Fixation Control before and after Treatment for Neovascular Age-Related Macular Degeneration

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Purpose. We studied changes in visual acuity (VA), fixation stability, and location of the preferred retinal locus (PRL) after treatment for unilateral neovascular age-related macular degeneration (AMD) for previously untreated eyes. Concomitant changes in fixation stability, PRL, and VA in the untreated fellow eye were also analyzed.

Methods. Pre- and posttreatment tests of visual acuity, fixation stability, and PRL location in both the treated and the untreated eyes were performed on 13 patients undergoing three monthly intravitreal injections of ranibizumab in one eye.

Results. For the treated eyes there were improvements in VA and fixation stability but no changes in the location of the PRL. No significant changes in any of the three variables were found in the untreated eye.

Conclusions. For previously untreated eyes, the improvement in visual acuity after intravitreal ranibizumab injections was accompanied by improvement in fixation stability. (*Invest Ophthalmol Vis Sci.* 2011;52:4208–4213) DOI:10.1167/iovs.10-7026

Age-related macular degeneration (AMD) is one of the main causes of low vision and legal blindness in the developed world.[1] AMD involves the progressive dysfunction and death of the macula's photoreceptors that may eventually lead to loss of acuity and other visual functions.[2,3] After the fovea is damaged by disease, the ocular motor system needs to acquire a new reference area in a part of the retina where vision remains intact. Bilateral foveal damage in monkeys[4] showed that this adaptation involves two independent processes: the stabilization of fixation and ocular motor adaptation for searching and positioning the images of visual targets at a consistent location in the peripheral retina. In patients with central vision loss, the damaged fovea cannot generate the input for proper eye movement control and fixation stability,[5–8] resulting in unstable fixation, especially shortly after the onset of the disease.[6–8] As part of the adaptation to the loss of central vision, patients learn to use a part of their eccentric retina for fixation,[9,10] a location referred to as a "pseudofovea"[8] or preferred retinal locus (PRL).[11] In cases of geographic atrophy in the dry form of the disease, the PRL tends to remain in a stable location.[12] Multiple PRLs tend to be associated with recent onset of the disease and/or relative scotomata.[6,13–15]

Neovascular or exudative AMD is the less common but more severe form of AMD,[16–19] accounting for approximately 10% of the cases but approximately 90% of severe vision loss caused by the disease. Neovascular AMD is characterized by abnormal blood vessels growing beneath the retinal pigment epithelium that cause irreversible damage to the photoreceptors and rapid vision loss.[20] One of the most recent treatments for neovascular AMD involves intravitreal injections of ranibizumab (Lucentis; Genentech, South San Francisco, CA), which binds to and inhibits the biological activity of the human vascular endothelial growth factor A (VEGF-A). Data from the MARINA,[21] ANCHOR,[22] and PIER[23] clinical trials testing the efficacy and safety of intravitreal ranibizumab demonstrated that this drug leads to improvements in retinal morphologic parameters and to either improvement or stabilization in visual acuity. Ranibizumab does not significantly regress the choroidal neovascularization (CNV) lesion, and improvement in visual acuity after treatment involves the diminished leakage of blood and fluid from the abnormal CNV vessels reducing the macular edema.[24] The large clinical trials investigating anti-VEGF therapy usually report changes in visual acuity as the main functional outcome measure, but visual acuity is only one of many outcomes that may not follow a common course. For instance, contrast sensitivity is a good indicator of change after treatment even when acuity does not show an improvement,[25,26] and visual acuity and multifocal electroretinogram measures correlate with a reduction in macular thickness only at the beginning of the disease.[27] Other variables that affect vision also come into play, including scarring and atrophy of the photoreceptors and of the pigment epithelium. These variables affect the relationships among visual function and the various measures of anatomical and physiological change, and must be studied to understand the course of the disease and the effects of treatment.[28]

We do not know if the rapid anatomical changes produced by anti-VEGF therapy are associated with changes in fixation stability and whether the latter are related to changes in visual acuity. We also do not know whether the PRL moves closer to the fovea after treatment, provided the fellow eye does not suffer changes or treatment. To examine these issues, patients with unilaterally active neovascular AMD were assessed before and after a course of three monthly intravitreal injections of ranibizumab. Acuity, fixation stability, and PRL location changes were obtained for the treated and the fellow untreated eye.

