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Evaluation of retinal function improvement in neovascular age-related macular degeneration after intravitreal aflibercept injections with the use of the assessment of retinal sensitivity

The use of the assessment of retinal sensitivity in anti-VEGF treatment – a STROBE-compliant observational study

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Abstract

This study compares 2 methods of macular function evaluation: the microperimetric examination (mean central retinal sensitivity and fixation stability) and the distance best-corrected visual acuity (BCVA) examination, which is the most frequently used method of assessing macular function in patients with newly diagnosed wet age-related macular degeneration (AMD) who have been treated with anti-vascular endothelial growth factor (VEGF) drug (aflibercept).

Prospective analysis was conducted on 44 eyes of 44 patients treated with intravitreal injection of anti-VEGF (aflibercept) because of newly diagnosed neovascular AMD. According to the research protocol, all patients had a 6-month follow-up. The response to treatment was monitored functionallybyMP-1 microperimetry, fixation, and distance BCVA assessment after injection. Improvement of retinal sensitivity and BCVA was found under aflibercept treatment. There was statistically significant improvement in retinal sensitivity in the MP-1 study 3 and 6 months from the beginning of anti-VEGF therapy. Moreover, a significant improvement in retinal sensitivity between 3 and 6 months of observation was demonstrated. At the same time, up to 3 months from the beginning of treatment, BCVA improved significantly compared to the baseline value. In the 6th month of the study BCVA remained stable without further significant improvement.

Microperimetric examination with medium sensitivity and fixation stability assessment is a very valuable test determining the retinal function. It is clear that examining the macular morphology itself in modern diagnostics is not enough to assess retinal function. Microperimetry technique is a valuable tool for functional long-term evaluation of retinal function (also for a period of more than 3 months).

Abbreviations: AMD = age-related macular degeneration, BCVA = best-corrected visual acuity, CNV = choroidal neovascularization, MD = mean defect of retina, MS = mean retinal sensitivity, OCT= optical coherence tomography, VEGF = vascular endothelial growth factor.

Keywords: aflibercept, age-related macular degeneration, fixation stability, microperimetric examination, microperimetry, retinal sensitivity

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1. Introduction

Age-related diseases such as age-related macular degeneration (AMD) and cataract are increasingly important healthcare concerns. They are common causes of visual acuity loss and reduced life quality of elderly. Conditions that limit the final results after cataract surgery may coexist.[1] In their cross-sectional population-based studies, La Cour et al found that age-standardized 1-year incidence of legal blindness resulting from AMD is present in 212 cases per million and that about 45% of eyes with AMD have visual acuity reduced up to 20/200 (logMAR 1.0) or worse.[2]

The pathophysiology and risk factors for AMD are complex, and the symptoms manifest in different forms.[3,4] The neovascular form of the disease, also known as wet AMD, is characterized by the formation of subretinal choroidal neovascularization (CNV). It is the main sight-threatening complication of AMD which tends to affect the center of the fovea. The patients affected by neovascular AMD often experience quick deprivation of the central vision, so early visual stabilization is a crucial step in preventing vision loss.[5]

Since 2007, when the 1st anti-vascular endothelial growth factor (anti-VEGF) agents were approved as a medication for wet AMD, blindness caused by neovascular AMD and it has declined significantly.[5,6] Using a reliable method of macular function monitoring is important to prevent disease progression and vision loss. The best-corrected visual acuity (BCVA) examination is known to be insensitive in monitoring foveal lesions,[7] so a more suitable functional method such as microperimetry seems to be necessary.[8]

The concept of microperimetry was introduced for clinical use in 1981.[9] Microperimetry is a noninvasive method to analyze fixation and central visual field defects via topographic imaging. Thanks to the autotracking system the technique is suitable for macular visual field examination for patients with nonfoveal or unstable fixation, which continuously adapts to eccentric fixation or fixation losses during the examination.[10,11] The adaptation of the tracking system is particularly important in the later stages of macular disease.[12] The examination starts with fundus photography and determination of the region of interest. Data from microperimetry are mapped directly on a digital image of the fundus, allowing a precise comparison of the locus of retinal sensitivity loss and retinal morphologic changes.

Additionally, the microperimetry allows analysis of fixation stability during the examination.

Meleth et al categorized the fixation stability into 3 levels (stable, relatively unstable, and unstable) based on the percentage of loci fixation within a circle of 2 and 4 degrees of diameter.[13] The most commonly studied parameters in microperimetry are mean sensitivity (MS), the mean of the differential light sensitivity obtained across all the qualified stimulus locations, and the mean defect (MD), which gives an overall value for the total amount of visual field loss. The MD value becomes more negative as the overall field worsens. Deterioration of visual function is indicated by a more negative MS and more positive MD.[14]

The results of experimental treatments assessing the clinical usefulness of microperimetry in the examination of macular function in patients with nonwet AMD have been discussed[15,16] and presented[17] in the previous studies. This study compares 2 methods of macular function evaluation: the microperimetric examination (mean central retinal sensitivity and fixation stability) and the BCVA examination, which is the most frequently used method of assessing macular function in patients with newly diagnosed wet AMD, who have been treated with anti-vascular endothelial growth factor (VEGF) (aflibercept).

