Ranibizumab Treatment for Pigment Epithelial Detachment Secondary to Neovascular Age-Related Macular Degeneration

Post Hoc Analysis of the HARBOR Study

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Purpose: To analyze the effect of baseline presence and height of pigment epithelial detachments (PEDs) on visual and anatomic outcomes at 24 months in patients with neovascular age-related macular degeneration (AMD) treated with ranibizumab.

Design: Post hoc analysis of HARBOR, a 24-month, phase III, randomized, multicenter, double-masked, active treatment-controlled study (clinicaltrials.gov identifier, NCT00891735).

Participants: One thousand ninety-seven patients with neovascular AMD.

Methods: Intravitreal ranibizumab 0.5 mg or 2.0 mg monthly or pro re nata (PRN) after 3 monthly loading doses.

Main Outcome Measures: We evaluated the effect of presence and height of baseline PED on several outcomes at 24 months, including best-corrected visual acuity (BCVA), change in PED height, resolution of PED, and number of injections in the PRN arms. Development of macular atrophy at month 24 by presence or absence of PED was evaluated.

Results: Five hundred ninety-eight (54.5%) patients showed PED at baseline. In the ranibizumab 0.5-mg PRN group, mean numbers of injections were similar for patients with PED present or absent at baseline (14.0 vs. 12.5). Mean BCVA gains from baseline to 24 months were seen in all treatment groups and were comparable in patients with or without PED at baseline treated with ranibizumab 0.5 mg monthly (PED present at baseline, +9.0 letters; PED absent at baseline, +11.3 letters), 0.5 mg PRN (present, +8.4; absent, +7.9), 2.0 mg monthly (present, +7.1; absent, +11.1), or 2.0 mg PRN (present, +7.2; absent, +8.8). When analyzed by baseline PED height, mean BCVA gains were demonstrated and comparable in all treatment groups at 24 months except for patients treated with ranibizumab 2.0 mg monthly in the extra-large group (PEDs >352 μm; mean BCVA change, −0.8 letters). At 24 months, 53.2% (0.5 mg monthly), 44.5% (0.5 mg PRN), 70.4% (2.0 mg monthly), and 57.3% (2.0 mg PRN) of patients showed complete resolution of PED.

Conclusions: Ranibizumab 0.5 mg given monthly or PRN effectively treated PEDs in patients with neovascular AMD, and significant vision gains resulted regardless of PED status and height at baseline. In this analysis, there was no additional vision benefit with a higher dose of ranibizumab (2.0 mg). Ophthalmology 2016;123:2213-2224 © 2016 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Retinal pigment epithelial detachments (PEDs) are associated with many retinal diseases, including neovascular age-related macular degeneration (AMD), can cause significant vision loss, and are difficult to treat. Pigment epithelial detachments are seen in up to 62% of patients with advanced neovascular AMD.1,2 The pathogenesis of PEDs is not completely understood,3 but PED at baseline has been shown to be a predictor of vision loss in patients with AMD.4 Approximately 50% of patients with newly diagnosed PEDs will experience significant loss in visual acuity (>3 lines) 1 year from diagnosis without treatment.5 Thus, PEDs are an important marker of disease severity and progression in neovascular AMD.

