

Correlation of OCT Characteristics and Retinal Sensitivity in Neovascular Age-Related Macular Degeneration in the Course of Monthly Ranibizumab Treatment

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PURPOSE. To evaluate the functional treatment response 3 months and 12 months after monthly ranibizumab in neovascular age-related macular degeneration (NAMd).

METHODS. Twenty-six eyes showing treatment-naïve NAMd were examined with the Heidelberg Spectralis OCT (SD-OCT) and the Nidek MP-1 microperimeter (MP) at baseline, after 3 months, and after 12 months of monthly ranibizumab therapy. Each test point of light sensitivity was transferred to the corresponding location on SD-OCT, and subsequently the microperimetric results were evaluated with respect to the following OCT findings: neovascular complex (NVC), subretinal fluid (SRF), intraretinal fluid (IRF), intraretinal cystoid space (IRCS), serous pigment epithelium detachment (SPED), and fibrovascular pigment epithelium detachment (FPED).

RESULTS. Loci of an initial NVC improved significantly from a mean retinal sensitivity value of 2.6 dB \pm 0.8 dB at baseline to 7.4 dB \pm 0.9 dB ($P < 0.0001$) at month 12. Initial SRF, IRF, and IRCS improved significantly from a mean value of 5.1 dB \pm 0.9 dB to 12.4 dB \pm 0.9 dB ($P < 0.0001$), 4.0 dB \pm 1.0 dB to 9.3 dB \pm 0.9 dB ($P < 0.0001$), and 3.4 dB \pm 0.9 dB to 8.2 dB \pm 0.9 dB ($P < 0.0001$), respectively. An initial SPED improved significantly from a mean retinal sensitivity value of 1.9 dB \pm 1.1 dB at baseline to 9.4 dB \pm 1.1 dB ($P < 0.0001$) at month 12; a FPED improved significantly from 5.2 dB \pm 0.9 dB at baseline to 7.6 dB \pm 0.9 dB ($P < 0.0001$) at month 12.

CONCLUSIONS. Functional benefit could be detected at all locations of macular pathology, with a lower benefit in the case of FPED and in the case of additional IRCS, and a marked benefit for all types of macular edema. (<https://eudract.ema.europa.eu/>, number 2006-005684-26.) (*Invest Ophthalmol Vis Sci.* 2013;54:1310-1315) DOI:10.1167/iovs.12-11046

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The clinical course of neovascular age-related macular degeneration (NAMd) is multifactorial and undergoes a series of morphological changes in the retina, below the retina, and at the level of the retinal pigment epithelium (RPE). These alterations include neovascularization, sub- and intraretinal exudation, and pigment epithelium detachment and are associated with unpredictable progression leading to a substantial visual function loss.¹⁻³ Current treatment strategies target the inhibition of vascular endothelial growth factor (VEGF) as one of the leading pathogenetic factors in development and progression of age-related macular degeneration (AMD). The significant morphological and functional benefit of anti-VEGF treatment has been reported in several studies.⁴

Ranibizumab, a humanized monoclonal antibody fragment, has been shown to be an effective inhibitor of VEGF and has been approved by the US Food and Drug Administration for treatment of NAMd.^{5,6}

The long-term results of the MARINA trial cohort show a >15-letter visual acuity (VA) gain in 30% of patients and a >15-letter loss in only 9% after 2 years. Characteristics of patients losing vision were a better baseline VA, a larger total lesion area as assessed by fluorescein angiography, and larger areas of leakage at baseline.⁷

Spectral-domain optical coherence tomography (SD-OCT) plays a pivotal role in the diagnosis of AMD and subsequently in treatment and retreatment decisions, enabling a deeper insight into the histology-like depiction of retinal layers, especially the photoreceptor layer and the pigment epithelium.

As shown in our previous study, the concept of structure-function correlation through an exact manual superimposition of the retinal sensitivity map to SD-OCT data using Spectralis OCT and fundus-related microperimetry (MP-1; Nidek, Gama-gory, Japan) enabled the identification of consistent associations between high-resolution imaging and visual function.⁸

In an extended step, the functional treatment response of distinct initial SD-OCT findings was evaluated using the follow-up mode of both imaging devices.

Comprehension of the dynamic therapeutic response morphologically and functionally enables exact evaluation of treatment success, as well as the detection of prognostic factors resulting from characteristic SD-OCT findings.