2. Materials and methods

This study was conducted in the following 3 ophthalmologic university center's: the Department of Ophthalmology, School of Medicine in Katowice, Medical University of Silesia; the Department of General Ophthalmology, Medical University of Lublin; and the Ophthalmology Eye Hospital in Bydgoszcz. The research was consistent with the Declaration of Helsinki. The study was approved by the Bioethics Committee of the Medical University in Katowice (KNW/0022/KB1/38/I/15). Informed written consent was obtained from the patient for publication of this case report and accompanying images.

Prospective analysis was conducted on 44 eyes of 44 patients (24 women and 20 men) aged from 60 to 88 years (mean SD, 75.9 ± 6.1 years) treated with an intravitreal injection of anti-VEGF (aflibercept) because of newly diagnosed neovascular AMD. The inclusion criteria for the study group were: age >50 years, CNV resulting from AMD, confirmed by fluorescein angiography and optical coherence tomography (OCT). The exclusion criteria in the observational study were the previous anti-VEGF treatment as well as: dominant subretinal hemorrhage covering the center of the macula, dominant geographic atrophy covering the center of the macula, dominant scarring covering the center of the macula, and unregulated glaucoma or ocular hypertension, active or suspected eye or eye area infections, cataract worse than grade 2 (according to Lens Opacities Classification System III), and lack of patient consent.

The study was based on the evaluation of functional parameters of the retina and not on changes in morphology. Before the intravitreal treatment, all patients underwent an ophthalmic examination, including: distance BCVA examination using the Snellen visual acuity chart under identical testing conditions, slit lamp examination including anterior segment, lens, vitreous and meticulous fundus evaluation using indirect ophthalmoscopy, and the intraocular pressure that was tested with a Goldmann applanation tonometer. The fluorescein angiography was carried out using a Fundus Camera FF 450 plus IR (Carl Zeiss Meditec AG, Jena, Germany). The morphology of the macular area was examined precisely by OCT (3D OCT 2000; Topcon). During microperimetric examination (MP-1; Nidek), MS, MD, and fixation stability were measured.

For intravitreal therapy, 2.0 mg of aflibercept (Eylea; Bayer Pharma AG, Berlin, Germany) was administered with a sterile technique via the pars plana at 3 to 4 mm posterior to the limbus. After the initial treatment phase, which included 3 consecutive intravitreal injections at monthly intervals, an additional injection was conducted in month 5. According to the research protocol, all patients had a 6-month follow-up. Control tests were conducted after the 3rd intravitreal aflibercept injection and 6 months after the beginning of treatment. The response to treatment was monitored functionally by MP-1 microperimetry and distance BCVA assessment after the injection. Goldmann III stimuli and a 4-2 staircase strategy were used, and a circular test grid with 74 stimulus locations covering an area of 20° was applied. Differential light threshold values were compared by calculating the mean of the central 4° (12 test points) to assess the central macular retinal sensitivity. Any potential complications of intravitreal aflibercept injection were also noted. The data samples of the observation are shown in (Figs. 1–3).