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Table 1. For the Treated Eye, Pre- and Posttreatment Acuity and Fixation Stability Means (SD)

	Pre-treatment	Post-treatment
Acuity (logMAR)	0.79 (0.48)	0.62 (0.49)*
Fixation stability ($\log_{10}$BCEA)	0.39 (0.71)	−0.06 (0.68)†

* $P = 0.01$, one tail; †$P = .004$, one tail.

Methods

Participants

Fifteen patients (10 women, age 79.5 ± 7.0 years [mean ± SD]) with a confirmed diagnosis of neovascular AMD were recruited from referrals to the Retina Clinic at the Toronto Western Hospital. They were all suitable candidates for an initial 3-month treatment course of monthly injections (one eye only) with intravitreal ranibizumab. All participants had a history of vision loss within the preceding 2 months. Neovascular AMD diagnosis was confirmed with fluorescein angiography (FL) and optical coherence tomography (OCT) tests. Exclusion criteria were bilateral neovascular AMD (i.e., no evidence of leakage either on FL or OCT in the fellow untreated eye), coexisting ocular pathologies, cognitive impairment, a history of neurologic disease, or ineligibility for ranibizumab treatment.[26] The fellow eye of one of the participants was amblyopic. The fellow eye of five others had a large inactive submacular choroidal neovascular scar and the fellow eye in the remaining nine had drusen but no evidence of active neovascular AMD. During the course of the study, two patients developed neovascular AMD in the initially untreated eye. Because these eyes could no longer be used as controls for changes in the treated eyes due to repeated testing, data from these patients were removed from analysis, leaving a sample size of 13 (age 78.9 ± 7.4 years [mean ± SD]).

Informed consent was obtained from all participants and the research was approved by the University Health Network Research Ethics Board and conducted in accordance with the tenets of the Declaration of Helsinki.

Apparatus

Monocular PRL location and fixation stability were recorded using fundus-related microperimetry (MP-1; Nidek Technologies SRL, Padua, Italy). This instrument records fixation using an auto eye-tracking system that registers horizontal and vertical eye positions using anatomical landmarks (i.e., retinal blood vessels) while compensating for stimulus projection changes due to movements of the eyes. Fundus movement was recorded with an infrared camera at a rate of 25 Hz while the patient fixated on a target projected onto a graphics screen. The fixation target used was usually a 3 deg red cross but, for the patients who could not see it, a larger target up to 6 deg was used.

Procedure

There were two study visits for each patient, the first before their first injection and the second approximately 1 week after their third. Each study session lasted approximately 30 minutes and included the following tests:

1. Best-corrected monocular for the treated and untreated eyes (logMAR units) at 6 m using a computerized version of the Early Treatment Diabetic Retinopathy Study test (single line).
2. Fixation stability, PRL location, and fundus photography for each eye measured with the microperimeter (MP-1; Nidek Technologies). During testing, the nonviewing eye was patched and patients were instructed to keep their gaze in the middle of the fixation target while their eye position was recorded for 30 seconds, as recommended by the manufacturer. If because of blinks or recording problems, <15 seconds of fixation were obtained, the trial was repeated. A color fundus photograph of each eye was obtained at the end of the recording session.

Data Analysis

We have previously shown that the fixation stability measures provided by the microperimeter's current software (MP-1; Nidek Technologies) are too coarse[29]; instead, we evaluated fixation stability with a bivariate contour ellipse area (BCEA) originally described by Steinman[30] using the horizontal and vertical eye positions recorded by the microperimeter. The BCEA is given by the following formula:

$$\text{BCEA} = \pi\chi^2\sigma_x\sigma_y\sqrt{1-\rho^2}$$

where σ_x and σ_y are SDs of the horizontal and vertical eye positions, ρ is their Pearson product–moment correlation, and $\chi^2 = 2.291$ is the χ^2 value ($2df$) corresponding to a probability value of $P = 0.682$ (±1 SD). The BCEA represents the region over which eye fixations are found for a given percentage of the time, in our case 68.2%. Analysis was carried out in accordance with the guidelines described elsewhere[29] to reduce instrument artifacts and extreme data outliers. We made no attempt to determine statistically[6,7] whether one or more PRLs were exhibited by the patients and instead used a global BCEA as a measure of the instability of fixation.

