Preferential Hyperacuity Perimeter as a Functional Tool for Monitoring Exudative Age-Related Macular Degeneration in Patients Treated by Intravitreal Ranibizumab

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PURPOSE. To analyze the response to anti vascular endothelial growth factor (VEGF) treatment for exudative age-related macular degeneration (AMD), with respect to changes in the Preferential Hyperacuity Perimeter (PHP), best-corrected visual acuity (BCVA), and spectral-domain optical coherence tomography (SD-OCT), and to investigate whether the PHP score predicts the need for reinjection.

METHODS. Consecutive patients with newly diagnosed exudative AMD underwent the PHP metamorphopsia test, BCVA, and SD-OCT at five time points after initiation of ranibizumab therapy (0.05 mL/0.5 mg). At the third and sixth months, reevaluation for additional injections was done. The relationships between PHP, BCVA, and SD-OCT parameters over time as well as their ability to predict the need for reinjection were examined.

RESULTS. Analysis included 17 eyes (17 patients, 70% females; mean age, 83.2 years). The mean PHP metamorphopsia test score improved from 25.6 ± 41 (baseline) to 10.7 ± 20.1 (P < 0.05) over 6 months, after a mean of 4.2 (±1.0) injections. Mean reduction in SD-OCT parameters well reflected the functional improvements as evaluated by PHP (Spearman correlation = 0.9, P < 0.05). Mean BCVA did not improve over 6 months (0.6 vs. 0.58 logMAR), and neither correlated with SD-OCT morphologic changes (Spearman correlation = 0.1, P > 0.05) nor with PHP functional changes (Spearman correlation = 0.1, P > 0.05). The PHP predicted the need for reinjection with an accuracy of 75% (sensitivity, 83 ± 12%; specificity, 67 ± 15%), whereas a combination of all the measurements (PHP, BCVA, and SD-OCT) yielded an accuracy of 87% (sensitivity, 83 ± 12%; specificity, 90 ± 10%).

CONCLUSIONS. Improvement in the metamorphopsia test score after intravitreal injections of ranibizumab, as well as its ability to predict the need for retreatment, suggest that PHP may be used to monitor response to anti-VEGF therapy in patients with exudative AMD. (Invest Ophthalmol Vis Sci. 2011;52: 7012-7018) DOI:10.1167/iovs.11-7517

Age-related macular degeneration (AMD) is the leading cause of irreversible vision loss in the developed world among people older than 50 years of age. The exudative form is characterized by an abnormal growth of newly formed vessels (choroidal neovascularization [CNV]) within the macula. Ranibizumab (Lucentis; Genentech Inc., South San Francisco, CA) is a recombinant, humanized, monoclonal antibody antiangiogenic fragment (Fab) that neutralizes all biologically active forms of vascular endothelial growth factor A (VEGF). Intravitreal injections (IVIs) of ranibizumab constituted the first therapy for exudative AMD to show in two Phase III clinical studies an improvement in mean visual acuity (VA). These results were obtained by a fixed-dosing regimen of ranibizumab 0.5 mg or 0.3 mg monthly, injected over 24 and 12 months, respectively. Studies have shown that monthly visits, for both functional and morphologic monitoring, are necessary in patients undergoing intravitreal anti-VEGF treatment for AMD on an as-needed (pro re nata) basis, to take optimal retreatment decisions.

Without monthly monitoring many patients with CNV may seek medical intervention when the benefits of treatment may already be less than optimal. In fact, brain mechanisms that compensate for retinal malfunction often delay the symptoms related to changes in the subretinal space and in the subretinal pigment epithelium (RPE) space (i.e., metamorphopsia, scotoma, or blurring), which are due to CNV activation.

High costs and limitation of human resources make frequent fluorescein angiography (FA) and optical coherence tomography (OCT) imaging unrealistic. Therefore, in patients with AMD treated by intravitreal anti-VEGF, monitoring with sensitive psychophysical tools could advance the time of CNV reactivation and improve the outcome of treatment.