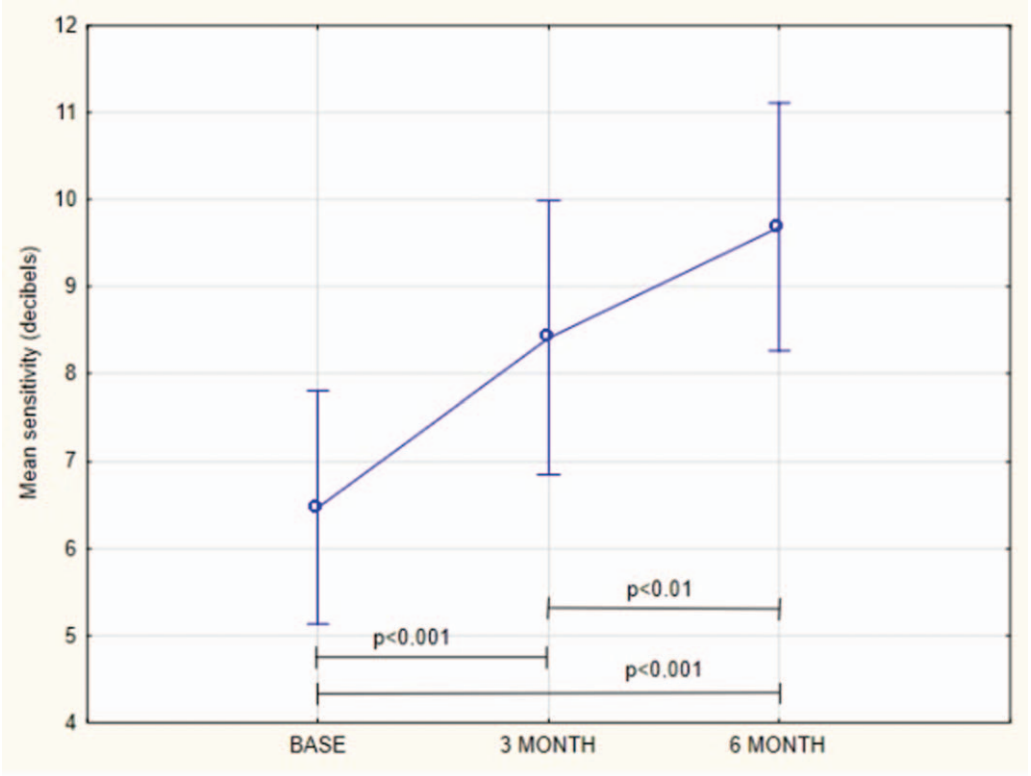

Figure 1. Initial central retinal sensitivity evaluated by MP-1 (Nidek) microperimetry in dB, month 3, and month 6 under anti-VEGF (aflibercept) treatment. VEGF = vascular endothelial growth factor.

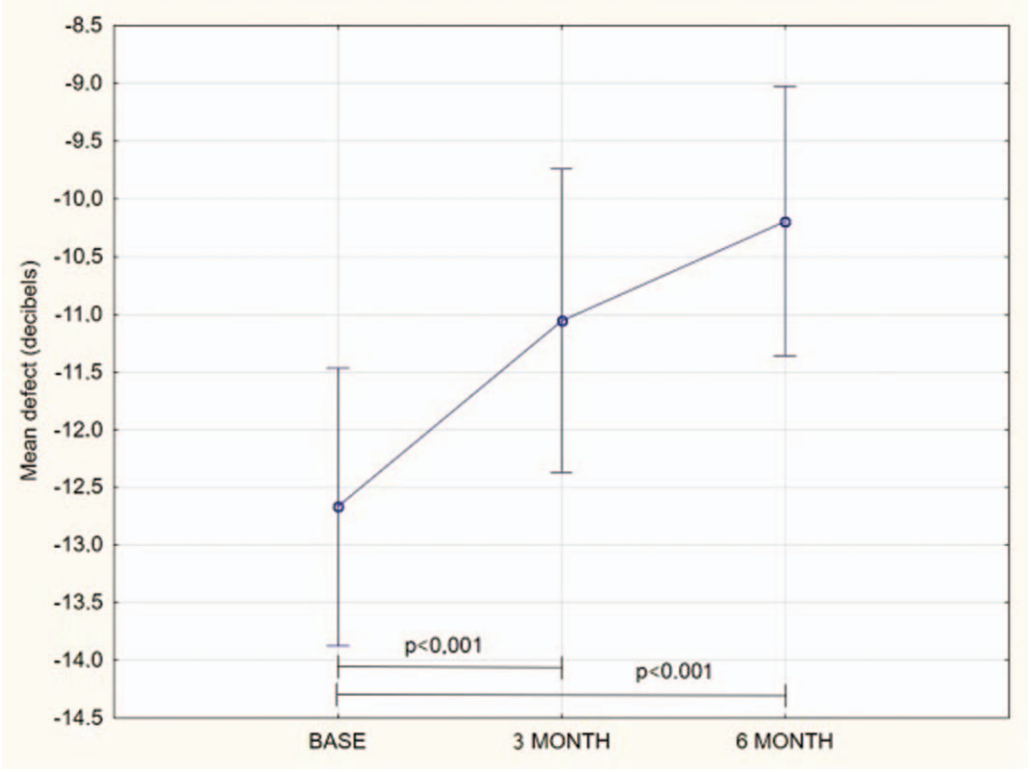

Figure 2. Initial central retinal mean defect evaluated by MP-1 (Nidek) microperimetry in dB, month 3, and month 6 under anti-VEGF (aflibercept) treatment. VEGF = vascular endothelial growth factor.

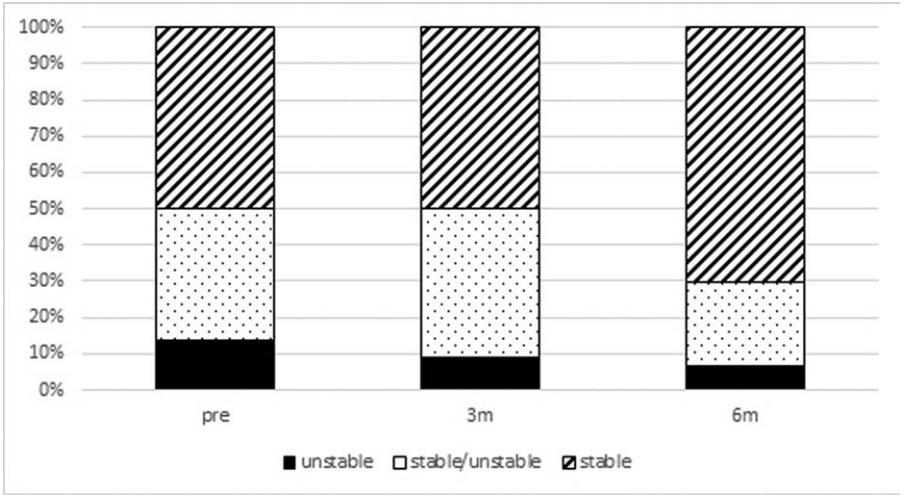

Figure 3. Fixation properties before, month 3, and month 6 under anti-vascular endothelial growth factor (aflibercept) treatment: the number and percentage of patients.

