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Analysis of Functional Dissociations between Best Corrected Visual Acuity and Microperimetric Parameters in Neovascular Age-Related Macular Degeneration Patients Underwent to Three Monthly Ranibizumab Injections

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Abstract

Background: To analyze the sensitivity of best corrected visual acuity and microperimetry to detect significant visual changes after 3 intravitreal ranibizumab in exudative age-related macular degeneration.

Design: Prospective, open-label study.

Participants: 50 eyes of 50 naïve patients affected by neovascular age-related macular degeneration were enrolled.

Methods: Enrolled patients underwent to a loading phase of 3 monthly intravitreal injections of ranibizumab. Best-corrected visual acuity was investigated with the ETDRS chart at 4 m. Central retinal sensitivity was tested with microperimetry using a Goldmann III stimulus to 33 points over the 12° central of the macula with a 4-2 double staircase strategy.

Main outcome measures: Comparison of changes in mean 4° central retinal sensitivity and best-corrected visual acuity in "BCVA relatively stable patients" (defined as change ≤ ± 4 ETDRS letters after treatment). Analysis of a possible relationship between changes in best-corrected visual acuity and 4° central retinal sensitivity in "mean 4° central retinal sensitivity relatively stable patients" (defined as change in mean retinal sensitivity ≤ ± 2dB)

Results: Mean best-corrected visual acuity improved of 5.90 ± 11.29 ETDRS letters (P=0.0006). Total mean retinal sensitivity improved +1.59 ± 2.12 dB (P<0.0001), while in the 4° central retinal area the increase was +1.36 ± 3.45 dB (P=0.0078). 38% of patients (19 eyes) were considered as "BCVA relatively stable patients". In this subgroup, Pearson's correlation analysis showed a direct correlation between changes observed with both methods (r = 0.71; P = 0.002). 48% of patients (24 eyes) were considered as "Mean 4° central retinal sensitivity relatively stable patients". In this subgroup, Pearson's correlation analysis didn't show a relationship between changes observed with both methods (r = 0.11; P = 0.56).

Conclusions: Microperimetry central retinal sensitivity seems to be an important to complete the functional evaluation in patients with wet age-related macular degeneration after 3 intravitreal ranibizumab.

Keywords: Microperimetry; BCVA; Central retinal sensitivity; Ranibizumab, Wet age-related macular degeneration

Introduction

Neovascular age-related macular degeneration (nAMD) is the leading cause of irreversible blindness in people ≥ 50 years old in the industrialized world [1].

Recently, the most promising treatment of all forms of nAMD is represented by intravitreal anti-Vascular Endothelial Growth Factor (anti-VEGF) drugs [2]. In fact, two of the most important prospective, randomized, large-scale clinical trials on nAMD treatment with intravitreal anti-VEGF have demonstrated a statistically significant improvement in best-corrected visual acuity (BCVA) [3,4].

Ranibizumab, a recombinant, humanized monoclonal antigen-binding antibody fragment that neutralizes all isoforms of VEGF-A (Lucentis, Genentech, Inc., South San Francisco, CA), was approved in the United States and Europe in 2006 for the treatment of nAMD [4].

BCVA using the Early Treatment Diabetic Retinopathy Study (ETDRS) chart has been considered the gold standard tool in order to assess the visual status in macular disorders and a primary end point to evaluate the functional outcome of new drugs in nAMD. On the other hand, it may not provide a complete functional assessment in nAMD patients [5,6].

Microperimetry MP1 (Nidek, Padova, Italy) is a relatively new

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equipment providing an objective and quantitative information about whole macular function in patients with nAMD [7]. Moreover, it is increasingly being recognized as a useful clinical tool in the assessment of various retinal pathologies [8-13].