PATIENTS AND METHODS

The present study was conducted at the Department of Ophthalmology of the Medical University of Vienna. The study was approved by the local ethics committee and adhered to the tenets of the Declaration of Helsinki. Every patient gave written informed consent prior to study inclusion. Twenty-six eyes with untreated subfoveal choroidal neovascularization secondary to AMD were included. Each patient received

TABLE 1. Mean Retinal Sensitivity Change and Standard Deviation in Decibel for the Corresponding Outer Retinal Layer Condition

Finding	Sensitivity Change Baseline to 3 Months		Sensitivity Change Baseline to 12 Months		Sensitivity Change 3 to 12 Months		Eyes	Test Points
	Mean ± SD, dB	P Value	Mean ± SD, dB	P Value	Mean ± SD, dB	P Value		
RPE absent	4.4 ± 0.3	< 0.0001	5.6 ± 0.4	< 0.0001	1.2 ± 0.4	= 0.0204	23	183
RPE discontinuous	3.7 ± 0.2	< 0.0001	4.4 ± 0.4	< 0.0001	0.7 ± 0.2	= 0.1133	26	419
IS/OS absent	3.8 ± 0.2	< 0.0001	5.0 ± 0.3	< 0.0001	1.2 ± 0.3	< 0.0001	26	369
IS/OS discontinuous	4.1 ± 0.3	< 0.0001	4.6 ± 0.4	< 0.0001	0.5 ± 0.3	= 0.8558	26	268
ELM absent	3.6 ± 0.2	< 0.0001	4.4 ± 0.3	< 0.0001	0.8 ± 0.2	= 0.0106	26	421

Condition of outer retinal layers at baseline and mean retinal sensitivity change with standard error in decibels (dB) and P value from baseline to month 3, from baseline to month 12, and from month 3 to month 12 after monthly ranibizumab injections.

intravitreal injections of 0.5 mg ranibizumab at monthly intervals for 1 year. A complete clinical examination with slit-lamp biomicroscopy, ophthalmoscopy, and fundus photography, as well as fluorescein angiography (FA), SD-OCT, and microperimetry, was performed at baseline, month 3, and month 12. OCT images were obtained with a spectral-domain imaging device (Spectralis HRA + OCT; Heidelberg Engineering, Heidelberg, Germany). The infrared+OCT tool of the Spectralis OCT was used to assess a horizontal volume scan involving 49 scans with 25 frames. The scan diameter was 6000 μm. The Micro Perimeter 1 (MP-1; Nidek) was used to perform fundus-monitored microperimetry. Microperimeter settings were based on a 4-2-1 staircase strategy with Goldmann III-size stimuli (stimulus intensity range, 0–20 dB). A Cartesian grid with 33 stimulus locations covering the central area of 12° × 12° was selected, while a 3° ring was used as the fixation target.

VirtualDub (version 1.8.6; available at www.virtualdub.org) software and Paint.NET (version 3.36; available at www.getpaintnet.net) software were used to manually superimpose MP-1 color fundus photographic (FP) images, including the sensitivity map of each eye, on corresponding infrared images of the SD-OCT.

ImageJ software (available at http://rsbweb.nih.gov/ij/) was used to transfer each stimulus location in the sensitivity map to the corresponding location of the SD-OCT B-scan true to scale.⁸ The microperimetry spot size measures 132 μm, assuming a diameter of 26 arc minutes (or 0.433333°) for a Goldmann III stimulus.

Image Analysis

After transfer of each stimulus location of the FP to the SD-OCT B-scan, the retinal morphology at each test point was evaluated using the following tags: neovascular complex (NVC), fibrovascular pigment

epithelium detachment (FPED), serous pigment epithelium detachment (SPED), subretinal fluid (SRF), intraretinal fluid (IRF) and intraretinal cystoid space (IRCS). Simultaneously the integrity of the photoreceptor inner and outer segment layer (IS/OS), the RPE, and the external limiting membrane (ELM) was evaluated. The OCT reading was reviewed by an experienced reader (MEK).

For each morphologic alteration, the corresponding retinal sensitivity results were identified at baseline, at month 3, and at month 12. Use of the follow-up mode of the SD-OCT device and the microperimeter device guaranteed exact results.

