment epithelium; Sig., significance; SRT, subretinal tissue; Std.er, standard error.

been done using microperimetry in eAMD and these have shown a significant improvement of retinal sensitivities during the treatment with anti-VEGF. In many of these studies, the retinal sensitivities of the macular area were measured, however, without taking into account the morphological structures of the measured areas (Cho et al., 2013; Ozdemir et al., 2012; Prager et al., 2008; Squirrell et al., 2010).

With simultaneous use of microperimetry and retinal OCT, however, it is possible to obtain information on the sensitivity and structure of specific loci of the macula. In earlier studies examining focal retinal pathology and retinal sensitivity point-to-point, Tezel et al. showed that chorioretinal scars, RPE atrophy, subretinal haemorrhage, and areas of neovascular membranes were associated with the presence of an absolute scotoma. In that study, microperimetry values were superimposed on colour fundus photographs and fluorescein angiograms. Sulzbacher et al. aligned the sensitivity map manually on the OCT image thus

giving a picture of the morphology at the stimulus location. Their results showed that the improvement in retinal sensitivity depended on the associated morphology with SRF and serous PED giving the best prognosis for improvement while the least improvement was discovered in loci with intraretinal cysts. To our knowledge, there are no previous 2-year studies analysing the effect of eAMD lesion components on retinal sensitivity during anti-VEGF treatment using the OCT/SLO (OPKO/OTI) microperimeter automatically aligning OCTs and microperimetries.

Our results are in line with earlier studies in showing a clear improvement of retinal sensitivity with anti-VEGF treatment within the first year of treatment, but not during the second year. The time span of earlier studies varies from 3 months up to 24 months (Parravano et al., 2010). As such, with the 2-year follow-up, our results represent one of the longest time spans among similar studies. The 2-year follow-up is relevant in the sense that we often see the degradation of vision over longer periods of eAMD treatment.

The problem with light sensitivity tissue correlations in AMD is that different lesion characteristics co-exist at the same locus. In our study, we used multivariate analyses to determine the predictive value of morphology. Our method of analysing the impact of the different lesion components confirmed their order of significance. We found the retinal sensitivity to be especially low at the sites of haemorrhage, atrophy, type 2 MNV and cysts. The decline in retinal sensitivity in atrophy is caused by the lack of viable photoreceptors whilst haemorrhages cause an optical hinder to viewing. In type 2 MNV the new vessels between the neurosensory retina and the RPE probably cause the decrease in sensitivity. The strong correlation between cysts and reduced retinal sensitivity here shows that cysts are an independent marker of retinal dysfunction, in accordance with the findings of Sulzbacher.

In conclusion, it appears that quite similar sets of lesion components are associated with baseline, 1- and 2-year retinal sensitivity losses and their prediction. Thus, a decline in visual activity during a longer follow-up is probably due to an enlargement of the same lesion components rather than the emergence of new ones.

One limitation of our study is that the retinal sensitivities were only analysed at baseline, 1 and 2 years. For an even deeper insight into the changes at an early stage, one will need to analyse data on monthly or even weekly basis. Of course, it would also be interesting to see results from an even longer follow-up. Another limitation is that the analysed data were only from patients who had a stable fixation so the results are representative of patients with a generally better baseline vision, probably less advanced AMD and perhaps better general health than average patients receiving anti-VEGF treatments.

Our study provides new perspectives on the predictive nature of different morphological components of AMD. We have shown that the most powerful predictors of retinal sensitivity loss during 2 years of anti-VEGF treatment were RPE atrophy, Type 2 MNV, cystoid intraretinal spaces and the presence of SRT. Type 1 MNV, PED and NED had lesser effects.

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