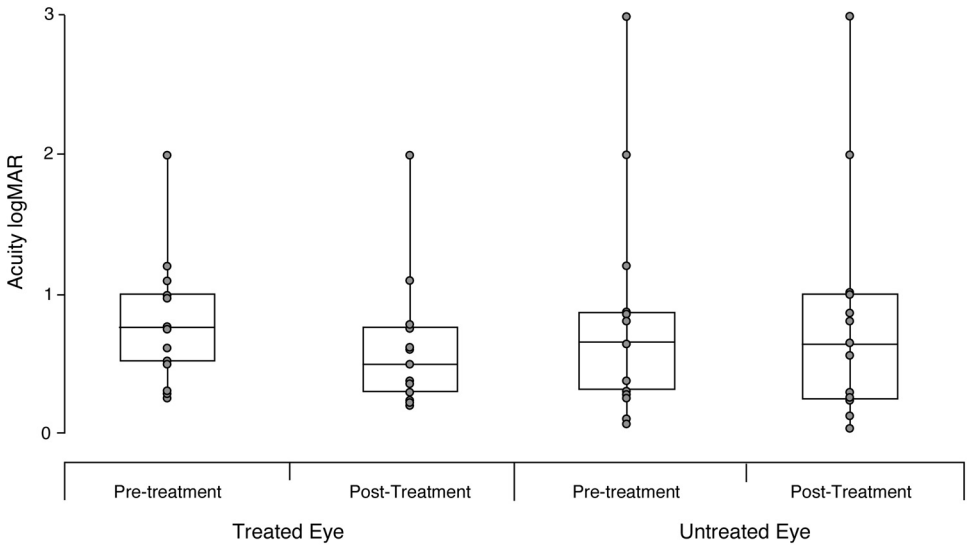

Figure 1. Box plots of the pre- and posttreatment monocular acuity (logMAR) values for the treated and untreated eyes. *Horizontal lines* show median values: 0.76, 0.50, 0.64, and 0.64, respectively (*left to right*).

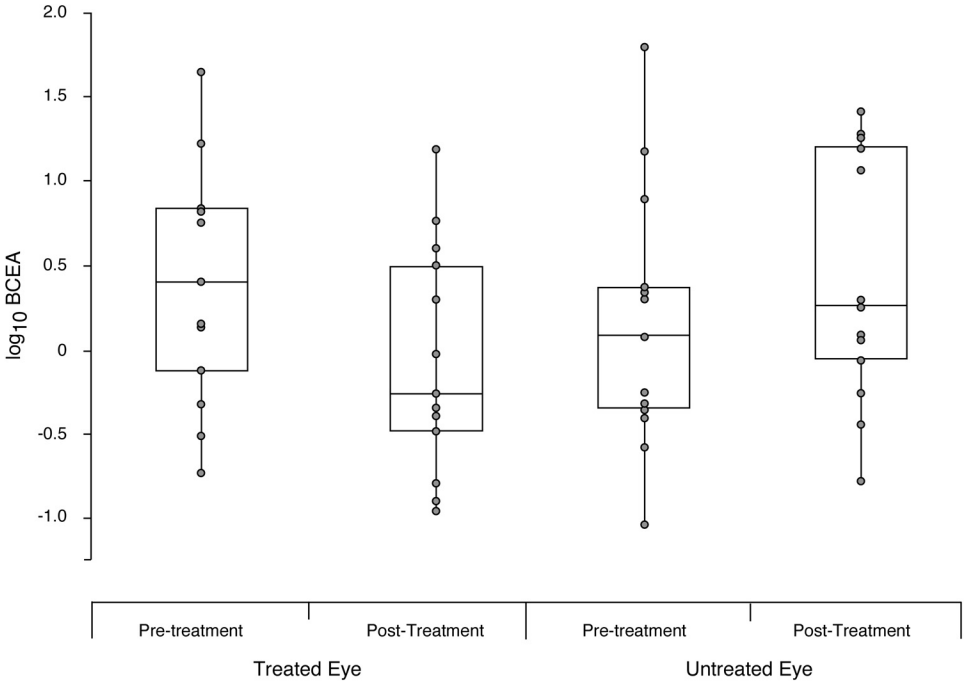

FIGURE 2. Box plots of the pre- and posttreatment fixation stability ($\log_{10}$ BCEA) values for the treated and untreated eyes. *Horizontal lines* show the $\log_{10}$-transformed median values corresponding to 2.52, 0.55, 1.22, and 1.82 deg^2, respectively (*left to right*).