Statistical Analysis

The effects of the OCT findings at baseline on retinal sensitivity levels and on changes in sensitivity levels due to therapy considering the three time points (baseline, 3 months, and 12 months) were evaluated using repeated measures analysis of variance (ANOVA) models. Within these ANOVA models, the repeated factor time and the random block factor patient were considered together with the respective OCT finding as a fixed factor. Results of the ANOVA models are presented as estimated means (± standard errors), including the respective P values. Changes due to therapy at 3 and 12 months are presented by the estimated mean differences (± standard error) and P values and were corrected for multiple pairwise comparisons by the Tukey-Kramer method.

RESULTS

A total of 827 locations detecting focal retinal sensitivity in 26 eyes of 26 patients with NAMD were evaluated before and at

TABLE 2. Mean Retinal Sensitivity Change and Standard Deviation in Decibel for the Corresponding OCT Alteration

Finding	Sensitivity Change Baseline to 3 Months		Sensitivity Change Baseline to 12 Months		Sensitivity Change 3 to 12 Months		Eyes	Test Points
	Mean ± SD, dB	P Value	Mean ± SD, dB	P Value	Mean ± SD, dB	P Value		
SPED	5.6 ± 0.4	< 0.0001	7.5 ± 0.8	< 0.0001	1.9 ± 0.7	< 0.0001	11	56
SRF	5.4 ± 0.4	< 0.0001	7.3 ± 1.0	< 0.0001	2.0 ± 0.4	< 0.0001	20	161
NVC	3.8 ± 0.0	< 0.0001	4.8 ± 0.5	< 0.0001	1.1 ± 0.6	= 0.0870	19	138
NVC without IRCS	4.9 ± 0.5	< 0.0001	5.9 ± 0.6	< 0.0001	1.1 ± 0.5	= 0.6129	17	88
NVC with IRCS	1.9 ± 0.7	= 0.1850	3.0 ± 0.8	= 0.0098	1.2 ± 0.5	= 0.777	11	50
IRCS	2.9 ± 0.5	< 0.0001	4.8 ± 0.6	< 0.0001	1.9 ± 0.4	< 0.0002	16	108
IRCS without NVC	3.8 ± 0.6	< 0.0001	6.4 ± 0.8	< 0.0001	2.7 ± 0.6	< 0.0009	14	58
IRF	5.1 ± 0.4	< 0.0001	5.4 ± 0.5	< 0.0001	0.3 ± 0.4	= 0.9778	20	159
IRF without NVC	5.8 ± 0.5	< 0.0001	6.0 ± 0.6	< 0.0001	0.1 ± 0.5	= 1.0	19	99
IRF with NVC	4.0 ± 0.6	< 0.0001	4.6 ± 0.8	< 0.0001	0.5 ± 0.6	= 0.999	13	60
FPED	2.4 ± 0.6	< 0.0001	2.5 ± 0.6	< 0.0001	0.1 ± 0.4	= 0.90	14	129

Initial SD-OCT findings at baseline and mean retinal sensitivity change with standard error in decibels (dB) and P value from baseline to month 3, from baseline to month 12, and from month 3 to month 12 after monthly ranibizumab injections. Number of eyes and number of test points refer to the presence of the respective finding.