Statistical analysis was carried out using the data analysis software system StatSoft, Inc (2014) (STATISTICA, version 12). To compare variables in the study intervals, variance analysis was used for repeated measurements with the posthoc Tukey HSD test. Results are presented as mean values, standard errors, and 95% confidence intervals. *P*-values <.05 were thought to establish statistically significant results.

3. Results

Before starting the anti-VEGF treatment, MS was 6.470 ± 0.662 dB. MS increased to 8.418 ± 0.780 dB 3 months after the 1st intravitreal injection and the increase was statistically significant ($P < .001$). At the final check-up 6 months after the beginning of observation, a further significant increase of MS to 9.688 ± 0.706 dB ($P < .01$) was noticed, in comparison with results in the 3rd month (Table 1, Fig. 4). Within 6 months of observation, a decrease of MD in 23% of the study group was noticed. Further reduction of the MD was found at 6 months after the beginning of observation, but it was not statistically significant in relation to the value in the 3rd month of study (Table 2, Fig. 5).

Fixation stability results obtained from patients at 3 check-ups were categorized into 3 groups: stable, relatively unstable, and unstable. Significant increase of eyes with stable fixation after 6 months of observation was found. At baseline, 50.0% of the eyes tested (22 of 44) presented a stable fixation, 36.3% of them (16 of 44) showed relatively unstable fixation, and 13.7% (6 of 44) were characterized as unstable fixation. After 6 months of treatment, 70.5% (31 of 44) showed a stable fixation, 22.7% (10 of 44) a relatively unstable fixation, and 6.8% (3 of 44) an unstable fixation (Table 3, Fig. 6).

The average distance BCVA before treatment was 0.37 ± 0.028. After 3 months of treatment (i.e., after the 3rd intravitreal injection), BCVA increased to 0.502 ± 0.038 and the increase was statistically significant ($P < .001$). After 6 months of observation, BCVA was stable compared to results in the 3rd month (0.513 ± 0.039 vs 0.502 ± 0.038) with no statistical significance (Table 4, Fig. 7).

Mean central retinal thickness (CRT) before the 1st intravitreal injection of anti-VEGF was 374.90 μm; whereas the mean CRT after 3 monthly anti-VEGF injections was 298.28 μm. In the 5th month of the observation, after 4 anti-VEGF intravitreal injections, the mean CRT was 292.04 μm. A significant improvement in CRT and retinal sensitivity was found after the 1st dose of the anti-VEGF intravitreal injections. The results shown that the anti-VEGF therapy leads to robust functional and morphologic results over months.

4. Discussion

Treatment with intravitreal anti-VEGF agents in patients with neovascular AMD strongly improved their visual prognosis. The number of patients with significant visual impairment decreased to 10% from nearly 50%.[18,19]

Visual acuity is the most common studied parameter in ophthalmic research, but is insufficiently sensitive to detect the early stages of macular functional loss or, in later stages of AMD, to detect loss, stabilization, or deterioration of macular function

Table 1

Initial central retinal sensitivity evaluated by MP-1 (Nidek) microperimetry in dB, 3, and month 6 under anti-vascular endothelial growth factor (aflibercept) treatment.

Mean sensitivity, dB	Mean	Standard deviation	−95.00%	+95.00%	ANOVA *P*
Base	6.470455	0.662788	5.133816	7.80709	<.001
3 months	8.418182	0.780411	6.844334	9.99203	
6 months	9.688636	0.706001	8.264849	11.11242	

ANOVA = analysis of variance.