Since 2005, Preferential Hyperacuity Perimeter (Foresee PHP; Notal Vision, Tel Aviv, Israel), a device for monitoring visual distortion, has been proposed as a tool to detect CNV activity. PHP has also been suggested as a tool for monitoring the therapeutic response to photodynamic therapy and anti-VEGF treatment in neovascular AMD. PHP uses the sensitive visual function of hyperacuity to detect and quantify the severity of visual defects associated with the development of CNV, such as metamorphopsia and scotoma within the central 14° of visual field. Recently, the home version of the PHP (Foresee Home), which is based on a technology similar to that of the earlier PHP (Foresee PHP), has shown good sensi-
tivity and specificity in discriminating between patients with newly diagnosed CNV and intermediate AMD.\textsuperscript{19}

In a previous pilot study we investigated the ability of this noninvasive eye exam to assess responsiveness to ranibizumab therapy;\textsuperscript{20} Here we analyzed the trends in best-corrected visual acuity (BCVA), PHP, and spectral-domain (SD)-OCT, over 6 months. The relationships between these measurements over time as well as their ability to predict need for reinjection were examined.

**METHODS**

Seventeen consecutive patients with newly diagnosed CNV arising from AMD underwent a treatment course of IVIs of ranibizumab (0.05 mL/0.5 mg) at the University Eye Clinic of Créteil between January and December 2009. Before administration of ranibizumab, patients were informed about the experimental aspects of the study and the need for repeating several examinations at each scheduled follow-up visit. A written informed consent according to the tenets of the Declaration of Helsinki, and in agreement with our local ethics committee, was obtained from each patient enrolled.

Criteria for inclusion were: (1) age $\geq$ 50 years old; (2) BCVA between 20/200 and 20/40, as evaluated by Early Treatment Diabetic Retinopathy Study (ETDRS) charts; (3) the presence of newly diagnosed subfoveal CNV secondary to AMD, showing at least 50% active lesion as evaluated by fundus biomicroscopy, FA, and infrared green angiography; and (4) subretinal fluid, cystic maculopathy, or 1-mm central macular thickness of at least 250 $\mu$m on OCT. Patients with previous treatment for exudative AMD in the study eye, refractive error of more than $\pm 6$ diopters, CNV attributable to causes other than AMD, active intraocular inflammation, or any other retinopathy (such as diabetic retinopathy, retinal venous occlusion, or epiretinal membrane) in the study eye, were excluded.

After an initial treatment course of three monthly IVIs of ranibuzum (loading phase), patients received further IVIs if any of the following conditions applied: BCVA loss of at least five letters associated with macular thickening; recurrence of fluid within a previously dry macula as evaluated by OCT; persistence of intra-/subretinal fluid as evaluated by OCT; central macular thickness (CMT) increase of at least 50 $\mu$m; newly onset macular hemorrhages; and persistence or recurrence of leakage from the lesions on FA.

From baseline (before the first IVI of ranibizumab) to the sixth month, each patient underwent a monthly assessment of BCVA measured at 4 m with standard ETDRS charts, and a complete ophthalmic examination that included slit-lamp biomicroscopy, intraocular pressure measurement, and SD-OCT using retinal angiography OCT (Spectralis Heidelberg Retinal Angiograph [HRA]-OCT; Heidelberg Engineering, Heidelberg, Germany). FA was performed in all patients at baseline and at the discretion of the examiner during follow-up.

In this study we used, at each follow-up visit, the “follow-up” protocol of HRA-OCT, which grants reacquisition of each OCT line actually referenced with the baseline acquisition. The retinal thickness of the 1-mm central retina (central macular thickness) was evaluated using a protocol of 19 horizontal lines. Several OCT parameters, reflecting the disease activity, were also evaluated on a single (for each eye) SD-OCT scan. For selection, scans had to show the lesion and the presumed fovea. Parameters measured in the selected scan included: maximal retinal thickness at the fovea, maximal height of subretinal fluid, maximal diameter of the largest retinal cyst, and maximal height of pigment epithelium detachment.