The Anti-Vascular Endothelial Growth Factor (VEGF) Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration study6,7 and the Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration8 established the efficacy of intravitreal ranibizumab
therapy (Lucentis; Genentech, Inc., South San Francisco, CA) in improving visual and anatomic outcomes in patients with neovascular AMD. At 24 months in these studies, 34% to 41% and 26% to 33% of ranibizumab-treated patients, respectively, gained 15 letters or more in best-corrected visual acuity (BCVA) from baseline.7,8 In these patients with neovascular AMD, ranibizumab was associated with arrested or decreased growth of and leakage from choroidal neovascularization (CNV). In other studies of patients with neovascular AMD, the subgroups with PED have been associated with worse visual acuity outcomes.4,5 Currently, there are few prospective studies that demonstrate effective therapy for PEDs associated with neovascular AMD. These analyses are limited by the use of time-domain optical coherence tomography (OCT) or do not focus specifically on eyes with PED, providing incomplete information regarding PED outcomes.9-14 The Prospective Optical Coherence Tomography Imaging of Patients with Neovascular AMD Treated with Intraocular Ranibizumab study15,16 evaluated an OCT-guided dosing regimen with ranibizumab 0.5 mg for the treatment of patients with neovascular AMD. This study found no correlation between PED at baseline or 3 months with visual acuity at 12 months. Additionally, limited data are available on the use of higher doses (2.0 mg) of ranibizumab to treat PEDs. Chan et al17 hypothesized that a greater concentration of ranibizumab may penetrate the retinal pigment epithelial (RPE) barrier and suppress CNV, leading to more rapid resolution of the PED. Although visual acuity outcomes were no different at 12 months between the 2.0-mg and 0.5-mg arms, the 2.0-mg regimen did result in more rapid reductions in percentage of PED height.17,18

The Phase III, Double-Masked, Multicenter, Randomized, Active Treatment-Controlled Study of the Efficacy and Safety of 0.5 mg and 2.0 mg Ranibizumab Administered Monthly or on an As-Needed Basis (PRN) in Patients with Subfoveal Neovascular Age-Related Macular Degeneration (HARBOR) was conducted to evaluate the potential beneficial effects of both a higher dose and pro re nata (PRN) dosing of ranibizumab in patients with subfoveal neovascular AMD.19,20 Neither the higher dose nor the more frequent dosing differed from their counterparts in the primary end point of mean change in BCVA from baseline to month 12. At month 24, mean changes in BCVA from baseline were similar among groups (+9.1, +7.9, +8.0, and +7.6 letters in the 0.5-mg monthly, 0.5-mg PRN, 2.0-mg monthly, and 2.0-mg PRN ranibizumab treatment groups, respectively).20 This report describes the results of an exploratory subgroup analysis of the HARBOR trial that analyzed the effect of baseline PED status (present or absent) and height on visual and anatomic outcomes in patients with neovascular AMD treated with standard-dose (0.5 mg) versus high-dose (2.0 mg) ranibizumab on a monthly or PRN dosing regimen.

Methods

This study was a post hoc analysis of the HARBOR study, the methods for which have been published previously.19 Briefly, HARBOR was a 24-month, phase III, randomized, multicenter, double-masked, active treatment–controlled study (clinicaltrials.gov identifier, NCT00891735) conducted at 102 investigator sites. The study protocol was approved by the respective institutional review boards before the start of the study. Written informed consent was provided by all participants before study participation. The study was conducted in accordance with Good Clinical Practice (International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use E6), applicable United States Food and Drug Administration regulations, and the Health Insurance Portability and Accountability Act.

Key inclusion criteria for the study eye included BCVA of 20/40 to 20/320 (Snellen equivalent) using Early Treatment Diabetic Retinopathy Study charts at a distance of 4 m; active subfoveal lesions with classic CNV, some classic CNV component, or purely occult CNV; total area of lesion less than 12 disc areas or 30.48 mm²; and total CNV area constituting 50% or more of total lesion area based on fluorescein angiography.

In HARBOR, all included patients (1 eye per patient) were randomized 1:1:1:1 to 1 of 4 ranibizumab treatment groups: 0.5 mg monthly, 0.5 mg PRN, 2.0 mg monthly, or 2.0 mg PRN. Randomized patients received 3 monthly doses of intravitreal ranibizumab 0.5 mg or 2.0 mg at the beginning of the study. The monthly groups then continued with monthly treatment, whereas the PRN groups were evaluated every month and were re-treated if there was a 5-letter (Early Treatment Diabetic Retinopathy Study) or more reduction in vision from the previous visit or any evidence of disease activity on spectral-domain OCT (Cirrus HD-OCT; Carl Zeiss Meditec, Dublin, CA), including the presence of a PED. Spectral-domain OCT was performed at each study visit and images were graded at baseline, day 7, and months 1 through 4, 6, 9, 12, 18, and 24.