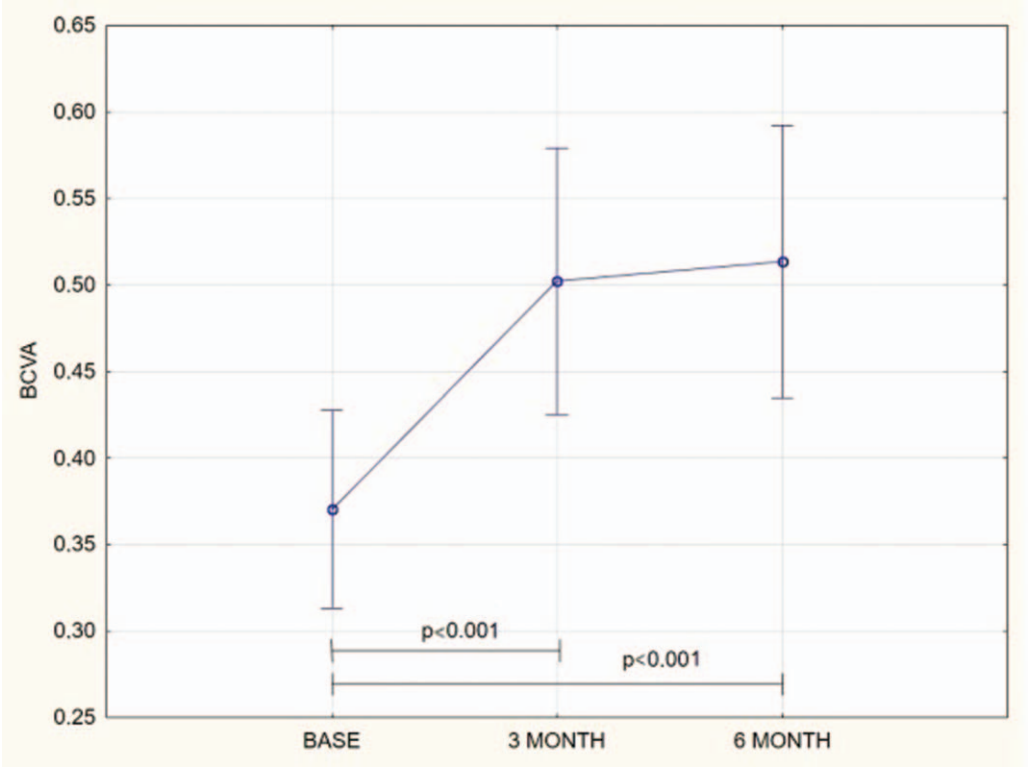

Figure 4. Initial distance best-corrected visual acuity (BCVA), month 3, and month 6 under anti-vascular endothelial growth factor (aflibercept) treatment.

exactly. The inclusion of microperimetry in clinical studies has provided interesting diagnostic as well as prognostic information on macular function of patients with AMD. This method not only allows to control of macular function but provides also an evaluation of the favorable or unfavorable effects of treatment.[20] A number of studies have shown that up to 12 months after anti-VEGF treatment, retinal sensitivity improves,[21–23] but some authors suggest that retinal sensitivity does not improve beyond the point measured after 1 week of treatment.[24,25]

This study shows that MS increased significantly throughout the entire 6-month follow-up period, in contrast to distance to BCVA, where significant improvement was noted only during the first 3 months of observation. This accords with other studies, where the authors showed that light sensitivity measured in microperimetry and visual acuity, improves up to 6 months[26] or even 12 months[21,27] during anti-VEGF therapy. Similar to the results presented in this article, Ozdemir et al, who found an increase of fixation stability and fixation location after intravitreal anti-VEGF treatment.[26]

There was an increase in fixation stability between the 1st, 2nd, and 3rd examination sessions in the better eye of patients in the AMD group. It was observed a significant increase of percentage of eyes with stable fixation after 6 months of observation. It is already known that fixation stability in people with acquired macular disease can be improved through training, potentially leading to improved performance in visual tasks. The extrafoveal preferential retinal locus (PRL) is developed on which eye movements are centered. It is possible to improve visual performance in patients with macular disease following fixation training on a new PRL. However, the location with greatest sensitivity on microperimetry is unlikely to represent the location with the best visual acuity, even if eccentricity is taken into account.[28]

Microperimetry is a valuable tool to assess macular functions in patients with AMD, especially when BCVA alone can be misleading. Tran and Herbort showed that more than a third of patients with AMD had bad or very bad results in a microperimetry examination in parallel with good visual acuity.[29] On the contrary, longitudinal functional improvement of the retina after intravitreal anti-VEGF treatment was observed and presented in the results of this article. Within 6 months of observation, mean sensitivity of the retina increased by 33% (6.47 dB at baseline vs 9.688 dB after 6 months).

Table 2

Initial central retinal mean defect evaluated by MP-1 (Nidek) microperimetry in dB, month 3, and month 6 under anti-vascular endothelial growth factor (aflibercept) treatment.

Mean defect, dB	Mean	Standard deviation	−95.00%	+95.00%	ANOVA *P*
Base	−12.6705	0.595504	−13.8714	−11.4695	<.001
3 months	−11.0568	0.652815	−12.3733	−9.7403	
6 months	−10.1955	0.577823	−11.3607	−9.0302	

ANOVA = analysis of variance.