PHP (Foresee) was performed at five time points: baseline, 1 week, 1 month, 3 months, and 6 months after initiation of a course of IVIs of ranibizumab (0.05 mL/0.5 mg). PHP (Foresee) is a macular perimetry device that uses a method based on the human visual function of hyperacuity, which gives it the capability of detecting functional changes. Hyperacuity (also termed “Vernier acuity”) is defined as the ability to perceive a difference in the relative spatial localization of two or more visual stimuli. The hyperacuity threshold may be as low as 5 to 6 seconds of arc. Retinal elevation, such as that which occurs in AMD, causes a shift in the regular position of photoreceptors. It is hypothesized that such a shift causes an object to be perceived at a different location from its true location in the visual field. This perceived shift in object location, which is recorded by the PHP, takes advantage of the human phenomenon of hyperacuity and may be, in fact, the anatomical explanation for metamorphosis. All examinations were performed under the supervision of a trained physician (GQ).

During the test, the patient’s visual attention is drawn to a fixation cue displayed at the center of a touch screen. When the device automatically recognizes that the patient is ready to respond, a stimulus briefly presented on the display. Each stimulus consists of a dotted line, in which few dots are misaligned relative to the main axis of the stimulus. If the degree of misalignment exceeds a personal threshold, the patient may perceive an artificial distortion. The patient’s task is to identify where the distortion appears and to mark this location on the display. A succession of such stimuli is flashed on various locations of the display, to cover the entire macular field. When a stimulus is flashed on a location that corresponds to a healthy portion of the retina, the artificial distortion is readily detected. If the stimulus is flashed on a location that corresponds to a CNV lesion, RPE elevation may create the perception of a pathologic distortion. In the patient’s perception, competition for visual attention takes place between the artificial and pathologic distortions. If the pathologic distortion is more prominent than the artificial distortion, the patient is more likely to perceive the former and ignore the latter. During the test, varying sizes of artificial distortions are displayed, allowing quantification of the degree of the pathologic distortion. A compilation of the errors performed during the test enables location of the visual distortions as well as estimation of their severity. For severity measurements we have used the “PHP test score” (a continuous, global score, between $-30$ and $+600$, that represents the log [Probability (Responses pattern $\backslash$ CNV)/Probability (Responses pattern $\backslash$ Intermediate))]. This score is basically the same score that has been used in the PHP for the last few years and has been validated as a classifier to discriminate between patients with intermediate nonneovascular AMD and patients with neovascular AMD (CNV). Usually this score is normalized to values of $P$ between 0 and 1 (which indicates the probability of nonneovascular AMD eyes to have such a visual field defect). Since in posttreatment mode all patients have CNV (and the question had changed from “what is the likelihood of this eye to have CNV” to “what is the activity level of the CNV”), we used this score in its nonnormalized manner to prevent the “ceiling effect.”

**Statistical Analysis**

Descriptive statistics were performed to present the trends of change for the different features: BCVA converted to the logarithm of the minimum angle of resolution (logMAR), the SD-OCT parameters investigated (central macular thickness [CMT], maximal retinal thickness at the fovea [MRTF], maximal height of subretinal fluid [MHSRF], maximal diameter of the largest retinal cyst [MDRC], and maximal height of pigment epithelium detachment [HPED]), the “combined parameter” [sum the last four former parameters] and PHP measurements represented as “test score” (Test score $= \log [\text{Probability (Responses pattern } \backslash \text{CNV)/Probability (Responses pattern } \backslash \text{Intermediate})]$).

Since the normality assumption was not satisfied for the measurement variables, we used nonparametric tests: the Spearman correlation was evaluated, to examine the degree of correlation between OCT average parameters change, logMAR BCVA average change, and PHP test score average change. Differences between baseline and 6-month visits were compared using Wilcoxon signed-rank test.

For the question of whether an increase in PHP test score, within the individual, was associated with an increase in SD-OCT combined parameter, we removed the differences between subjects and looked only at changes within subjects by multiple regression method, using the SD-OCT data as the outcome variable and the PHP test score and
This is a text file that contains a table and some explanatory text. The table is a demographic and clinical data of patients treated by intravitreal ranibizumab injection for exudative macular degeneration. The explanatory text discusses the predictors of need for reinjection and the results of the study.
months, \( P < 0.05 \), maximal height of subretinal fluid (71.8 \( \mu m \) at baseline, 17.7 \( \mu m \) at 6 months, \( P < 0.05 \)), maximal diameter of the largest retinal cyst (106.85 \( \mu m \) at baseline, 32.9 \( \mu m \) at 6 months, \( P < 0.05 \)), and maximal height of pigment epithelial detachment (184 \( \mu m \) at baseline, 128.4 \( \mu m \) at 6 months, \( P = 0.052 \)), as evaluated by SD-OCT, well reflected the functional PHP improvements, showing a significant correlation with metamorphopsia changes (Spearman correlation = 0.9, \( P < 0.05 \)). Mean BCVA did not improve over 6 months (0.6 vs. 0.58 logMAR).