The pre- and posttreatment difference in the location of the PRL was examined using the differential map analysis feature of the microperimeter (MP-1; Nidek Technologies), which calculates differences in degrees between the centroids of two fixation examinations for the same patient. Based on previous data,[29] a patient's foveal location on the fundus photograph was estimated to be at 15.5 deg (horizontally) and −1.3 deg (vertically) from the middle of the optic disc. These values were used to estimate the distance between the PRL and the estimated location of the fovea pre- and posttreatment.

Shapiro–Wilk tests showed that the distributions the BCEA values were not normally distributed ($P < 0.05$) and a $\log_{10}$ transformation of the BCEAs was used to normalize them.

RESULTS

Treated Eye

After treatment, the mean change in the treated eye's acuity ($\Delta VA = VA_{pretreatment} - VA_{posttreatment}$) was a modest but statistically significant improvement [$t(12) = 2.98$, $P = 0.01$] of 0.17 logMAR units (median = 0.08), ranging from an improvement of 0.6 to a decrement of 0.1 (Table 1, Fig. 1).

The mean change in fixation stability ($\Delta BCEA = \log_{10}BCEA_{pretreatment} - \log_{10}BCEA_{posttreatment}$) showed an improvement of 0.46 $\log_{10}deg^2$ (range: improvement of 1.91 to decrement of 0.17), which was also statistically significant ($P = 0.004$; Fig. 2). Correlations between fixation stability and visual acuity were significant, both pre- [$r(11) = 0.66$, $P = 0.006$] and posttreatment [$r(11) = 0.60$, $P = 0.01$].

The correlation between ΔBCEA and ΔVA was also significant [$r(11) = 0.53$, $P = 0.03$], even after using the pretreatment acuity scores as a covariate [$r(10) = 0.52$, $P = 0.04$, one-tail] (Fig. 3).

Figure 4 shows the fixation dispersions and their corresponding acuity values pre- and posttreatment.

To examine the effects of regression to the mean, the change in VA was analyzed using the pretreatment acuity values as a covariate. The resulting correlation was nonsignificant [$r(11) = 0.20$, $P = 0.26$]. A similar analysis of ΔBCEA as a function of the pretreatment BCEA also yielded a nonsignificant correlation [$r(11) = 0.42$, $P = 0.08$].

For the centroids of the pre- and posttreatment fixation dispersions, the mean of the change in distance from the fovea was 1 ± 3.26 deg (mean ± SD) after treatment, which was not statistically significant [$t(11) = 1.63$, $P = 0.13$]. Analysis of the changes in the PRLs' retinal quadrants using Kendall's coefficient of concordance (W) showed that the distributions of locations before and after treatment were also not significantly different ($W = 0.51$, $P = 0.41$).

Untreated Eye

As expected, for the untreated eye there were no significant changes in acuity [$t(12) = 1.61$, $P = 0.13$] or fixation stability [$t(12) = 2.12$, $P = 0.06$] between the two tests. The correlation between ΔBCEA and ΔVA was also nonsignificant [$r(11) =$