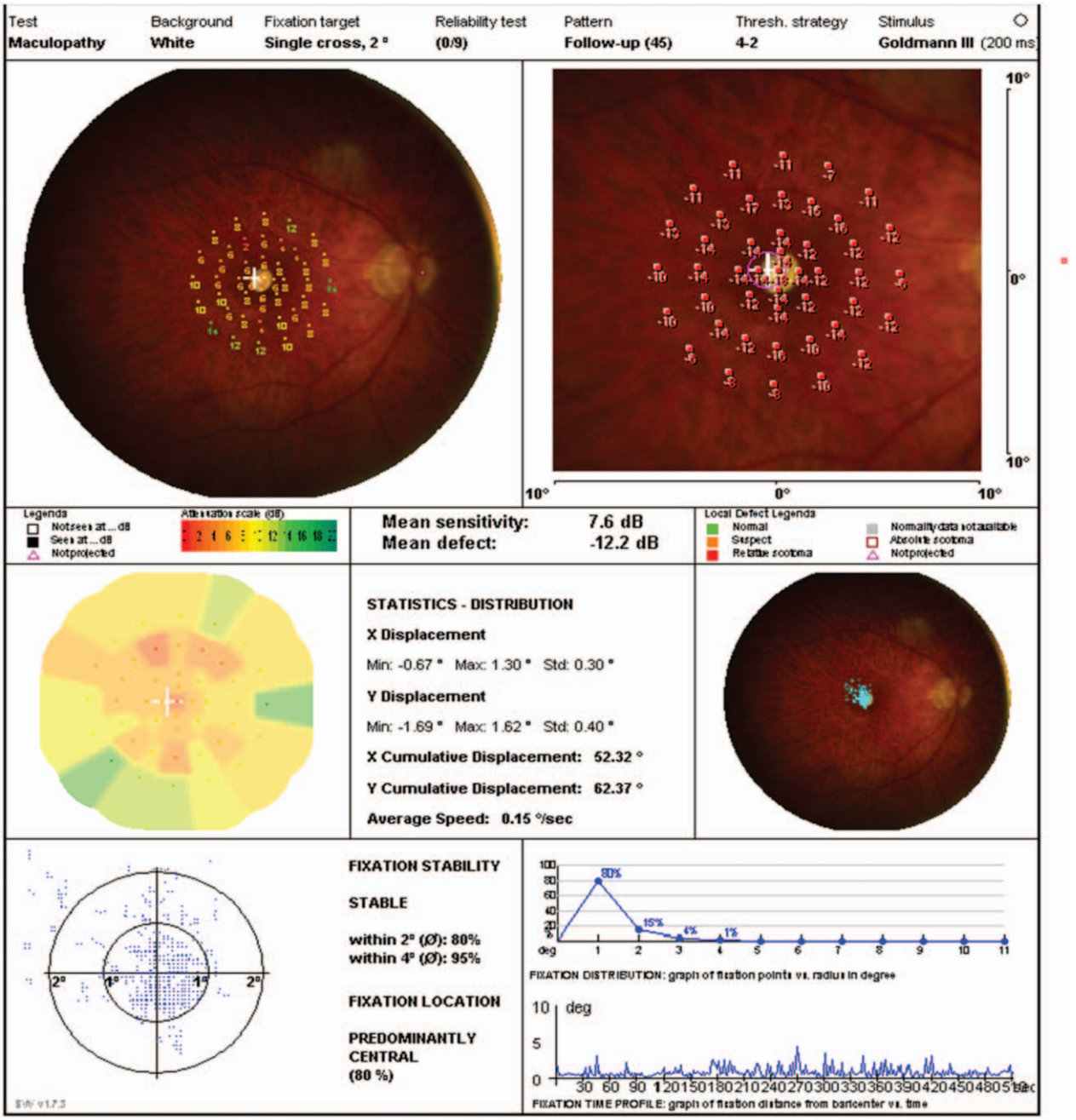

Figure 5. Sample of the result at the beginning of the study (right eye).

There are some limitations of the results obtained in the study, which could easily mask changes between visits. The main changes concern the learning effects and the time of background adaptation that required for microperimetry examination. The fact is that the patient performs better results each time after new examination. Also, because of the relativelysmall sample group and relatively short follow-up period, further longitudinal studies are necessary to establish the influence of intravitreal anti-VEGF

Table 3

Fixation properties before, month 3, and month 6 under anti-vascular endothelial growth factor (aflibercept) treatment: the number and percentage of patients.

	Base (pretreatment) – number of patients	3 months – number of patients	6 months – number of patients
Unstable	6	4	3
stable/unstable	16	18	10
Stable	22	22	31