The mean baseline central macular thickness was 404.5 ± 153 \( \mu m \). It significantly reduced to 286.3 ± 65 \( \mu m \) at 6 months (Wilcoxon signed-rank test, \( P < 0.05 \)). Mean reduction in “combined OCT parameter” (central macular thickness, maximal retinal thickness at the fovea, maximal height of subretinal fluid, maximal diameter of the largest retinal cyst, and maximal height of pigment epithelium detachment) was also recorded at 6 months (Wilcoxon signed-rank test, \( P < 0.05 \)).

The correlation coefficient between SD-OCT measurements and PHP metamorphopsia test scores at the five time points within subjects was 0.5 (\( P < 0.05 \)), which indicates whether an increase in PHP test score, within the individual, was associated with an increase in OCT combined parameter (Fig. 4, case presentation).

The formal analysis and the quantification of the relationships between functional and morphologic changes are presented in Table 4. There was a significant correlation between the PHP metamorphopsia changes and the OCT anatomic changes (Spearman correlation = 0.9, \( P < 0.05 \)). This indicates that the PHP metamorphopsia changes (average) and the OCT anatomic changes have relationships along time. The reason for this strong correlation (although the curves do not have the exact same trend) is that we used nonparametric analysis (Spearman correlation), since we could not assume normal distribution; nonparametric analysis reflects trends regardless their quantitative strength.

No correlation was found (Spearman correlation = 0.1, \( P = 0.5 \)) between the PHP metamorphopsia changes and the mean BCVA changes. Also, no correlation between the mean BCVA changes and the OCT anatomic changes was found (Spearman correlation = 0.2, \( P = 0.3 \)).

A repeated-measures ANOVA showed a negative significant effect of treatment (improvement over time) on PHP test score, BCVA, and SD-OCT combined parameter (Type III tests of fixed effects, \( P < 0.05 \)).

In the current series, the OCT combined parameter, at 3 and 6 months, predicted the need for reinjection, with an accuracy of 67\% [threshold-combined = 450 \( \mu m \)]; sensitivity, 67 ± 15\%; specificity, 67 ± 15\%. The BCVA predicted the need for reinjection with an accuracy of 40\% [threshold-logMAR = 0.6 \( \mu m \)]; sensitivity, 42 ± 17\%; specificity, 38 ± 17\%]. The Preferential Hyperacuity Perimeter predicted the need for reinjection with an accuracy of 75\% [threshold-test score = 8.0]; sensitivity, 83 ± 12\%; specificity, 67 ± 15\%].

Combination of BCVA (logMAR) and OCT (combined parameter), at 3 and 6 months, predicted the need for reinjection with an accuracy of 75\% [threshold-model = 0.35]; sensitivity, 83 ± 12\%; specificity, 62 ± 15\%.

**Table 3.** Medians (Interquartile Range) of Functional and Morphologic Characteristics of Patients with Exudative Macular Degeneration, at Baseline (before Intravitreal Ranibizumab Injection), 1 Week, 1 Month, 3 Months, and 6 Months after Initiation of Intravitreal Ranibizumab Injections