In addition, retinal function is assessed by using microperimetry in relation to the fundus, and thus spatial light increment sensitivity can be mapped [14]. Moreover, the auto-tracking system corrects for involuntary eye movements allowing an exact point by point correlation between anatomic abnormalities and retinal sensitivity, even in patients with an unstable fixation, providing new insights into the functional impact of neovascular AMD [15,16]. These central visual field functions are important in day-to-day activities such as those involving contrast and color sensitivity [17].

Previously published data have demonstrated agreement between improvements in BCVA and mean retinal sensitivity in nAMD patients treated with anti-VEGF drug (bevacizumab [18] or ranibizumab [19-23]). However, the importance of microperimetry rests on the possibility to detect more subtle changes than visual acuity. This means threshold changes when visual acuity remains relatively stable. For this reason, the aim of this study was not only to analyze overall functional response in nAMD patients with microperimetry, but also to highlight, if one exists, a different behavior in these subgroups of patients using BCVA or MP1 parameters after a loading phase of 3 monthly intravitreal injections of ranibizumab in naïve nAMD.

Materials and Methods

Data from a prospective consecutive case series were analyzed. All the patients were examined at Retina Unit of Pisa University (Italy) from March 2009 to March 2011. The study was performed in adherence to the tenets of the Declaration of Helsinki; all patients signed an informed consent form.

Fifty nAMD naïve patients were enrolled. All patients underwent a loading phase with 3 consecutive intravitreal injections of 0.5 mg/0.05 mL ranibizumab at monthly intervals (baseline, month 1 and month 2), according to the usual procedure with topical anesthesia and surface disinfection with 5% povidone-iodine.

Follow-up visits were scheduled at 3 and 25 days after each injection. At the first follow-up visit only fundus examination was performed for safety reasons. BCVA and OCT measurements were carried out 25 days after each injection. FA and MP1 measurement were performed at baseline and 25 days after the end of the loading phase.

The inclusion criteria were: 1) diagnosis of active subfoveal Choroidal Neovascularization (CNV) in AMD, including all subtype of lesions; 2) age ≥ 50 years; 3) no previous treatments for AMD; 4) willingness to adhere to the scheduled visits during the follow-up period.

The exclusion criteria were: 1) retinal angiomatous proliferation or polypoidal choroidal vasculopathy because response to anti-VEGF therapy may be considerably different from typical neovascular AMD lesions; 2) sub-retinal, intra-retinal, or pre-retinal hemorrhage of >1 disk area; 3) extensive geographic atrophy defined as ≥ 1 areas within the central macular of atrophy >1 disk diameter; 4) co-morbidities that could interfere with follow-up (i.e, glaucoma, diabetic retinopathy, corneal opacity); 5) history of poor vision due to conditions other than AMD; 6) active clinical ocular infection requiring treatment (i.e uveitis); 7) current use of any other investigational drug or device; 8) history of vitrectomy.

Clinical diagnosis of active subfoveal CNV in AMD was performed by fundus examination, fluorescein (FA) and indocianine (ICGA) angiography and optical coherence tomography (Heidelberg Engineering, HRA + OCT Spectralis, Dosenheim, Germany).

Baseline visit included: slit-lamp examination, IOP measurement with Goldmann applanation tonometry, BCVA with ETDRS score, dilated fundus examination, retinal sensitivity evaluation with Microperimetry (MP1, Nidek Technologies, Padua, Italy), FA and ICGA, and foveal thickness measured by OCT.

BCVA has been measured by Early Treatment for Diabetic Retinopathy Study (ETDRS) charts at a distance of 4 m according to the Study Protocol [24].

MP1 testing parameters were: a grid of 33 stimuli covering the central 12° (centered onto the fovea); stimulus size Goldmann III, with 200 milliseconds projection time; white, monochromatic background at 4 apostilb (asb); a bright red cross of 4° in size was used as the fixation target. The starting stimulus light attenuation was set at 10 dB. A 4-2-1 double-staircase strategy was used with an automatic eye tracker that compensates for eye movements. The fellow eye was patched. Pre-test training was performed, and a 5-minute mesopic visual adaptation was allowed before starting the test. All subjects underwent microperimetry with dilated pupil. Mean overall threshold value (dB) and 4° central area threshold value (dB) were investigated for each patient at baseline and final visit. If no threshold value was detected, the corresponding area was defined as absolute scotoma. Total number of absolute scotoma locations as well as the number of absolute scotoma locations in the 4° central area was taken into consideration for the statistical analysis.