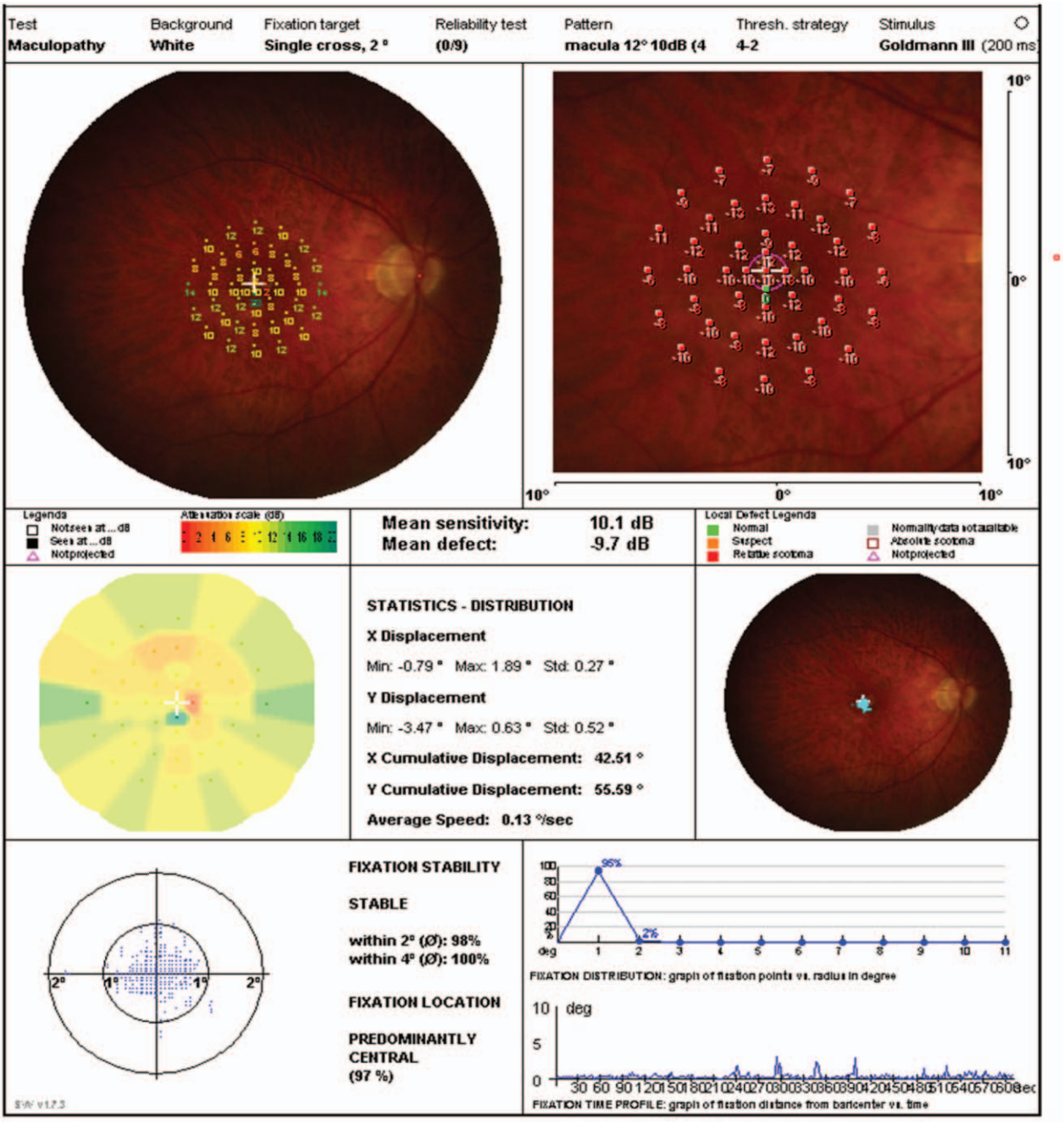

Figure 6. Sample of the result after 3 months of observation (right eye).

(aflibercept) treatment on retinal sensitivity. Similar to the results of this study, Prager et al found significant increase in mean retinal sensitivity MS (by 69%) after anti-VEGF(bevacizumab) treatment (3.78 dB vs 5.46 dB).[30] Parravano et al found an improvement of fixation stability in 33.3% of patients and continuous significant increase in retinal sensitivity measured by

Table 4

Initial distance best-corrected visual acuity (BCVA), month 3, and month 6 under anti-vascular endothelial growth factor (aflibercept) treatment.

BCVA	Mean	Standard deviation	−95.00%	+95.00%	ANOVA *P*
Base	0.370455	0.028265	0.313452	0.427457	<.001
3 months	0.502273	0.038123	0.425390	0.579155	
6 months	0.513636	0.039095	0.434793	0.592480	

ANOVA = analysis of variance.