Pigment epithelial detachment was defined as a discrete or localized dome-shaped or irregular elevation of the RPE on OCT that was optically empty (i.e., serous) with a focus of neovascularization at the edge or that was comprised heterogeneous tissue of mixed reflectivity or layering within the sub-PED compartment. To evaluate the effect of baseline PED height on outcomes, patients were separated into quartiles according to PED height with spectral-domain OCT analysis (i.e., each group comprised 25% of patients with PED at baseline in the study). Pigment epithelial detachment type (i.e., serous, fibrovascular) at baseline was not assessed during image grading. Pigment epithelial detachment height was measured by a masked grader as the distance between the RPE–Bruch’s membrane complex at the base and the peak of the PED. After documenting PED presence at baseline (PED height, >0 μm), if the PED height measurement was 0 at a subsequent visit, then the PED was considered completely resolved. Pigment epithelial detachments in HARBOR ranged from approximately 35 to 1400 μm in height at baseline. For the quartile analysis, small PEDs were defined as 35 to 164 μm (mean ± standard deviation [SD], 126.0±27.7 μm), medium PEDs were defined as 164.5 to 233 μm (mean ± SD, 196.8±20.8 μm), large PEDs were defined as 233.25 to 351 μm (mean ± SD, 282.0±33.3 μm), and extra-large PEDs were defined as 352 to 1395.5 μm (mean ± SD, 515.6±161.7 μm) in height. This analysis was performed on the intent-to-treat population, which included 1 patient who was randomized but not treated. Only baseline values are included for this patient. This subgroup analysis of the HARBOR
study evaluated patients with or without PED at baseline and the effect of baseline PED height across several exploratory end points up to 24 months, including patients’ BCVA, change in BCVA from baseline, resolution of PED, change in PED height from baseline, and number of injections in the PRN treatment groups. In addition, the development of macular atrophy was assessed at month 24 in patients with no detectable atrophy at baseline (ranibizumab treatment groups pooled). Macular atrophy was identified as a well-defined area of depigmentation with increased visibility of choroidal vessels on either color fundus photography or fluorescein angiography. Any atrophy immediately within, adjacent to, and nonadjacent to CNV lesions (active or regressed) was included. Atrophy associated with RPE tears was excluded. The atrophy analysis excluded 32 eyes for which atrophy status could not be determined at month 24.

**Statistical Analysis**

Student t-tests were used to compare differences in group means of outcome measures by baseline PED status. To evaluate differences between treatment groups and differences between quartiles, analysis of variance and Tukey’s honest significant difference tests were used. Statistical analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC).

**Results**

Of the 1097 included patients, 598 (54.5%) showed a PED at baseline. Overall, 154 patients (0.5 mg monthly), 146 patients (0.5 mg PRN), 158 patients (2.0 mg monthly), and 140 patients (2.0 mg PRN) showed a PED at baseline. One patient included in the baseline analyses was randomized to ranibizumab 0.5 mg monthly and had a medium PED, but was not treated. At baseline, patients with PED had reduced central foveal thickness (328.6 vs. 363.1 μm) and higher BCVA (55.7 letters [approximate Snellen equivalent, 20/80] vs. 51.9 letters [approximate Snellen equivalent, 20/100]) than patients without PED (P < 0.0001 for both comparisons; Table 1). Baseline characteristics were similar across quartile groups and mean PED height measurements at baseline were 126.0 μm (small), 196.8 μm (medium), 282.0 μm (large), and 515.6 μm (extra large; Table 2). Additionally, baseline characteristics were similar across treatment groups (Table 3).