Fixation location and fixation stability were also evaluated by microperimetry test and graded in a 3-points scale [18]. Location was classified as predominantly central (more than 50% of the preferred fixation points located within the central area, 3 points), poor central (more than 25% but <50% of preferred fixation points located within the central area, 2 points), and predominantly eccentric fixation (<25% of the preferred fixation points within the central area, 1 point). Fixation stability was classified as stable (>75% of the fixation points inside the 2° diameter circle, 3 points), relatively unstable (<75% of fixation points inside the 2° diameter circle but >75% inside the 4° diameter circle, 2 points), and unstable (<75% of the fixation points inside the 4° diameter circle, 1 point).

Primary end point was to analyze in "BCVA relatively stable patients" (defined as change in BCVA ≤ ± 4 ETDRS letters after treatment) if there is a different behavior in comparison to mean 4° central retinal sensitivity. On the other hand, also in "mean 4° central retinal sensitivity relatively stable patients" (defined as change in mean retinal sensitivity ≤ ± 2dB) a possible relationship with change in BCVA was taken into consideration for statistical analysis.

Secondary endpoints were to perform the same analysis in "BCVA reducing patients" (defined as change in BCVA > -4 ETDRS letters) and "BCVA improving patients" (defined as change in BCVA > +4 ETDRS letters) in comparison to mean "4° central retinal sensitivity" and, vice versa, "mean 4° central retinal sensitivity reducing patients" (defined as change in mean retinal sensitivity > -2dB) and "mean 4° central retinal sensitivity improving patients" (defined as change in mean retinal sensitivity > +2dB). Moreover, also variations of microperimetric indices in the global sample size were considered as secondary endpoints.

Definition of "BCVA relatively stable patients" was based on

the paper of Shah et al. [25]. They have demonstrated that standard deviation (SD) of test-retest differences for ETDRS chart measurements was ± 4 letters. Moreover, a5 or more ETDRS letter deterioration in BCVA was a retreatment criterion in the PrONTO study [26] and is listed on the European Medicines Agency (EMEA) product label as one of the criteria for retreatment of nAMD with intravitreal ranibizumab [27].

On the other hand, mean retinal sensitivity has not yet been considered as a functional tool in large clinical trials on anti-VEGF therapy. So, a common convention for what represents a significant improvement in central retinal sensitivity measured with the MP1 has not yet been defined. Test–retest variability of microperimetry using the Nidek MP1 in patients with macular disease has been investigated by few authors. Richter-Mueksch S et al. have defined a significant gaining in mean retinal sensitivity in patients underwent to vitreo-macular surgery for macular hole as ≥ 1 dB [10]. Yodoy et al. have arbitrarily defined a gaining ≥ 2 dB in patients underwent to photodynamic therapy for polypoidal choriovasculopathy as a significant improvement in mean retinal sensitivity [11]. Squirrell et al. have analyzed the test-retest variability in a control group of ten patients with stable dry AMD (presence of intermediate or large macular drusen [drusen ≤ 63 μm] and pigmentary changes) and they have found a repeatability coefficient of 1.45 dB. They have concluded that a change in the mean retinal sensitivity of ≥ 2.0 dB represented a change in retinal sensitivity after treatment not related to test-retest variability [23]. Also Chen et al. have investigated the test-retest variability in mean retinal sensitivity in test-naïve patients with macular diseases. They have found a coefficient of repeatability of 1.8 dB, suggesting that a change ≥ 2.5dB was necessary to exceed test-retest variability [28]. From these data, even though we acknowledge the lack of general agreement in the medical literature, we have defined patients with a change ≤ ± 2dB as "stable patients". Moreover, to compare different units (dB and ETDRS letters), we transformed changes after treatment in percentage.

