Relationship of Retinal Morphology and Retinal Sensitivity in the Treatment of Neovascular Age-Related Macular Degeneration Using Aflibercept

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PURPOSE. To relate the functional response to distinct morphological features of the retina during aflibercept treatment for neovascular AMD (nAMD).

METHODS. A total of 726 retinal locations in 22 consecutive eyes presenting with treatmente-naive nAMD underwent a standardized examination with spectral-domain optical coherence tomography (SD-OCT) and topographic microperimetry (MP) at baseline, after 3 and 12 months of continuous intravitreal aflibercept therapy. The retinal sensitivity at each stimulus location was registered to the corresponding location on SD-OCT morphology. Subsequently, the microperimetric responses were evaluated with respect to the following underlying SD-OCT features: neovascular complex (NVC), subretinal fluid (SRF), intraretinal fluid (IRF), intraretinal cystoid space (IRC), serous pigment epithelium detachment (sPED), and fibrovascular pigment epithelium detachment (fPED).

RESULTS. Baseline sensitivity was reduced to mean values of 1.8 dB in NVC, 2.2 dB in IRC, 2.8 dB in IRF, 2.6 dB in sPED, 3.6 dB in SRF, and 4.6 dB in fPED. Improvements in retinal sensitivity were most pronounced during the initial 3-month interval, when significant recovery was documented for SRF and sPED with +4.0/5.5 dB (P < 0.0001) and to a lesser extent for IRF, IRC, sPED, with +1.1, 1.7, 2.3 dB, respectively. From month 3 to 12, the additional benefit ranged from 0.3 to 1.0 dB (P > 0.05 for each category).

CONCLUSIONS. Significant functional benefits following intravitreal aflibercept treatment could be detected on all defined morphological pathologies. The level of improvement varied dependent on the associated feature with the best prognosis for visual improvement in SRF and sPED and least with intraretinal fluid and particularly intraretinal cysts.

Keywords: neovascular AMD, microperimetry, spectral-domain OCT

Recently, the progression of neovascular AMD, one of the most frequent macular disease entities, to a severe sight-threatening manifestation can successfully be prevented by modern pharmacological interventions. In particular, the introduction of intravitreal anti-VEGF agents greatly improved the visual prognosis for patients with neovascular AMD.1,2 The proportion of patients experiencing substantial visual loss (>15 letters) was reduced from 47.1% to 10%.1 Excellent efficacy of monthly ranibizumab treatment (Lucentis; Genentech, South San Francisco, CA, USA), an affinity-matured anti-VEGF antibody fragment that binds all VEGF-A isoforms, was demonstrated in the MARINA3 and ANCHOR4 trials and supported by the subsequent HARBOR study.5 Bevacizumab (Avastin; Roche, Basel, Switzerland) is the parent molecule of ranibizumab and is approved for the treatment of several systemic malignancies. Its intravitreal use has become widely adopted as an off-label, cost-effective alternative to ranibizumab, with recent randomized controlled data demonstrating comparable efficacy in treating neovascular AMD, although at the burden of monthly retreatments to achieve equivalent visual outcomes.6,7

The investigation of efficacy and safety in wet AMD (VIEW 1 and 2 studies), the largest therapeutic trial in neovascular AMD, evaluating intravitreal aflibercept demonstrated that a dose of 2 mg of aflibercept administered monthly or every 8 weeks was noninferior to 0.5 mg of ranibizumab dosed monthly, both with a loading dose of three monthly injections.8,9 Intravitreal aflibercept is a fusion protein of key domains from human VEGF receptors 1 and 2 with the constant region (Fc) of human IgG. Its binding affinity was suggested to be substantially greater than that of bevacizumab or ranibizumab.10

Clinically, the therapeutic response to intravitreal aflibercept is rapid, significant, and maintained both at the functional and morphological level.8,9 While the central best-corrected visual acuity (BCVA) improves, central retinal thickness (CRT) decreases.