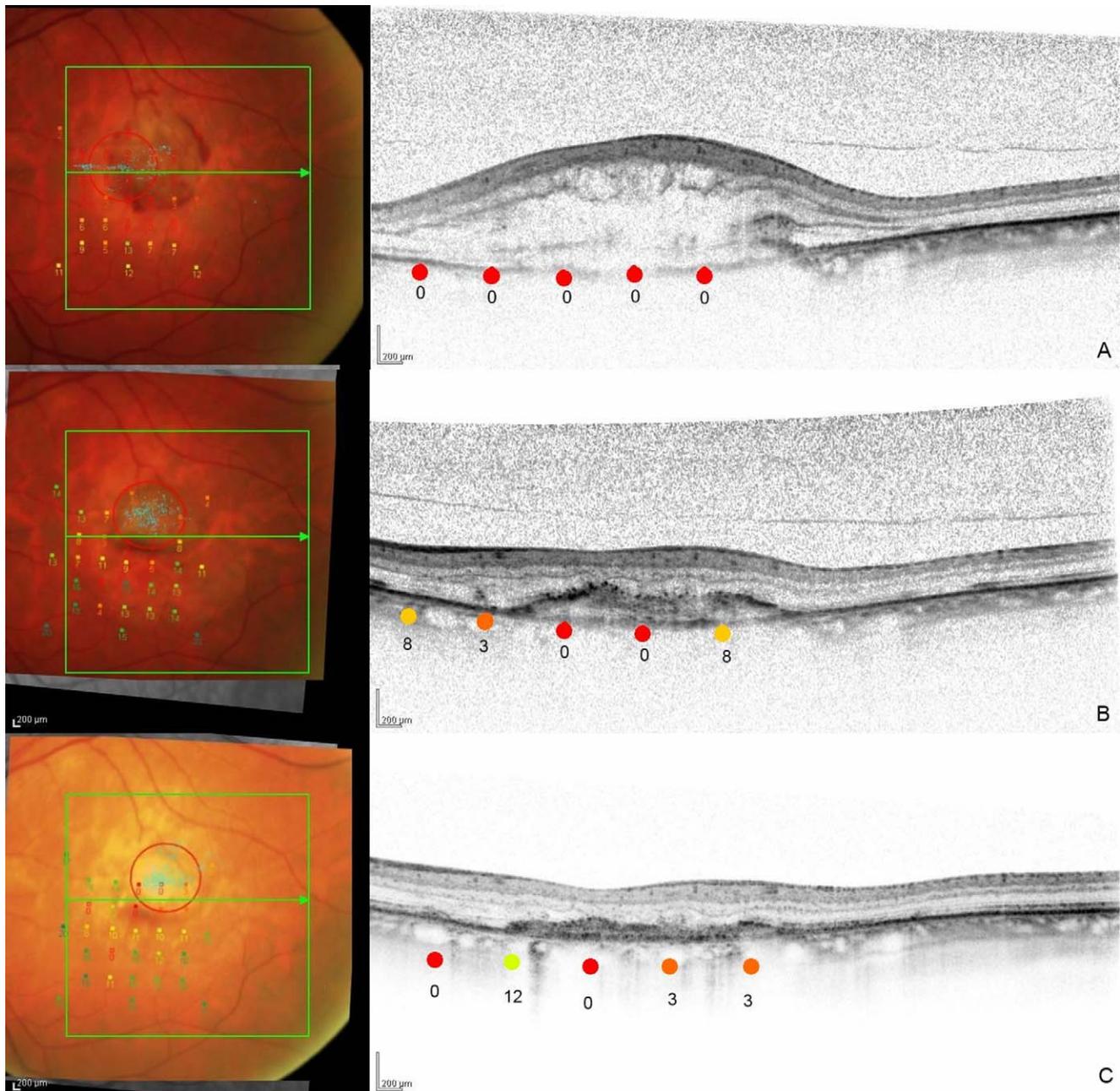


FIGURE 1. SD-OCT B-scans with corresponding retinal sensitivity values in decibels (dB). The microperimetry spot size measures 132 μm . Male patient, 69 years old, with classic CNV showing a neovascular complex with additional intraretinal cystoid space. At baseline (A) there is a total functional loss beneath the NVC lesion site. After 3 months (B) and 12 months (C), the edema was resorbed completely with development of a fibrotic scar. The functional benefit was limited.

months 3 and 12 following monthly intravitreal ranibizumab injections. Loci of an initial NVC (with and without additional IRCS) improved significantly from a mean retinal sensitivity value of $2.6 \text{ dB} \pm 0.8 \text{ dB}$ at baseline to $6.3 \text{ dB} \pm 0.8 \text{ dB}$ at month 3 and to $7.4 \text{ dB} \pm 0.9 \text{ dB}$ ($P = 0.0870$) at month 12 after monthly ranibizumab.

In the case of an initial NVC without additional IRCS, a significant increase of mean retinal sensitivity from $2.6 \text{ dB} \pm 0.9 \text{ dB}$ at baseline to $7.4 \text{ dB} \pm 0.9 \text{ dB}$ ($P < 0.0001$) at month 3 and to $8.5 \text{ dB} \pm 0.9 \text{ dB}$ ($P = 0.6129$) at month 12 was observed. Loci of an initial NVC with additional IRCS showed only a slight increase of mean retinal sensitivity from $2.5 \text{ dB} \pm 1.0 \text{ dB}$ at

baseline to $4.4 \text{ dB} \pm 1.0 \text{ dB}$ ($P = 0.1850$) at month 3 and to $5.6 \text{ dB} \pm 1.0 \text{ dB}$ ($P = 0.777$) at month 12.