In addition, number of scotoma points, changes of fixation stability and fixation location was taken into consideration for statistical analysis.

Statistical was performed by using the Graphpad Prism software package, version 5.0 (Graphpad Software Inc., San Diego, CA). t-test was applied for statistical analysis when appropriate. Pearson's correlation coefficient (r) was used for data correlation. Modifications after treatment were converted into percentage. The level of significance was set at $P<0.05$.

Results

Sixty-one patients affected by wet AMD were considered. Eleven patients were excluded: 1 for previously photodynamic therapy with Verteporphin (V-PDT) and 4 for injections of bevacizumab; 1 because concomitant primary open angle glaucoma and 1 for diabetic retinopathy; 4 because AMD-related hemorrhagic choroidal neovascular lesions more than 1 disk area.

Fifty patients were included in the study. The mean age was 75.0 ± 8.28 years (range 59 to 88 years). 30 males and 20 females were studied, 41 eyes were phakic and 9 were pseudophakic. Age-related macular degeneration lesions were classified as follows: 21 (42.0%) as classic or predominantly classic, 20 (40.0%) as minimally classic and 9 (18%) as occult. Macular hemorrhage <1 disk area was present in 18 eyes (36%) and absent in 32 (64%). Sample clinical characteristics are described in Table 1.

Mean total BCVA, expressed as the number of ETDRS letters read, improved from 34.6 ± 15.4 at baseline to 40.5 ± 16.3 after the third injection with a mean change of +5.90 ± 11.3 letters (P = 0.001) (Table 2).

Both mean 12° and 4° central retinal sensitivity significantly increased after treatment (+ 1.6 ± 2.12 dB, + 25.3%, P < 0.001 and +1.4 ± 3.45 dB, + 46.9%, P=0.008, respectively) (Table 2). The number of 12° and 4° central retinal absolute scotoma points reduced significantly at final visit (P = 0.003 and P=0.025, respectively) (Table 2).

Microperimetry examinations showed also improvement in fixation stability and fixation location (P < 0.05) (Table 2).

According to the previously described criteria, 38% of patients (19 eyes) were considered as "BCVA relatively stable patients". In this

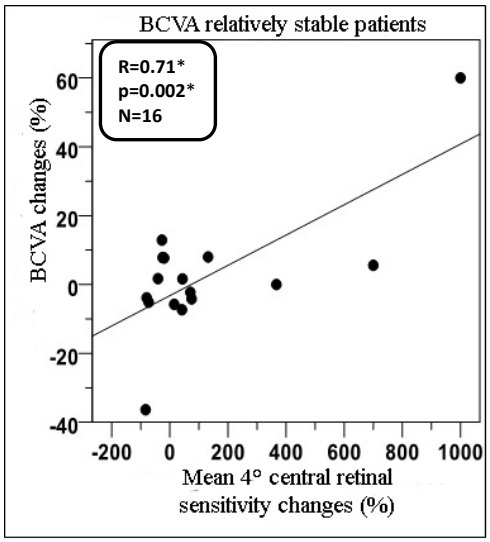

Figure 1: Pearson's correlation coefficient for the "BCVA relatively stable patients" group.

Age (years)	
Mean ± SD	75 ± 8.8
Range	59 to 88
Gender	
Male	30 (60%)
Female	20 (40%)
Eye laterality	
Right	28 (56%)
Left	22 (44%)
Lens status	
Phakic	41 (82%)
Pseudophakic	9 (18%)
Diagnosis	
Classic or predominantly classic	21 (42%)
Minimally classic	20 (40%)
Occult	9 (18%)
Macular hemorrhage < 1 disk area	
Present	18 (36%)
Absent	32 (64%)
Total number of eyes	**50**

SD: Standard Deviation

Table 1: Demographics.

group, BCVA showed a smaller increase (+0.2 ± 2.8 ETDRS letters; +0.4%; P=0.807), while mean 4° central retinal sensitivity increased by +7.8% from baseline (+0.3 ± 3.1dB; P = 0.703) (Table 3). Pearson's correlation analysis showed a direct correlation between changes observed with both methods (r = 0.71; P = 0.002) (Figure 1).