However, cumulative evidence suggests that the correlation between BCVA and CRT is poor.11 In contrast to quantitative overall thickness measurements, qualitative morphologic features appear to present a more solid correlation with functional prognosis.12,13 Spectral-domain optical coherence tomography

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imaging allows for a precise mapping of retinal morphology due to high-resolution raster scanning, while microperimetry provides a functional topographic map of location- and intensity-based retinal sensitivity. A detailed evaluation of the functional treatment response depending on distinct SD-OCT findings was assessed using the concept of structure-function correlation.\textsuperscript{12}

The exact manual superimposition of the retinal sensitivity map to morphological SD-OCT data using Spectralis-OCT and the fundus-related microperimetry (MP-1; Nidek, Gamagory, Japan) enables the precise evaluation of treatment success as well as the detection of prognostic factors resulting from characteristic SD-OCT findings.\textsuperscript{14,15}

In this study, a standardized quantitative relationship between the functional recovery in decibel and the descriptive morphologic change was provided characterizing the therapeutic response of neovascular AMD to intravitreal aflibercept treatment.

METHODS

Patients

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 Declaration of Helsinki. Every patient gave written informed consent prior to study inclusion. Twenty-two consecutive patients with untreated active subfoveal choroidal neovascularization (CNV, or juxtapfoveal lesions with leakage affecting the fovea) secondary to AMD were included.

Patients had to be 50 years of age or older with BCVA between 25 and 75 Early Treatment Diabetic Retinopathy Study (ETDRS) letters (20/320–20/40 Snellen equivalent) and the CNV had to cover at least 50% of the total lesion area. Active CNV was confirmed by leakage activity as shown in fluorescein angiography (FA). Advanced CNV with scarring manifestation showing no leakage in FA were not included into the study. Mean patients age was 78.3 (range, 57–89 years), 7 eyes (32%) were pseudophakic, 7 eyes (32%) had unstable extrafoveal fixation and refractive error ranged from −3.75 to +2.00 sphere and from 0.00 to 1.75 cylinder. At baseline the fellow eye of 15 patients (68.2%) was dry without former treatment, five patients (22.8%) had wet AMD and received ranibizumab injection, two patients had Kuhnt Maculopathy and did not receive any further treatment. Eyes with significant lens opacity (cataract grade 2 or more according to the Lens Opacities Classification System) were not included into the study. Each patient received a fixed regimen of intravitreal aflibercept during 12 months. A loading dose of three, consecutive, monthly injections was followed by a retreatment regimen of either 4 or 8 weeks.\textsuperscript{8,9} There where nine participants receiving 0.5 mg aflibercept every 4 weeks (0.5q4), five participants receiving 2 mg aflibercept every 4 weeks (2q4), and eight participants receiving 2 mg aflibercept every 8 weeks (2q8). A complete clinical examination with slit-lamp biomicroscopy, ophthalmoscopy, and fundus photography as well as FA, SD-OCT, and microperimetry was performed at baseline, month 3 and 12.

Determination of Retinal Morphology and Sensitivity

Optical coherence tomography images were obtained using a spectral-domain imaging device (Spectralis HRA + OCT; Heidelberg Engineering, Heidelberg, Germany). The infrared-OCT tool of the Spectralis OCT was used to obtain a horizontal volume scan involving 49 scans with 25 frames, in 5 of 22 eyes only 37 scans were obtained due to fixation problems of the patients. Mean image quality was 24.5 dB (range, 15–34 dB). Separation between B-scans was 0.41°, independently if 49 or 37 scans were obtained. The scan width used was 6000 μm. The vertical dimension of the A-scan was 1536 per B-scan. 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 presented for 200 ms. (stimulus intensity range, 0–20 dB). A Cartesian grid with 33 stimulus locations (a standardized quadratic grid of 5 × 5 and eight peripheral points) covering the central area of 12° × 12° was selected, while a 3° ring was used as the fixation target. The period of adaptation to background luminance was 10 minutes while the mean exam duration was 9 minutes and 51 seconds (range, 7 minutes 41 seconds to 12 minutes 12 seconds). Patient’s fixation was relatively unstable with a mean value of 41.5% within 2° and 76.2% within 4° at baseline. The mean bivariate contour ellipse area (BCEA) value encompassing 68% of fixation points was 10.28 minarc\textsuperscript{2} interquartile range (IQR) 0.95–55.18 minarc\textsuperscript{2}.