**Vision Outcomes**

**Pigment Epithelial Detachment Status at Baseline**

Mean BCVA gains from baseline to 24 months were similar in patients with PED present at baseline who received any of the 4 ranibizumab treatment regimens (Fig 1A). Mean BCVA gains from baseline to 24 months were comparable in patients with or without PED at baseline treated with ranibizumab 0.5 mg monthly (PED present at baseline, +9.0 letters; PED absent at baseline, +11.3 letters), ranibizumab 0.5 mg PRN (PED present at baseline, +8.4 letters; PED absent at baseline, +7.9 letters), or ranibizumab 2.0 mg PRN (PED present at baseline, +7.2 letters; PED absent at baseline, +8.8 letters). In the ranibizumab 2.0 mg monthly group, there was a trend toward greater mean BCVA gains at 24 months in patients without PED at baseline (+11.1 letters) compared with those with PED present at baseline (+7.1 letters; P = 0.08). In all ranibizumab groups combined, patients with PED at baseline gained a mean of 7.9 letters at 24 months from baseline compared with 9.7 letters in patients without PED at baseline (P = 0.08; Fig 1B). Because patients with PED started with better vision than those without PED at baseline (55.7 vs. 51.9 letters), the month 24 mean BCVA also was better in patients with PED at baseline (64.4 letters) compared with patients without PED at baseline (62.0 letters; P = 0.03).

**Pigment Epithelial Detachment Height at Baseline**

Mean BCVA gains were demonstrated in all treatment groups at 24 months when analyzed by baseline PED height, except for patients treated with ranibizumab 2.0 mg monthly in the extra-large PED group (PEDs ≥352 μm; Fig 2A). In patients with small PEDs, mean change from baseline in BCVA at month 24 was +8.2 letters (0.5 mg monthly), +10.0 letters (0.5 mg PRN), +11.1 letters (2.0 mg monthly), and +6.7 letters (2.0 mg PRN). Mean change from baseline in BCVA at month 24 was +9.8 letters (0.5 mg monthly), +12.3 letters (0.5 mg PRN), +8.3 letters (2.0 mg monthly), and +7.9 letters (2.0 mg PRN) in patients with medium PEDs. Patients with large PEDs had mean BCVA gains at month 24 of +11.3 letters (0.5 mg monthly), +7.7 letters (0.5 mg PRN), +10.2 letters (2.0 mg monthly), and +6.4 letters (2.0 mg PRN). Mean changes from baseline in BCVA at month 24 were +6.4 letters (0.5 mg monthly), +5.3 letters (0.5 mg PRN), −0.8 letters (2.0 mg monthly), and +7.7 letters (2.0 mg PRN) in the extra-large PED group. In all ranibizumab groups combined, patients gained a mean of 9.1 letters (small), 9.0 letters (medium), 8.9 letters (large), and 4.7 letters (extra large; P = 0.051; Fig 2B).

**Anatomic Outcomes**

Ranibizumab therapy led to resolution of PEDs in approximately 56% of patients at month 24. In patients with PED at baseline, PEDs completely resolved in 53.2% and 44.5% of patients treated with ranibizumab 0.5 mg monthly and 0.5 mg PRN, respectively (Fig 3). There was a trend for greater PED resolution in eyes treated with the 2.0-mg dose of ranibizumab (PED completely resolved: 70.4% of patients treated with ranibizumab 2.0 mg monthly and 57.3% of patients treated with 2.0 mg PRN). Pigment epithelial detachment height decreased over 24 months in each treatment group, with the greatest decrease from baseline occurring in the ranibizumab 2.0 mg PRN treatment group (Fig 4). At month 24, the decreases in PED height from baseline were −155.9 μm (0.5 mg monthly), −165.8 μm (0.5 mg PRN), −191.1 μm (2.0 mg monthly), and −201.6 μm (2.0 mg PRN).