On the other hand, in the subgroup "Mean 4° central retinal sensitivity relatively stable patients" were included 48% of patients (24 eyes). They reported a mean increase of 4° central retinal sensitivity of +15.8% (+0.3 ± 0.9 dB; P = 0.129), while mean change in BCVA was only +5.3% (+1.7 ± 10.3 ETDRS letters; P = 0.438) (Table 4). Interestingly, there no correlation was seen between changes reported by BCVA and 4° central retinal sensitivity (r=0.11; P=0.67) (Figure 2).

Also for all the other subgroups of patients ("BCVA reducing patients" and "BCVA improving patients"; "mean 4° central retinal sensitivity reducing patients" and "mean 4° central retinal sensitivity improving patients") Pearson's correlation coefficient was not statistically significant (P>0.05).

No ocular or systemic adverse events related to the drug or the injection procedures were reported during the follow-up.

Discussion

In the recent past, the management of the nAMD has been deeply changed by the introduction of new diagnostic and therapeutic techniques.

Macular function of patients with nAMD is usually tested only by BCVA, even though it does not consider several pathophysiological aspects of vision [5,6].

	Baseline	Final	Difference (n ± SD)	Difference (%)	P value (2-tailed)
BCVA (ETDRS letters ± SD)	34.6 ± 15.4	40.5 ± 16.3	5.9 ± 11.3	+ 17.0	0.001
12° retinal sensitivity (dB ± SD)	6.3 ± 3.6	7.9 ± 4.0	+1.6 ± 2.1	+25.3	<0.001
4° central retinal sensitivity (dB ± SD)	2.9 ± 3.1	4.2 ± 3.8	1.3 ± 3.4	+46.9	0.008
12° scotoma points (n ± SD)	9.6 ± 9.3	6.6 ± 8.2	-3.0 ± 6.8	-31.2	0.003
4° scotoma points (n ± SD)	2.4 ± 2.0	1.8 ± 1.9	-0.6 ± 1.8	-24.6	0.025
2° central retinal fixation stability (% ± SD)	48.1 ± 28.3	58.0 ± 27.0	9.9 ± 24.8	+20.6	0.007
4° central retinal fixation stability (% ± SD)	77.5 ± 25.4	84.9 ± 19.5	7.4 ± 24.6	+9.5	0.039
Fixation stability (n)	P1 = 22 (44%) P2 = 11 (22%) P3 = 17 (34%) 1.90 ± 0.89	P1 = 22 (44%) P2 = 11 (22%) P3 = 17 (34%) 2.22 ± 0.81	0.32 ± 0.84	+16.8	0.025
Location fixation (% ± SD)	36.1 ± 30.7	48.1 ± 29.8	12.0 ± 28.4	+33.2	0.004
Location fixation (n)	P1 = 17 (34%) P2 = 19 (38%) P3 = 14 (28%) 1.92 ± 0.77	P1 = 9 (18%) P2 = 26 (52%) P3 = 15 (30%) 2.12 ± 0.69	0.20 ± 0.73	+10.4	0.039
Foveal thickness (µm ± SD)	363.7 ± 116.2	237.6 ± 111.9	-126.1 ± 133.2	-34.7	< 0.001

BCVA: Best Corrected Visual Acuity; SD: Standard Deviation
Fixation stability: P1 = Point 1, Instable
P2 = Points 2; relatively instable
P3 = Points 3; stable
Location fixation: P1 = Point 1, predominantly eccentric
P2 = Points 2; poor central
P3 = Points 3; predominantly central

Table 2: Difference between baseline and final follow-up.