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Before Treatment</th>
<th>1 Week after</th>
<th>1 Month after</th>
<th>3 Months after</th>
<th>6 Months after</th>
</tr>
</thead>
<tbody>
<tr>
<td>VA, logMAR</td>
<td>0.7 (0.6)</td>
<td>0.7 (0.6)</td>
<td>0.7 (0.49)</td>
<td>0.7 (0.7)</td>
<td>0.7 (0.7)</td>
</tr>
<tr>
<td>CMT, ( \mu m )</td>
<td>397.0 (122)</td>
<td>309.0 (76)</td>
<td>296.0 (54)</td>
<td>261.0 (77)</td>
<td>286.0 (47)</td>
</tr>
<tr>
<td>MHSRF, ( \mu m )</td>
<td>0.0 (118)</td>
<td>0.0 (0)</td>
<td>0.0 (0)</td>
<td>0.0 (0)</td>
<td>0.0 (0)</td>
</tr>
<tr>
<td>MRTF, ( \mu m )</td>
<td>365.0 (135)</td>
<td>318.0 (127)</td>
<td>298.0 (141)</td>
<td>271.0 (98)</td>
<td>267.0 (56)</td>
</tr>
<tr>
<td>HPED, ( \mu m )</td>
<td>146.0 (62)</td>
<td>131.0 (78)</td>
<td>112.0 (62)</td>
<td>111.0 (65)</td>
<td>111.0 (79)</td>
</tr>
<tr>
<td>MDRC, ( \mu m )</td>
<td>78.0 (165)</td>
<td>0.0 (0)</td>
<td>0.0 (0)</td>
<td>0.0 (0)</td>
<td>0.0 (0)</td>
</tr>
<tr>
<td>Combined, ( \mu m )</td>
<td>727.0 (367)</td>
<td>513.0 (122)</td>
<td>458.0 (191)</td>
<td>408.0 (240)</td>
<td>449.0 (187)</td>
</tr>
<tr>
<td>PHP (Test Score)</td>
<td>20.08 (46.3)</td>
<td>13.79 (26.3)</td>
<td>8.64 (32.9)</td>
<td>8.57 (21.8)</td>
<td>7.71 (18)</td>
</tr>
</tbody>
</table>

Data are shown as mean ± SD.

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**FIGURE 1.** Changes in BCVA (logMAR) over 6 months.

**FIGURE 2.** Changes in OCT combined parameter over 6 months.
Combination of BCVA (logMAR), PHP (test score), and each OCT parameter (including CMT, MRTF, HPED, and MDRC, in addition to the combined parameter) predicted the need for reinjection, at 3 and 6 months, with an accuracy of 87% [(threshold-model = 0.36); sensitivity, 83 ± 12%; specificity, 90 ± 10%]. The probability of χ² test on the log ratio was P < 0.0003. The odds ratio (95% confidence interval) of the model parameters were: PHP test score, 0.96 (0.86,1.06)/CMT, 1.01 (0.96,1.06)/MRTF, 0.88 (0.75,1.02)/HPED, 0.88 (0.77,1.00)/MDRC, 0.98 (0.89,1.08)/combined, 1.17 (0.99,1.39)/logMAR, 0.000067 (2.693E-10,16.30). The area under the receiver operating characteristics curve was 0.96.

**DISCUSSION**

To date, there are still no simple and reproducible functional tests that reflect the morphologic state of the macula in patients affected with exudative AMD. In a previous study we
investigated the short-term morphologic and functional changes after a single IVI of ranibizumab in a series of patients with AMD affected with newly diagnosed CNV, and found a strong correlation between functional PHP metamorphopsia changes and morphologic OCT changes.20

In the present study, a consecutive series of 17 patients affected with newly diagnosed exudative AMD who underwent a series of IVIs of ranibizumab over a period of 6 months were prospectively evaluated with respect to functional (BCVA and PHP metamorphopsia test) and morphologic changes (SD-OCT parameters). After the loading phase (three monthly treatments), patients underwent repeated IVIs of ranibizumab on the basis of BCVA (loss of at least five letters) and OCT changes (persistence/recurrence of intra/subretinal fluid, CMT increase of at least 50 μm). This allowed analyzing the prediction of need for reinjection at standardized time points (at 3 and 6 months from baseline evaluation) on the basis of the PHP metamorphopsia test. To the best of our knowledge, this represents the first study to investigate the utility of PHP as a tool to detect recurrences and, thus, to take retreatment decisions, in patients undergoing anti-VEGF treatment for exudative AMD.