Loci of an initial SRF improved significantly from a mean retinal sensitivity value of $5.1 \text{ dB} \pm 0.9 \text{ dB}$ at baseline to $10.5 \text{ dB} \pm 0.9 \text{ dB}$ ($P < 0.0001$) at month 3 and to $12.4 \text{ dB} \pm 0.9 \text{ dB}$ ($P < 0.0001$) at month 12. Loci of an initial IRF improved significantly from $4.0 \text{ dB} \pm 1.0 \text{ dB}$ at baseline to $9.1 \text{ dB} \pm 0.9 \text{ dB}$ ($P < 0.0001$) at month 3 and remained stable at $9.3 \text{ dB} \pm 0.9 \text{ dB}$ ($P = 0.9778$) at month 12. IRF without additional NVC was associated with a mean retinal sensitivity value of $4.6 \text{ dB} \pm 0.9 \text{ dB}$ at baseline, improved to $10.5 \text{ dB} \pm 0.9 \text{ dB}$ ($P < 0.0001$) at month 3, and remained stable at $10.6 \text{ dB} \pm 0.9 \text{ dB}$ ($P = 1.0$).

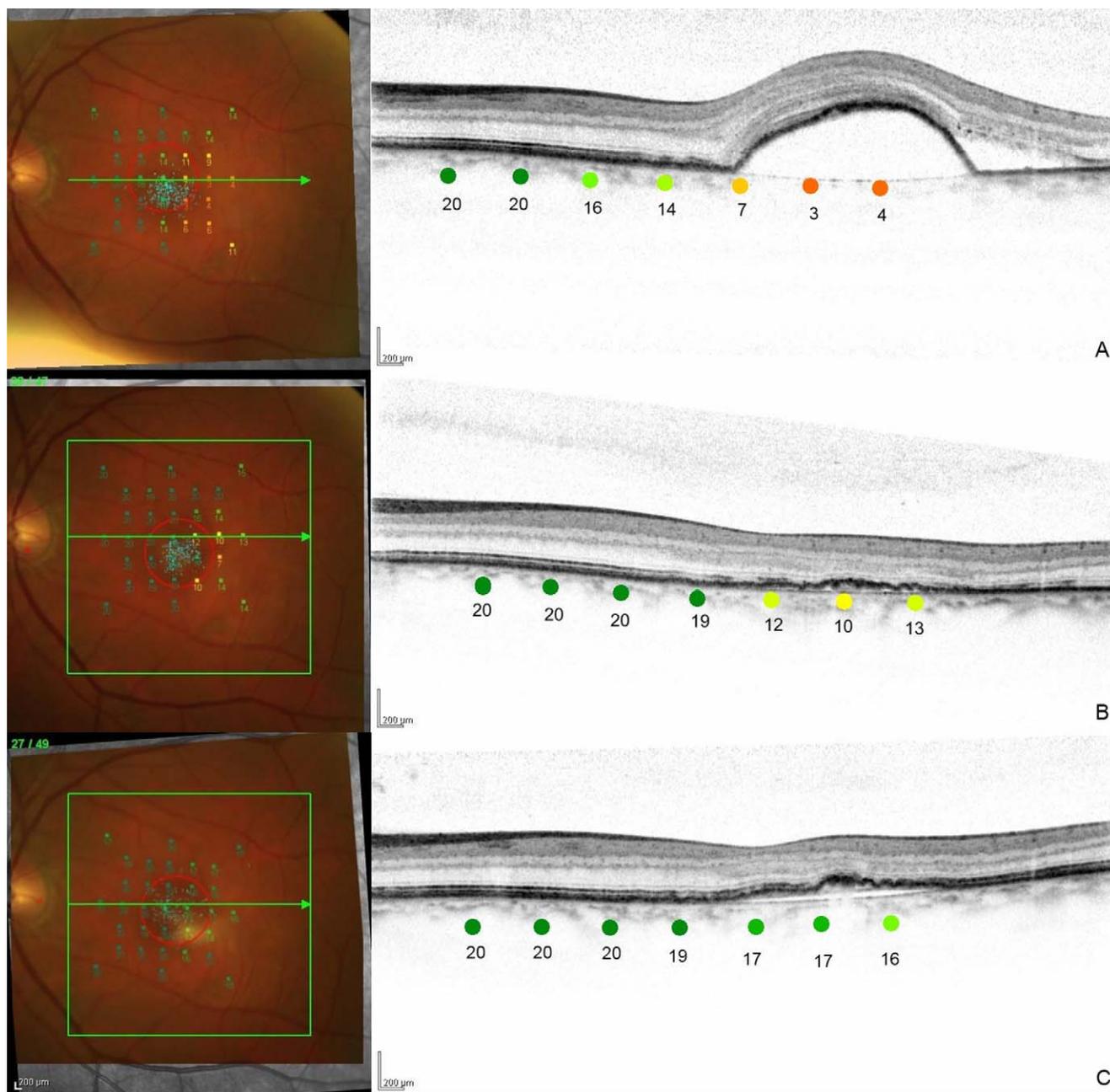


FIGURE 2. SD-OCT B-scans with corresponding retinal sensitivity values in decibels (dB). The microperimetry spot size measures 132 μm. Male patient, 68 years old, with occult CNV showing a serous pigment epithelium detachment (SPED). At baseline (A) there is a distinct functional loss beneath the SPED lesion site. After 3 months (B), the SPED flattened to almost normal retinal configuration with a marked functional benefit. After 12 months (C), the SD-OCT showed the same morphology with another increase in retinal sensitivity.

IRF with an additional NVC was associated with a mean retinal sensitivity value of 3.1 dB ± 1.0 dB at baseline, improved to 7.1 dB ± 0.9 dB (*P* < 0.0001) at month 3, and remained stable at 7.6 dB ± 0.9 dB (*P* = 0.9991) at month 12.

Loci of initial IRCS improved significantly from a mean retinal sensitivity value of 3.4 dB ± 0.9 dB at baseline to 6.3 dB ± 0.9 dB (*P* < 0.0001) at month 3 and to 8.2 dB ± 0.9 dB at month 12 (*P* = 0.0002), with an even greater benefit if IRCS occurred without NVC. In that case, function improved from 4.1 dB ± 0.9 to 7.9 dB ± 0.9 dB (*P* < 0.0001) after 3 months and to 10.6 ± 0.9 dB (*P* < 0.0001) after 12 months.