	Baseline	Final	Difference (n ± SD)	Difference (%)	P value (2-tailed)
BCVA (ETDRS letters ± SD)	37.3 ± 18.2	37.5 ± 18.9	0.2 ± 2.8	+ 0.4	0.807
12° retinal sensitivity (dB ± SD)	7.2 ± 3.9	8.8 ± 4.0	1.6 ± 2.3	+21.4	0.010
4° central retinal sensitivity (dB ± SD)	3.5 ± 3.7	3.8 ± 3.6	0.3 ± 3.1	+7.8	0.703
2° central retinal fixation stability (% ± SD)	54.5 ± 31.6	62.2 ± 28.5	7.7 ± 25.8	+14.0	0.213
4° central retinal fixation stability (% ± SD)	80.3 ± 22.0	87.9 ± 15.2	7.6 ± 21.5	+9.4	0.142
Location fixation (% ± SD)	39.8 ± 36.2	54.5 ± 29.9	14.7 ± 33.6	+36.9	0.073

BCVA: Best Corrected Visual Acuity; SD: Standard Deviation

Table 3: BCVA relatively stable patients.

	Baseline	Final	Difference (n ± SD)	Difference (%)	P value (2-tailed)
BCVA (ETDRS letters ± SD)	31.6 ± 17.8	33.3 ± 18.9	1.7 ± 10.3	+ 5.3	0.438
12° retinal sensitivity (dB ± SD)	4.8 ± 3.6	5.7 ± 3.5	0.9 ± 1.6	+17.7	0.017
4° central retinal sensitivity (dB ± SD)	1.8 ± 2.4	2.1± 2.5	0.3 ± 0.9	+15.8	0.129
2° central retinal fixation stability (% ± SD)	45.6 ± 29.8	54.6 ± 29.4	9.0 ± 21.6	+19.6	0.045
4° central retinal fixation stability (% ± SD)	73.8 ± 28.4	82.3 ± 22.8	8.5 ± 21.0	+11.6	0.048
Location fixation (% ± SD)	29.0 ± 31.7	43.8 ± 31.5	14.8 ± 29.5	+51.1	0.022

BCVA: Best Corrected Visual Acuity; SD: Standard Deviation

Table 4: Mean 4° central retinal sensitivity relatively stable patients (change < ± 2dB).

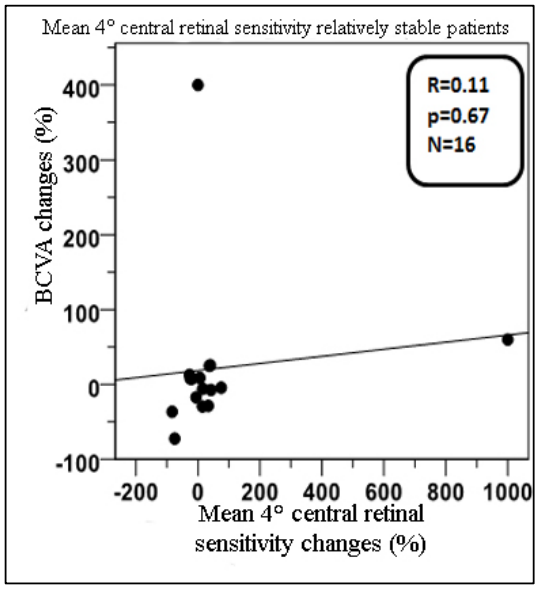

Figure 2: Pearson's correlation coefficient for the "Mean 4° central retinal sensitivity relatively stable patients" group.