Mean amount of false positive was 0.58 of 10 reliability test stimuli of the blind spot (range, 0–2). Background luminance was set at 1.27 cd/m\textsuperscript{2}.

Data Analysis and Correlation

VirtualDub (Ver.1.8.6; available in the public domain at www.virtualdub.org) software and Paint.NET (Ver.3.36; available in the public domain 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. The corresponding infrared-OCT image of SD-OCT was generated by VirtualDub software and imported to Paint.NET software. Subsequently, the fundus photograph with the sensitivity map was cut and matched to the infrared picture according to retinal landmarks by adapting the opacity mode. Finally, the OCT scan shown by the green arrow at locations of the light presentation was selected and matched with the adapted fundus sensitivity map. Subsequently, Image J software (http://imagej.nih.gov/ij/; provided in the public domain by the National Institutes of Health, Bethesda, MD, USA) was used to transfer each stimulus location in the sensitivity map to the corresponding location of the B-scan in SD-OCT true to scale.\textsuperscript{14} The microperimetry spot size measured 132 μm assuming a diameter of 26 arc minutes (or 0.45°) for a Goldmann III stimulus.

The majority of the cases showed very good agreement in correct alignment of image superimposition and light stimulus transfer. Some remaining concerns were possible inaccuracies of the devices themselves; the Spectralis was observed to sometimes miss the targeted scan line, the MP1 was observed to show a certain degree in test-retest variability of point wise sensitivity (PWS).\textsuperscript{16} Fundusphoto adaption to the size of the infrared beam of the SD-OCT also may have induced inaccuracies. For that reason, the appearance of the retinal vessels in both modalities before and after superimposition was used for ensuring correct alignment and measurement. After transferring 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 (IPED), serous pigment epithelium detachment (SPED), subretinal fluid (SRF), intraretinal fluid (IRF), and intraretinal cystoid spaces (IRC). The Table summarizes the grading definitions\textsuperscript{18} of the morphologic entities imaged by SD-OCT. Evaluation took into
account that these findings could appear as individual and/or combined manifestations (e.g., NVC+IRCS). Accordingly, the integrity of the photoreceptor inner and outer segment layer (IS/OS), the RPE, and the external limiting membrane (ELM) were evaluated. The IS/OS was graded as complete if the hyporeflective line (interface) between the IS/OS, also termed as inner segment ellipsoid band (ISe band) was present and as altered if the ISe band was interrupted for greater than 50%. The RPE layer was graded as complete if the hyporeflective band was continuous and as altered if the RPE was disrupted and only partly visible. The ELM was graded as intact if present or altered if absent.

Optical coherence tomography (OCT) was performed using SD-OCT device and microperimeter device facilitated reliable results. Out of the 726 locations transferred 19 testing points constituted missing values and were therefore not included in the statistical analyses. Since we do not assume any relationship between missingness and the actual value of the observation (“missing at random”) we believe that simply omitting these items did not bias our results.

### Statistical Analysis

Repeated measures analysis of variance (ANOVA) models were performed to evaluate the treatment effect on retinal sensitivity levels in the course of 1 year (measured at baseline, month 3, and 12). Additionally, the random block factor patient was included in the ANOVA models. Separate ANOVA models were performed for the different SD-OCT findings, considering only locations with the specific feature at baseline. In a first step, locations with the SD-OCT finding with and without combined manifestations were analyzed, whereas in a second step only locations with individual manifestations of the particular finding were used for analyses. Results of the ANOVA models are presented by the estimated means (±standard errors). Changes due to therapy at 3 and 12 months are presented by the estimated mean differences (±standard error) and P values are corrected for multiple pairwise comparisons by the Tukey-Kramer method.