Loci of an initial SPED improved significantly from a mean retinal sensitivity of 1.9 dB ± 1.1 dB at baseline to 7.4 dB ± 0.9

dB (*P* < 0.0001) at month 3 and to 9.4 dB ± 1.1 dB (*P* < 0.0001) at month 12, whereas loci of a FPED showed a flatter curve of recovery from 5.2 dB ± 0.9 dB at baseline to 7.6 dB ± 0.9 dB (*P* < 0.0001) at month 3 and remained stable at 7.6 dB ± 0.9 dB (*P* = 0.9) at month 12.

The macular sensitivity response of the outer retinal layers showed that loci of a primary absent RPE layer improved significantly from a mean retinal sensitivity value of 3.0 dB.

Loci of a primary absent RPE layer improved significantly from a mean retinal sensitivity value of 3.0 dB ± 0.7 dB at baseline to 7.4 dB ± 0.7 dB (*P* < 0.0001) at month 3 and to 8.6 dB ± 0.8 dB (*P* < 0.0204) at month 12.

Loci of a primary discontinuous RPE layer improved significantly from a mean retinal sensitivity value of $6.4 \text{ dB} \pm 0.7 \text{ dB}$ at baseline to $10.1 \text{ dB} \pm 0.7 \text{ dB}$ ($P < 0.0001$) at month 3 and remained stable at $10.8 \text{ dB} \pm 0.7 \text{ dB}$ ($P < 0.1133$) at month 12.

Loci of a primary absent IS/OS layer improved significantly from a mean retinal sensitivity value of $3.7 \text{ dB} \pm 0.6 \text{ dB}$ at baseline to $7.5 \text{ dB} \pm 0.6 \text{ dB}$ ($P < 0.0001$) at month 3 and to $8.7 \text{ dB} \pm 0.6 \text{ dB}$ ($P < 0.0001$) at month 12.

Loci of a primary discontinuous IS/OS layer improved significantly from a mean retinal sensitivity value of $7.5 \text{ dB} \pm 0.6 \text{ dB}$ at baseline to $11.6 \text{ dB} \pm 0.6 \text{ dB}$ ($P < 0.0001$) at month 3 and remained stable at $12.0 \text{ dB} \pm 0.7 \text{ dB}$ ($P = 0.8558$) at month 12.