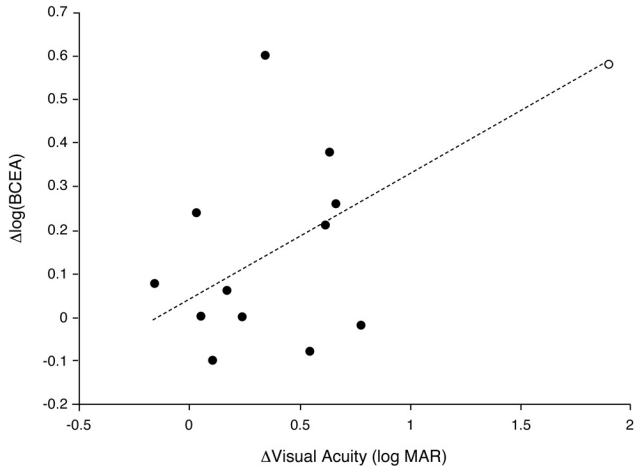

FIGURE 3. For the treated eye, change in fixation stability (ΔBCEA) as a function of the change in visual acuity (ΔVA). The bivariate functional equation[31] of the fitted line is: $y = 0.041 + 0.29x$. The data point shown as an *unfilled circle* is not an extreme outlier by standard criteria[32]; that is, its z scores of 2.79 for fixation stability and 1.75 for visual acuity are both smaller than the usual criterion of $z \geq 3.29$ ($P < 0.001$, two-tailed test).