### Results

A total of 726 individual locations detecting focal retinal sensitivity in 22 eyes of 22 patients with neovascular AMD were evaluated at baseline and at months 3 and 12 during a fixed regimen of intravitreal aflibercept injections and correlated with the defined morphological entity on corresponding SD-OCT images. In general, improvement of retinal sensitivity was found in the majority of retinal sites with morphologic alterations under aflibercept treatment. Functional recovery was most pronounced from baseline to month 3 and less intensive during follow-up between month 3 and 12. Mean BCVA behaved in a similar pattern and increased from 51.6 ± 14.9 letters at baseline to 60.4 ± 13.1 letters at month 3 (P = 0.0048) and remained stable at 60.2 ± 14.9 letters (P = 0.975) at month 12 (the second P value refers to the BCVA change between month 3 and 12).

In general, the degree of functional loss was dependent on the morphological lesion type. The improvement of retinal sensitivity under therapeutic recovery was also strongly influenced by the type of morphologic alteration.

### Retinal Recovery at Sites of Neovascular Activity

#### Loci of NVC (with and without additional findings) improved significantly from a mean retinal sensitivity value of 1.8 ± 0.6 dB at baseline to 4.4 ± 0.7 dB (P < 0.0001) at month 3 and to 5.4 ± 0.7 dB (P = 0.0270) at month 12 (Fig. 1).

The first P value of each phrase refers to the sensitivity change between baseline and month 3, the second P value refers to the sensitivity change between month 3 and month 12.

Consistently, with a NVC as an individual manifestation a significant increase of mean retinal sensitivity from 2.0 ± 0.8 dB at baseline to 4.8 ± 0.9 dB (P < 0.0001) at month 3 and to a lesser extent 5.6 ± 1.0 dB (P = 0.3878) at month 12 was observed (Fig. 2). Sites of NVC with additional IRC, however, showed only a limited increase of retinal sensitivity from a mean of 1.4 ± 0.6 dB at baseline to 2.4 ± 0.8 dB (P = 0.720) at month 3 followed by a stabilization at 1.9 ± 1.0 dB (P = 0.880) at month 12 (Figs. 3, 4).

#### Loci with SRF (with and without additional findings) improved significantly from a mean retinal sensitivity value of 3.6 ± 1.0 dB at baseline to 7.5 ± 1.0 dB (P < 0.0001) at month 3 and to 8.5 ± 0.9 dB (P = 0.1873) at month 12. In SRF as an individual manifestation a significant increase of mean retinal sensitivity from 3.7 ± 1.0 dB at baseline to 7.9 ± 1.1 dB (P < 0.0001) at month 3 and to a lesser extent 8.9 ± 1.1 dB (P = 0.2911) at month 12 was observed (Fig. 2).

#### Loci with IRF (with and without additional findings) improved significantly from 2.8 ± 0.8 dB at baseline to 5.2 ± 0.9 dB (P < 0.0001) at month 3 and 5.9 ± 0.8 dB (P = 0.5912) at month 12. Intraretinal fluid as individual manifestation was associated with a mean retinal sensitivity value of 6.6 ± 1.4 dB at baseline and improved to 8.9 ± 0.9 dB (P = 0.2524) at month 3 decreasing to 6.6 ± 1.3 dB (P = 0.316) at month 12. Intraretinal fluid with an additional NVC was associated with a mean retinal sensitivity value of 0.8 ± 1.4 dB at baseline and remained stable at 0.5 ± 1.1 dB (P = 0.9177) at month 3 and improved to 6.5 ± 1.5 dB (P = 0.0005) at month 12. Loci of IRC (with and without additional findings) improved significantly from a mean retinal sensitivity value of 6.1 ± 1.3 dB at baseline to 8.5 ± 1.3 dB (P = 0.0005) at month 12.
2.2 ± 0.6 dB at baseline to 3.9 ± 0.7 dB \((P = 0.0009)\) at month 3 and to 4.2 ± 0.7 dB at month 12 \((P = 0.7855)\).