Mean PED height decreased over 24 months regardless of PED height at baseline (Fig 5). In the small, medium, and extra-large PED groups, patients treated with ranibizumab 2.0 mg monthly had a slightly greater mean decrease in PED height than those treated with other ranibizumab regimens, but this difference was not statistically significant (P = 0.07). Patients with a small PED at baseline demonstrated mean decreases in PED height at month 24 of −76.3 μm (0.5 mg monthly), −57.4 μm (0.5 mg PRN), −88.0 μm (2.0 mg monthly), and −73.3 μm (2.0 mg PRN; P = 0.61). In patients with a medium PED at baseline, mean decreases in PED height at month 24 were −110.2 μm (0.5 mg monthly), −115.5 μm (0.5 mg PRN), −165.0 μm (2.0 mg monthly), and −136.4 μm (2.0 mg PRN; P = 0.06). In patients in the large PED group, the largest
mean decrease in PED height at 24 months was seen with ranibizumab 0.5 mg monthly (−204.5 μm) compared with −161.1 μm (0.5 mg PRN), −199.06 μm (2.0 mg monthly), and −182.28 μm (2.0 mg PRN; P = 0.47). The largest mean decreases in PED height overall at 24 months were seen in patients in the extra-large PED group (ranibizumab 0.5 mg monthly, −257.3 μm; 0.5 mg PRN, −277.4 μm; 2.0 mg monthly, −349.3 μm; 2.0 mg PRN, −387.5 μm; P = 0.08). Figure 6 shows a case example of a patient with an extra-large PED at baseline that resolved by month 24 after ranibizumab 0.5-mg monthly treatment.

### Number of Ranibizumab Injections

In patients with PED present at baseline in the ranibizumab 0.5-mg PRN group, a similar number of injections was needed in all 4 PED height quartiles over 2 years with the presence of PED as a re-treatment criterion (small, 12.2 injections; medium, 13.6 injections; large, 14.0 injections; extra large, 15.6 injections; P = 0.16; Fig 7). These patients required a mean of 14.0 injections over 2 years compared with 12.5 injections in patients with PED absent at baseline. Patients treated with ranibizumab 0.5 mg PRN with complete resolution of PED at month 24 required 12.7 injections compared with 16.3 injections in patients without complete resolution of PED (P = 0.0004). In the ranibizumab 2.0-mg PRN group, patients with PED present at baseline required a mean of 11.6 injections over 2 years compared with 10.7 injections in patients with PED absent at baseline. A similar number of injections also was needed across PED height quartiles in the ranibizumab 2.0-mg PRN group over 2 years (small, 10.7 injections; medium, 10.6 injections; large, 11.0 injections; extra large, 14.3 injections). Patients treated with ranibizumab 2.0 mg PRN with PED resolution at month 24 required a mean of 15.0 injections compared with 15.0 injections in patients without PED resolution (P < 0.0001).

### Macular Atrophy

Among study eyes with no detectable atrophy at baseline (all ranibizumab groups pooled), a similar rate of macular atrophy was seen at month 24 in eyes with PED at baseline (n = 131/404 [32%]) and in eyes without PED at baseline (n = 98/342 [29%]; Fig 8A). Among study eyes with PED at baseline and no detectable atrophy at baseline (all ranibizumab groups pooled), a higher rate of macular atrophy was present immediately within, adjacent to, and nonadjacent to CNV lesions at month 24 in eyes with complete flattening of PED (n = 101 [44%]) than in eyes with PED still present (n = 30 [17%]; P < 0.0001; Fig 8B). Macular atrophy development at month 24 was independent of PED size at baseline (small, 29%; medium, 42%; large, 34%; extra large, 25%; P = 0.09).