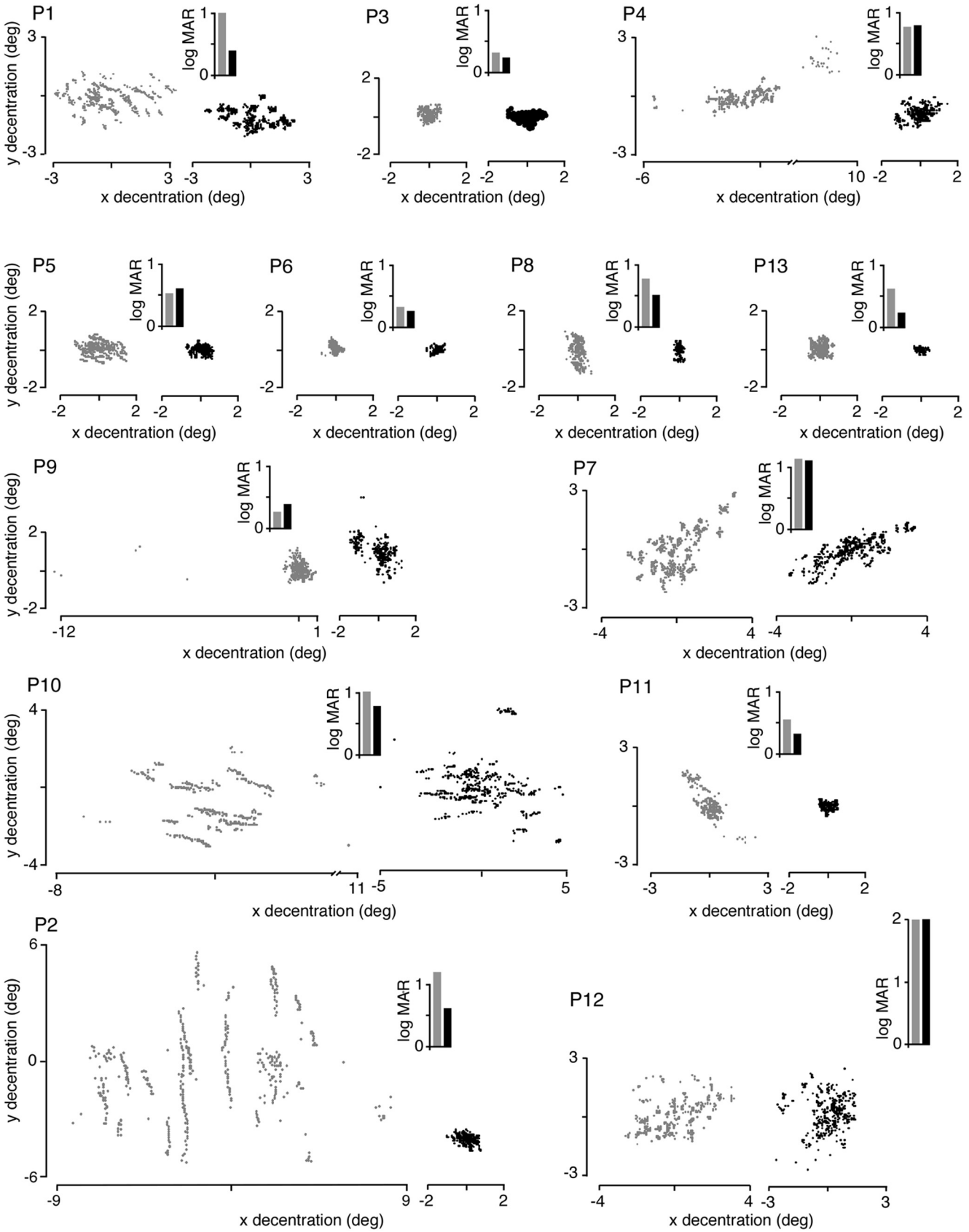

Figure 4. For the 13 patients, pretreatment (*gray*) and posttreatment (*black*) fixation dispersions (outliers removed) and logMAR values for the treated eye.

−0.14, $P = 0.33$]. The change in VA with the pretreatment acuity values as a covariate yielded a nonsignificant correlation [$r(11) = -0.07$, $P = 0.41$] and a similar analysis of ΔBCEA also yielded a nonsignificant correlation [$r(11) = 0.42$, $P = 0.08$].

The correlations between fixation stability and visual acuity were significant before [$r(11) = 0.52$, $P = 0.03$] and after treatment [$r(11) = 0.52$, $P = 0.03$].

Discussion

The present study showed that a 3-month treatment with ranibizumab to a previously untreated eye was followed by improvements in visual acuity and in fixation stability. Some of the patients with poorer initial acuity or fixation stability appear to have improved more, but this effect was not statistically significant. Although some studies have found a relationship between visual acuity and fixation stability,[29,30,33] a significant correlation between fixation stability and acuity has not always been found,[7,8,10,34] perhaps because such correlation is a function of at least two factors.

Timberlake et al.[34] proposed that the precision of fixation depends on two kinds of input: the retinal slip or visual error generated by the target's image on the retina and the extraretinal signal from the eye muscles.[35,36] The relative weight of these inputs changes as a function of eccentricity, with retinal slips decreasing sharply away from the fovea and the proprioceptive signal becoming more important for peripheral vision. For patients with central vision loss, these two factors would differentially affect those with relative scotomas and/or islands of good vision close to the fovea and patients with absolute central scotomas.

The second factor affecting the correlation between fixation stability and visual acuity has to do with the differences between the two eyes. In previous research comparing the fixation stability of patients with large interocular differences in acuity, we found[33] that fixation stability is determined by the better eye. Although the fixation stability of the worse eye dramatically improves during binocular viewing, the fixation stability of the better eye is the same regardless of whether viewing is monocular or binocular. The correlation between fixation stability and visual acuity is thus reduced when both eyes, instead of the better eye only, are included in the analysis. In the case of sudden changes in the retina's health it may be important to know the initial differences between the worse and the better eye to better understand the relationship between their acuity and fixation stability. This research could be performed on patients at risk of developing neovascular AMD.[37]

It is well known that as a single measure of visual function, visual acuity has limitations because it is the last of many functions to show deterioration with aging[38] as well as with AMD.[39] It has been found that eyes whose fellow eye suffers from exudative AMD themselves have a compromised foveal function, even when they exhibit good acuity.[40] Data reported by Eisner and colleagues[41] show that for eyes with nonexudative macular degenerative changes and one or more high-risk fundus characteristics for future vision loss (focal hyperpigmentation, more than minimal drusen confluence, and large drusen size), a number of other visual functions such as dark adaptation, absolute sensitivity, S cone–mediated sensitivity, and color matching are compromised significantly. Improvements in visual acuity and retinal thickness can be demonstrated within 4 weeks after treatment with ranibizumab, whereas retinal sensitivity as measured by microperimetry shows a trend of progressive improvement until 24 weeks.[42] It is not known whether improvements in fixation control show a similar trend.

A complete understanding of the visual changes that accompany treatments of retinal disease should include ocular motor control[43] in addition to measures of retinal function and sensitivity other than acuity.[44] Further research into the functional and anatomical consequences of treatment for neovascular AMD will provide additional insight not only into its effects but also into the adaptation processes that the visual system must undergo when macular function is compromised and is later improved by treatment.

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