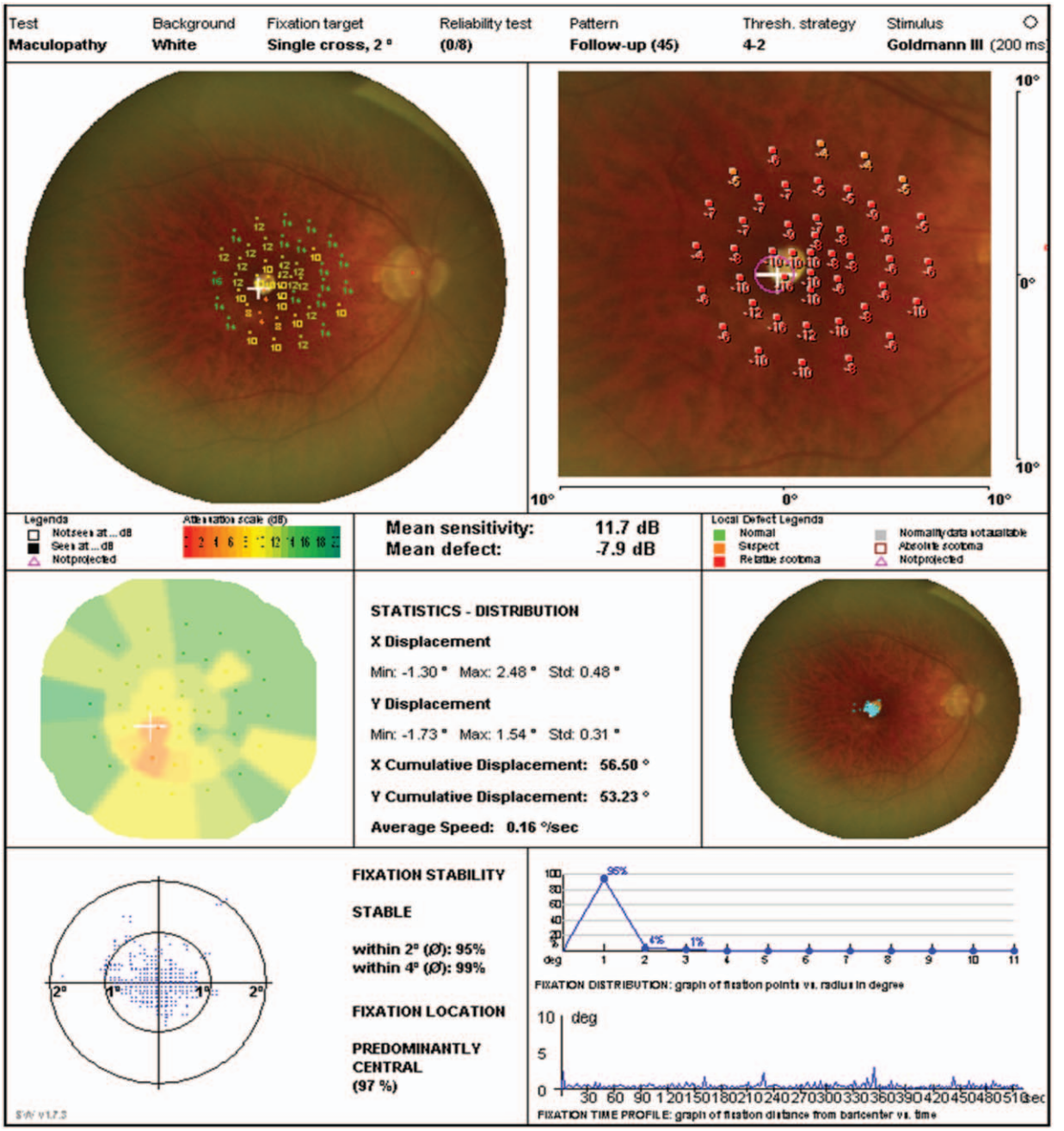

Figure 7. Sample of the result after 6 months of observation (right eye).

microperimetry during a 24-month observation, but the improvement of visual acuity was noted only up to 4 weeks after intravitreal anti-VEGF (ranibizumab) treatment and remained stable during the following weeks.[31] In a recent study Sulzbacher et al showed that after intravitreal anti-VEGF (aflibercept) treatment, functional macular recovery (MP-1 microperimetry) was more pronounced from baseline to month 3 and less intensive during the follow-up between months 3 and 12. BCVA increased significantly 3 months after starting the treatment and remained stable at month 12, which is consistent with results of the study presented in this article. Functional improvement depended on the morphologic pathologies of the retina, with better effects in cases of subretinal fluid and serous pigment epithelium detachment and worse effects in cases of intraretinal fluid and cysts.[19] It is necessary to find for parameters that could effectively assess the disease activity. The paper of Nagpal and colleagues describes comparison of microperimetry and OCTA in wet AMD. The results of 56 eyes were analyzed. All patients were treated with 3 injections of intravitreal anti-VEGF drug (the exact name is not given) at monthly intervals for 3 months. They were followed at 1, 2, 3, and 6 months from the baseline. There was a correlation described between optical coherence angiography (OCTA) features and MP3 results. Posttreatment with resolution of

neovascular network on OCTA, a significant improvement in retinal sensitivity was documented on MP3.[32]

The similar study was published by Wu and co-workers.[17] In this prospective study, 49 participants were examined: 41 participants had intermediate AMD, 8 had nonfoveal geographic atrophy due to AMD; they were followed-up for a period of 12 months, no treatment was applied. The visual acuity was 20/40 (logMAR 0.3) or better. Additionally, 10 normal subjects were examined, as a control.

There was a reduction in mean microperimetric pointwise sensitivity at 12 months compared with the baseline for intermediate AMD eyes and for geographic atrophy. A change in mean pointwise sensitivity was not identified over the 12-month period for control participants.

No changes in best-corrected visual acuity were identified in all groups over the 12-month period.

At the moment, ophthalmic diagnostics, for example, OCT and OCTA, have several parameters that can assess the CRT, the layered structure of the retina and the retinal perfusion parameters. However often, with a proper retinal morphology due to photoreceptor damage, the function of the macula could be impaired. This is called a "morphology-function paradox." Hence, ophthalmologists need additional tools for evaluation, prognosis and monitoring of progression, and response to treatment.

5. Conclusion

This study shows the treatment with aflibercept improved all tested functional parameters in patients with neovascular AMD. We have provided novel information on comparing of 2 methods of macular function evaluation: the microperimetric and the BCVA during the 6 months of the observation. Interestingly, MS increased significantly throughout the entire of 6-month follow-up period, in contrast to distance BCVA, where significant improvement was noted only during the first 3 months of observation. The decrease of MD in 23% of the study group was also noticed within 6 months of observation, and was more pronounced within the first 3 months. In our opinion, microperimetry provides additional, interesting information on macular function in patients with AMD treated with anti-VEGF injections. This examination allows for better understanding of clinical effects of the applied treatment. The larger cohort of patients with longer period of treatment and follow-up may be examined in the future.

Author contributions

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