Accordingly to previous published data, in our study ranibizumab treatment for nAMD showed efficacy to improve all mean functional parameters (BCVA and microperimetric indices) ($P < 0.05$) (Table 2) [19-23,29]. Furthermore, in agreement with Squirrell et al. the mean improvement in retinal sensitivity was found to be greater within the central field compared with the full macular field (+46.9% versus +25.3%) [23]. On the contrary, the mean reduction of the scotoma points was greater in the full macular field (-31.2% versus -24.6%). Therefore, our results suggest that successful treatment with ranibizumab leads to an improvement in retinal function, which is not limited to the foveal and parafoveal locations, but concerns the whole macular field. Moreover, these findings also suggest that the observed improvement in retinal function was not uniform across the macular field. These observations may represent the differential improvement in retinal function that would be expected after treatment of a focal disease such as a choroidal neovascular membrane.

However, the importance of microperimetry rests on the possibility to detect more subtle changes than visual acuity. This means threshold changes when visual acuity remains relatively stable (change in BCVA ≤ ± 4 ETDRS line).

Many authors have analyzed the role of microperimetry in nAMD patients after treatment [18-23,29], but none have focused on sub threshold changes using both BCVA and microperimetric indices.

Therefore, even if our results are not conclusive, they reveal that distant BCVA alone may underestimate the improvement in macular function that follows successful treatment with intravitreal ranibizumab. In fact, in all the sub-groups, changes measured as percentage were greater when measured by 4° central retinal sensitivity compared to BCVA, except for the "BCVA relatively stable" subgroup ($r = 0.71$; $P = 0.002$). Similar discrepancies between BCVA outcomes and retinal sensitivity data have been reported after the treatment of polypoidal choriovasculopathy with photodynamic therapy and vitreoretinal surgery for vitreomacular disease [10,11].

Furthermore, nAMD affects the entire macular region, while BCVA can assess only the foveal function, such as the 4° central retinal sensitivity, without evaluating the whole macular status. For this reason, analysis of whole macular function may be an important complementary tool to evaluate functional changes after treatment in nAMD patients.

Another important characteristic of microperimetry is represented by functional mapping: it may provide a greater accuracy of perceived visual function than BCVA alone. A recent work of Bansback et al. supports this hypothesis, demonstrating that in AMD patients, contrast sensitivity was better correlated to a person's health-related quality of life than to visual acuity [30]. If confirmed by other works, this could be really important because the introduction of new therapeutic agents is increasingly being scrutinized for the impact they have on improving health. If we are significantly underestimating the impact of macular disease on visual functioning, as our data suggest, then we may also be underestimating the therapeutic benefits of these new agents to treat macular disease.

Another important benefit of microperimetry is the possibility to evaluate fixation stability and fixation location, adding detailed information regarding the degree and pattern of functional damage in the whole macula. Fixation stability and fixation location are very important parameters to evaluate the life quality of the patient, because they are involved in daily activities, for example in the recognition of faces and symbols, orientation and reading. In our series of patients, both fixation stability and fixation location significant improved after treatment ($P<0.05$) (Table 2) and these outcomes are consistent with those of other papers [21,22,29].

On the basis of these results, fixation test on microperimetry could be used into visual rehabilitation clinics in order to suggest appropriate fixation training.

However, also limitation of our study should be mentioned. A potential limiting factor of microperimtric evaluation is represented by some technical problems such as patient inexperience and fixation loss. For such reasons, patients underwent a short training session before each repeat testing during the follow-up in order to minimize potential learning artifacts. Moreover, patient fatigue is an important limitation of microperimetry. Another potential limiting factor, suggested by glaucoma analysis, is that long-term fluctuation depends on the stage of the disease [31], so that fluctuation of microperimetry test might have different patterns at different stages of functional macular status in nAMD. Finally, the present study should be interpreted considering the limits of an uncontrolled study. For such reasons, prospective randomized studies are recommended to test the potentiality of microperimetry as a functional predictor.

In conclusion, microperimetry allows us a more accurate functional evaluation of nAMD patients, providing important information both for the baseline damage and the follow-up modifications after treatment with anti-VEGF drugs than alone BCVA, that seems to underestimate the functional benefit of new drugs for wet AMD.

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