Loci of a primary absent ELM layer was associated with a significant increase in mean retinal sensitivity of $4.8 \text{ dB} \pm 0.7 \text{ dB}$ at baseline to $8.3 \text{ dB} \pm 0.6 \text{ dB}$ ($P < 0.0001$) at month 3 and to $9.1 \text{ dB} \pm 0.7 \text{ dB}$ ($P = 0.0106$) at month 12.

DISCUSSION

The purpose of the present study was the assessment of a predictive value for the functional treatment response in NAMD based on OCT characteristics before treatment. State-of-the-art modalities were used to assess the structure-function relationship on the basis of topographic correlation using image processing software. This procedure allowed a point-to-point analysis of the morphological data and corresponding functional impact of microstructural alterations at baseline⁸ and in the course of monthly ranibizumab treatment.

Monthly ranibizumab treatment is associated with a VA improvement of 1 or 2 lines on average after 2 years (Marina Anchor Study).^{9,10} In the same trials, 10% of treated eyes lost more than 3 lines after 2 years.

VA losers had significantly better baseline VA, tended to be older, and had larger neovascular lesions with corresponding larger areas of leakage from CNV at baseline. There were no statistically significant differences between losers and gainers at baseline with respect to percentage of the lesion with classic CNV, total area of blood, area of fibrotic tissue, or area of serous retinal PED. VA losers and VA gainers differed in the extent of RPE abnormalities, with the areas of RPE abnormality increased in VA losers compared with VA gainers at month 24.⁷ Multiple investigations have reported that both the integrity of photoreceptor layer¹¹⁻¹⁴ and the external limit membrane¹⁵ have a significant impact on visual function.

The present point-to-point evaluation revealed that loci of an initial neovascular complex associated with a disrupted RPE and an absent photoreceptor integrity resolved with a significant functional increase in retinal sensitivity. Individual analysis of the RPE, the IS/OS, and the ELM revealed a significant retinal sensitivity increase independent of the altered retinal layer (Table 1). This demonstrates that reintegration of an initially disrupted RPE layer, an initially absent IS/OS layer, and an absent ELM is a possible phenomenon that is associated with a pronounced functional benefit. Another investigation showed that none of the outer retinal layers including ELM and IS/OS junction was associated with predictive VA development. However, VA improvement was observed also in eyes with discontinued outer retinal layers.¹⁶ Significant improvement of the IS/OS line was observed with concomitant increase of VA after treatment, which supports the hypothesis of photoreceptor regeneration.¹⁷

In the case of additional IRCS at loci of an initial NVC, low functional improvement was observed, and the edema resolved and a fibrotic scar developed (Fig. 1). Intraretinal

cystoid space was supposed to occur in progressed lesions and was found in the inner retinal layers. The present investigation shows that especially the combination of cystoid macular changes with a NVC is associated with only a limited increase of macular sensitivity, whereas IRCS without CNV showed a marked increase in retinal sensitivity (Table 2). In the case of pigment epithelium detachment, significant improvement of retinal sensitivity was observed, with a marked increase at loci of an initial SPED (Fig. 2) and a low increase at loci of an initial FPED. This is in accordance with another study postulating that tissue damage due to degeneration in the PED appears to be relevant to a secondary loss of VA despite vascular endothelial growth factor suppression.¹⁸ PED, either fibrovascular or serous, at baseline may represent a risk factor in terms of the visual function recovery. The risk of developing fibrovascular RPE tears during anti-VEGF therapy is 16.8%, with a higher risk in eyes with greater PED and greater amount of SRF.¹⁹ Natural history studies found a 10% to 12% prevalence for RPE tears and a 52.8% prevalence for a VA loss of greater 3 lines after a mean follow-up time of 10.7 months.²⁰

Loci of initial subretinal fluid recovered with a marked functional benefit after 3 months and a further significant increase in macular sensitivity until month 12, suggesting that continuing monthly treatment leads to a better functional outcome. Other studies confirmed this assumption by showing VA improvement and decrease in subretinal fluid.^{21,16}

To conclude our observations, we have shown that an initially disrupted RPE layer, an initially absent IS/OS layer, and an absent ELM may be associated with a marked functional benefit after ranibizumab treatment. An initial NVC without IRCS may resolve to normal retinal configuration with a marked functional benefit, whereas a NVC with additional IRCS is associated with fibrosis development and a reduced functional response. Retinal fluid, independent of subretinal or intraretinal location, is associated with a substantial functional benefit, whereas a PED shows various outcomes with better benefit in the case of a SPED and a lower benefit in the case of FPED.

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