Sites with a sPED (with and without additional findings) improved significantly from a mean retinal sensitivity of 2.6 ± 1.4 dB at baseline to 8.2 ± 1.6 dB \((P < 0.0001)\) at month 3 and to 9.1 ± 1.6 dB \((P = 0.5540)\) at month 12, whereas loci of a fPED (with and without additional findings) exhibited a flatter curve of recovery from 4.6 ± 1.1 dB at baseline to 6.9 ± 1.0 dB \((P < 0.0001)\) at month 3 and remained stable at 7.9 ± 1.1 dB \((P = 0.1655)\) at month 12.

Loci with sPED and fPED as individual manifestation showed similar results as in combination with additional findings. Serous pigment epithelial detachment improved significantly from a mean retinal sensitivity of 2.7 ± 1.8 dB at baseline to 7.3 ± 2.0 dB \((P = 0.0008)\) at month 3 and to 9.3 ± 2.0 dB \((P = 0.1666)\) at month 12, whereas sites with a fPED as individual manifestation consistently demonstrated a flatter curve of improvement from 6.7 ± 1.4 dB at baseline to 8.3 ± 1.4 dB \((P = 0.0447)\) at month 3 and to 9.3 ± 1.6 dB \((P = 0.5635)\) at month 12 (Fig. 5).

**Neurosensory Layers and Macular Sensitivity Response (Fig. 6)**

Loci of RPE layer alteration improved significantly from a mean retinal sensitivity value of 1.3 ± 0.5 dB at baseline to 3.5 ± 0.6 dB \((P < 0.0001)\) at month 3 and to 3.8 ± 0.7 dB \((P = 0.7907)\) at month 12.
Discontinued regimen.8,9
with aflibercept with no difference between a monthly or a

to ranibizumab, anatomical effects were found to be superior

sensitivity change between month 3 and 12.

affinity and durability,18,19 while functional results were similar

AMD. Aflibercept was formulated as a drug with superior

been approved as an alternative substance in neovascular

therapeutic response with the preexisting gold standard
corresponding functional impact of microstructural alterations
structure-function relationship on the basis of a topographic
neovascular AMD related to individual morphological charac-
function retinal response t o intravitreal aflibercept in
The purpose of the present study was the evaluation of the

discussion

FIGURE 3. Initial SD-OCT findings at baseline (as combined manifestations) and mean retinal sensitivity with error bars indicating one SD in
decibels at BL, month 3, and month 12 under aflibercept treatment. The absolute number of test points reflects the occurrence of the respective
finding. The P value at the 3 month bar refers to the sensitivity change between baseline and month 3, the P value at the 12 month bar refers to the
sensitivity change between month 3 and 12.

Retinal areas initially presenting an alteration of the IS/OS
layer showed an increase in sensitivity from 3.2 ± 0.7 dB at
baseline to 5.8 ± 0.7 dB (P < 0.0001) at month 3 and to 7.5 ±
0.7 dB (P < 0.0001) at month 12.

At sites of ELM layer alteration a significant increase of mean
retinal sensitivity of 4.0 ± 0.8 dB at baseline to 6.4 ± 0.8 dB (P
< 0.0001) at month 3 and to 7.7 ± 0.8 dB (P < 0.0001) at
month 12 was documented.

The purpose of the present study was the evaluation of the
functional retinal response to intravitreal aflibercept in
neovascular AMD related to individual morphological charac-
teristics. Advanced modalities were used to assess the retinal
structure-function relationship on the basis of a topographic
correlation using image processing software. This procedure
allowed a point-to-point analysis of morphological data and the

initial SD-OCT findings at baseline (as combined manifestations) and mean retinal sensitivity with error bars indicating one SD in
decibels at BL, month 3, and month 12 under aflibercept treatment. The absolute number of test points reflects the occurrence of the respective
finding. The P value at the 3 month bar refers to the sensitivity change between baseline and month 3, the P value at the 12 month bar refers to the
sensitivity change between month 3 and 12.