### Retinal Pigment Epithelium Tear Analysis

Overall, 28 of 598 patients (4.7%) with a PED at baseline experienced an RPE tear during the study. The distribution of RPE tears was similar across treatment groups, with a total of 5 patients (3%; 0.5 mg monthly), 6 patients (4%; 0.5 mg PRN), 7 patients (4%; 2.0 mg monthly), and 10 patients (7%; 2.0 mg PRN) who experienced tears (P = 0.44). There was no significant difference between the development of RPE tear in patients treated with ranibizumab

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**Table 1. Baseline Characteristics and Demographics of the Overall HARBOR Population by Pigment Epithelial Detachment Status at Baseline**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Absent at Baseline (n = 499)</th>
<th>Present at Baseline (n = 598)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men, no. (%)</td>
<td>224 (44.9)</td>
<td>222 (37.1)</td>
<td>0.0091</td>
</tr>
<tr>
<td>Mean age (SD), yrs</td>
<td>77.8 (8.7)</td>
<td>79.5 (7.9)</td>
<td>0.0007</td>
</tr>
<tr>
<td>Mean CFT (SD), μm</td>
<td>363.1 (154)</td>
<td>328.6 (131)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mean BCVA (SD), ETDRS letters</td>
<td>51.9 (13.0)</td>
<td>55.7 (12.4)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

BCVA = best-corrected visual acuity; CFT = central foveal thickness; ETDRS = Early Treatment Diabetic Retinopathy Study; HARBOR = Phase III, Double-Masked, Multicenter, Randomized, Active Treatment-Controlled Study of the Efficacy and Safety of 0.5 mg and 2.0 mg Ranibizumab Administered Monthly or on an As-Needed Basis (PRN) in Patients with Subfoveal Neovascular Age-Related Macular Degeneration; SD = standard deviation.

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**Table 2. Baseline Characteristics and Demographics of Patients with Pigment Epithelial Detachment at Baseline by Baseline Pigment Epithelial Detachment Quartile**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Small (35–164 μm; n = 147)</th>
<th>Medium (164.5–233 μm; n = 152)</th>
<th>Large (233.25–351 μm; n = 149)</th>
<th>Extra Large (352–1395.5 μm; n = 150)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men, no. (%)</td>
<td>51 (34.7)</td>
<td>51 (33.6)</td>
<td>60 (40.3)</td>
<td>60 (40.0)</td>
<td>0.5002</td>
</tr>
<tr>
<td>Mean age (SD), yrs</td>
<td>79.4 (8.3)</td>
<td>80.0 (7.5)</td>
<td>79.7 (7.9)</td>
<td>79.0 (8.0)</td>
<td>0.7516</td>
</tr>
<tr>
<td>Mean CFT (SD), μm</td>
<td>321.5 (138.1)</td>
<td>319.9 (130.7)</td>
<td>344.0 (134.1)</td>
<td>329.0 (120.8)</td>
<td>0.3701</td>
</tr>
<tr>
<td>Mean BCVA (SD), ETDRS letters</td>
<td>56.3 (12.2)</td>
<td>55.5 (12.5)</td>
<td>55.7 (12.2)</td>
<td>55.3 (12.9)</td>
<td>0.9226</td>
</tr>
<tr>
<td>Mean PED height (SD), μm</td>
<td>126.0 (27.7)</td>
<td>196.8 (20.8)</td>
<td>282.0 (33.3)</td>
<td>515.6 (161.7)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

BCVA = best-corrected visual acuity; CFT = central foveal thickness; ETDRS = Early Treatment Diabetic Retinopathy Study; PED = pigment epithelial detachment; SD = standard deviation.
Table 3. Baseline Characteristics and Demographics of Patients with Pigment Epithelial Detachment at Baseline by Treatment Group