Overall we found a significant correlation between the PHP metamorphopsia changes and the SD-OCT anatomic changes (Spearman correlation = 0.9, P < 0.05), whereas correlation between the PHP metamorphopsia changes and the mean BCVA changes, as well as between the mean BCVA changes and the OCT anatomic changes, were nonsignificant (0.67 and 0.7 Spearman correlation, respectively; P = 0.1). These results are not surprising. In fact, several studies have shown that distance VA has a poor degree of correlation with both quantitative (FA) and quantitative (OCT) assessments of macular morphology.22–24 Moreover, distance VA is not the best measure of visual function because it is a reflection of resolution at the foveola (representing the central 1° of visual field),25 and most CNV recurrences start as extrafoveal. Finally, clinical experience suggests that VA changes can lag behind morphologic worsening: in fact, brain mechanisms compensate for retinal malfunction and often delay the typical symptoms of CNV recurrence until the lesion is relatively large and subfoveal. On the other hand, the Preferential Hyperacuity Perimeter is based on the phenomenon of hyperacuity, the human ability to perceive minute differences in the relative spatial localization of two objects in space, and the brain is exceptionally sensitive to such deviation.

The 17 patients included in the present study underwent repeated injections (mean, 4.2 ± 1.0) over 6 months. By analyzing the 3- and 6-month time points, the PHP showed an accuracy of 75% (sensitivity, 83%; specificity, 67%) with respect to the prediction of need for reinjection. In patients undergoing intravitreal anti-VEGF treatment for AMD, monthly visits are necessary for monitoring outcomes and need for reinjection. In this context, the PHP represents an objective and easily performed functional test that, based on our findings, would seem extremely helpful to take optimal retreatment decisions in the clinical setting.

A home version of the PHP (Foresee Home) is currently under development. This home-based test, which has been designed for patients to self-monitor AMD, is also expected to serve as a follow-up tool for patients on a frequent basis.19 Our current results favor the idea that the home version (Foresee Home) may be effectively used to detect recurrences and, thus, to take optimal retreatment decisions, in patients undergoing anti-VEGF treatment for exudative AMD. If our preliminary results will be confirmed in the home environment, the home version of PHP (Foresee Home) would dramatically change current clinical practice, allowing for fewer monitoring visits.

Other techniques are presently being used to quantify metamorphopsia, such as the Amsler grid, orientation discrimination,25,26 texture discrimination,26,27 shape discrimination,28 and M-CHARTS.29 Comparison of the PHP to other methods in quantifying metamorphopsia (i.e., the Amsler grid and M-CHARTS) has already been described in previous studies.29,30 However, to the best of our knowledge, none of these methods has been examined in posttreatment mode to follow the effect of the anti-VEGF treatment. None of these methods was correlated either with the level of CNV activity or is being used to predict need for retreatment; therefore it is difficult to compare the use of PHP in posttreatment mode to follow the effect of the anti-VEGF treatment with other techniques. Such a study (designed for exploration of the different functional methods to follow response to treatment) is certainly needed.

In the present study we chose the PHP over other techniques because the PHP is the only method previously tested in indication of posttreatment follow-up.18,20 All these studies suggest usefulness of PHP in following anti-VEGF treatment and reasonably justify its selection.

Our study has several limitations. The number of eyes (n = 17) prospectively followed-up and included in the analysis is relatively small. Moreover, the follow-up was relatively short (6 months) and, thus, during the study period, at least six IVIs of ranibizumab were administered to the patients. Therefore, the present study does not provide definitive data on the correlation between progressive reduction of morphologic signs of disease activity (OCT parameters) and functional improvements, as evaluated by PHP, in eyes with CNV evolving toward quiescent inactive fibroatrophic lesions, as may happen after a certain number of repeated anti-VEGF treatments. In turn, the present study simply describes relatively preliminary testing of PHP in patients with neovascular AMD. A much larger study of the efficacy of the technique by a different version of the device (Foresee Home) is being conducted as an ancillary evaluation in the national Age-Related Eye Disease Study, Part 2 (AREDS-2), a multi-institutional controlled clinical trial (http://www.foreseehome.com/AREDS2_eye_disease_study.html).

In conclusion, our findings suggest that PHP may be considered a useful tool, not only to monitor response to anti-VEGF treatment, but also to detect recurrences, and thus to take optimal retreatment decisions, in patients undergoing anti-VEGF treatment for exudative AMD.

References