Several investigators have analyzed the impact of morpho-
logical features on retinal function. Shin et al.20 found that
restoration of foveal photoreceptor integrity and decreased
CNV thickness were closely associated with visual improve-
ment after treatment of neovascular AMD. However, Mathew et
al.21 concluded that none of the morphologic features at
baseline could predict the therapeutic change in visual acuity
by 12 months. Patient numbers were small and because only
the central foveal BCVA was assessed, no correlation between
retinal function and morphology could be found. In our study,
a more solid approach was selected, measuring retinal function
at a large number of retinal locations with the entire spectrum
of well-defined morphologic features, providing large data
ts and numbers of effective correlations. Clearly, microperimetric
assessment is a more reliable way to provide structure-function
relationships. Comparative testing of different morphologic
sites in one eye excludes the psychophysical errors, which
occur with interindividual functional testing.

Besides, the fundus monitoring feature of the micro-
perimeter is especially useful in individuals with macular
disease, who may have poor or unsteady fixation. Neverthe-
less, we would like to acknowledge that users should be aware
of possible floor, ceiling, and learning effects in the micro-
perimetry results, which could mask changes between
visits.22–24 As some items show a non normal distribution
especially at baseline with a lot of 0-dB values, sensitivity
analyses were performed using rank-transformed values instead
of the actual measured sensitivity levels to check the reliability
of our results. Background adaption of only 10 minutes can furthermore lead to an underestimation of the results especially in people with photoreceptor damage. The microperimetry results were examined in terms of absolute decibel values and no account for the potential age-related decline in sensitivity was made. As 7 of 22 eyes were pseudophakic, the mean absolute values do not account for the relative increase in sensitivity in pseudophakes compared with their age-matched counterparts.

The Comparison of Age-related Macular Degeneration Treatments Trials (CATT) study provided a large patient sample. However, only BCVA values were used to determine retinal function and morphologic determination was based on conventional stratus OCT with only six radial scans and no topographic raster pattern. In CATT, larger CNV area, greater total foveal thickness and RPE elevation were independently associated with less improvement at 1 year.25

Only SD-OCT providing dense pattern raster scanning allows for a distinct identification of the morphological microstructure of the retina, as used in our studies. Intraretinal cysts were identified in 43.5% and SRF was identified in 60.7% of visits by OCT, TD-OCT radial scanning demonstrated a significantly lower rate of detection with 71.8% when compared with Spectralis SD raster scanning with 92.0%.26 The results of this study are further supported by a previous finding in which macular function, as determined by focal macular ERGs, was improved in response to three consecutive bevacizumab injections, which is consistent with our findings during the loading interval.27 Our group has quantified the therapeutic response of intraretinal, subretinal and subpigment epithelial components in exudative AMD during anti-VEGF
therapy in an earlier study. Subretinal fluid was found to demonstrate greater positive sensitivity responses to therapeutic effects. The current analysis also indicates a superior functional outcome, if fluid is located underneath the retina and RPE.

A “protective” effect of subretinal fluid has recently been identified in several structure-function correlations in AMD and was presented at scientific meetings (Simader C, et al. IOVS 2014;55:ARVO E-Abstract 868), while other features are associated with a negative prognosis such as intraretinal cysts or persistent PED.

A study of Pelosini et al. highlighted the negative impact of intraretinal cystic changes to predict visual acuity in macular edema. A linear relationship between the amount of intraretinal tissue between the plexiform layers and BCVA was demonstrated. It is likely that cystic changes in the retina may represent chronic degenerations associated with loss in function and absence of regeneration rather than exudative fluid pooling. The “morphofunctional” evaluation of ranibizumab in neovascular AMD15 showed an identical therapeutic response of the corresponding OCT findings. The highest benefit was observed at loci of initial sPED, SRF, and NVC without IRC, whereas the lowest benefit was observed at loci of initial iPED, or NVC with cystic changes. The VIEW trials involving more than 2400 patients showed that intravitreal aflibercept dosed monthly (2q4 or 0.5q4) or every 2 months (2q8) after three initial monthly doses resulted in similar visual and anatomic outcomes as ranibizumab dosed monthly, as well as a decrease in the risk of vision loss.

**Figure 5.** (A–C) Spectral-domain OCT B scans with corresponding retinal sensitivity values in decibels. Macula of an 84-year-old female patient with occult CNV presenting a sPED nasal to the fovea and an iPED associated with a NVC temporal to the foveal area. At baseline, (A) a distinct functional loss beneath the iPED+NVC and the sPED lesion was found. After 3 months, (B) the PED lesions flattened to an almost normal RPE configuration together with a marked functional benefit. After 12 months, (C) SD-OCT imaging demonstrates a flat and linear RPE morphology with restoration of a primarily altered IS/OS junction and further recovered values in retinal sensitivity.
Furthermore all intravitreal aflibercept regimens were as effective as ranibizumab in increasing visual acuity and reducing retinal thickness and CNV size in the second year receiving mandatory quarterly dosing with intervening as-needed injections (capped PRN). As the visual acuity results of these trials did not show statistically significant difference between the different dosage regimens we suppose equal significance of retinal sensitivity results and disclaimed a subgroup analyses. Based on the small number of cases of our sample, results could be distorted especially in rare findings.

The current study could show similar efficacy of aflibercept and ranibizumab for their therapeutical response based on distinct OCT features. However, there seems to be a trend toward a superior response for aflibercept in features associated with PED, an alteration with deep subretinal location. Another study suggests that aflibercept may reduce the serous component of the PED, but the mature fibrocellular component may be resistant to treatment.

The option of a target-orientated application of anti-VEGF agents is still a challenge. Neovascular AMD often progresses to a chronic refractory disease despite multiple injections. To counteract these phenomena switching to a higher-dosed treatment and conversion to another drug was discussed in several studies. The Super-Dose Anti-VEGF (SAVE) study postulates that intravitreal injections of 2.0 mg ranibizumab leads to statistically significant VA gains and anatomic improvement in patients with persistent intraretinal, subretinal, or subretinal pigment epithelial fluid during a previous regimen of chronic monthly 0.5 mg ranibizumab injections. Another study states that conversion to aflibercept in eyes with refractory or recurrent neovascular AMD treated with multiple ranibizumab and/or bevacizumab injection results in maintenance of vision and improved anatomic outcomes, while allowing for slightly increased injection intervals. It remains to be proven that the long-term changes will respond in a functionally favorable way to pharmacologic intervention. Nevertheless, identification of the morphologic features and their functional value may help to decide upon the prognostic benefit of enhanced or switched regimens.

Concluding our observations we have shown that aflibercept has a beneficial effect on the anatomical recovery of the RPE layer, also the IS/OS line and the ELM. In general, evaluation of retinal sensitivity determined by microperimetric testing in distinct morphologic features assessed by raster SD-OCT imaging was successfully used to establish a topographic structure-function relationship in aflibercept treatment of neovascular AMD. A significant improvement of focal retinal function was documented in the majority of retinal sites and for the majority of morphologic features in a lesion specific degree. This improvement was most pronounced during the early therapeutic interval of 3 months, while the subsequent recovery was usually not significant. The level of functional improvement strongly depended on the morphologic entities with more benefit with subretinal and sub-RPE fluid, while the functional prognosis with intraretinal fluid and cysts was limited.

The identification of morphologic biomarkers to guide patient management is of utmost importance to reduce therapeutic complications, that is, geographic atrophy increasingly seen with continuous intravitreal VEGF inhibition and provide a practical and socioeconomically sound treatment strategy in large populations. Clear answers to this question will be provided by subgroup analysis of large randomized trials (VIEW, HARBOUR) providing adequate OCT follow-up that are underway.
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**APPENDIX**

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