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Ranibizumab 0.5 mg Monthly (n = 154)</th>
<th>Ranibizumab 0.5 mg Pro Re Nata (n = 146)</th>
<th>Ranibizumab 2.0 mg Monthly (n = 158)</th>
<th>Ranibizumab 2.0 mg Pro Re Nata (n = 140)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men, no. (%)</td>
<td>55 (35.7)</td>
<td>55 (37.7)</td>
<td>59 (37.3)</td>
<td>53 (37.9)</td>
<td>0.9799</td>
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<tr>
<td>Mean age (SD), yrs</td>
<td>79.7 (8.0)</td>
<td>78.8 (7.8)</td>
<td>80.5 (7.7)</td>
<td>79.0 (8.2)</td>
<td>0.2146</td>
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<tr>
<td>Mean CFT (SD), μm</td>
<td>322.4 (130.9)</td>
<td>348.1 (140.8)</td>
<td>315.2 (126.5)</td>
<td>330.0 (124.5)</td>
<td>0.1538</td>
</tr>
<tr>
<td>Mean BCVA (SD), ETDRS letters</td>
<td>56.2 (13.2)</td>
<td>55.6 (11.2)</td>
<td>56.6 (12.2)</td>
<td>54.1 (12.8)</td>
<td>0.3473</td>
</tr>
<tr>
<td>Mean PED height (SD), μm</td>
<td>272.4 (152.4)</td>
<td>296.7 (165.5)</td>
<td>264.2 (160.2)</td>
<td>291.3 (197.9)</td>
<td>0.2938</td>
</tr>
</tbody>
</table>

BCVA = best-corrected visual acuity; CFT = central foveal thickness; ETDRS = Early Treatment Diabetic Retinopathy Study; PED = pigment epithelial detachment; SD = standard deviation.

Discussion

This HARBOR subanalysis is the largest prospective study of neovascular AMD patients with PEDs treated with intravitreal ranibizumab injection. Over 24 months, ranibizumab-treated patients with PED gained a mean visual acuity of approximately 7 to 9 letters, and there was no difference in mean BCVA gains when compared with patients who did not have PED at baseline. In all ranibizumab treatment arms, PED height decreased regardless of PED height at baseline. Although patients treated with ranibizumab 2.0 mg had a slightly better anatomic response than those treated with ranibizumab 0.5 mg (mean change from baseline, −155.9 to −165.8 μm in the 0.5-mg group and −191.1 to −201.6 μm in the 2.0-mg group), no additional visual acuity benefit was seen. Additionally, patients who received a higher dose of ranibizumab (2.0 mg) also had higher rates of PED resolution (57%–70% vs. 45%–53% with 0.5 mg) but did not experience greater increases from baseline in visual acuity at 24 months (approximately 7 vs. 8–9 letters with 0.5 mg). These data suggest that complete resolution of the PED is not necessary for visual acuity gains. In fact, patients with an extra-large PED who received ranibizumab 2.0 mg monthly had a mean decrease in vision at 24 months, although there was a lot of variability in BCVA change from baseline at month 24 in these patients (range, −62 to 30 letters).

Interestingly, in this analysis we found that patients with PED at baseline had better vision at baseline (55.7 vs. 51.9 letters) and 24 months (64.4 vs. 62.0 letters) than patients without PED at baseline. Typically, PEDs are considered to be the most challenging AMD subtype to resolve anatomicallly. Yet, this and other analyses found that the visual prognosis may indeed be better for these patients as long as they do not experience RPE tears. Waldstein et al10 reported that patients with PED at baseline had significantly better vision than patients without PED at baseline (55 vs. 53 letters, respectively; P = 0.005). At week 52, after anti-VEGF therapy, patients with PED present still had better vision than patients without PED present (65 vs. 60 letters, respectively; P < 0.001). Rahimi et al21 reported that patients with chronic multilayered fibrovascular PED have been noted to have a favorable visual prognosis with chronic anti-VEGF therapy.

In HARBOR, patients with PED at baseline experienced visual acuity gains and reductions in PED height with PRN therapy using the presence of PED as a criterion for re-treatment. In patients with PED at baseline, gains in BCVA at month 24 in patients treated with ranibizumab PRN (7–8 letters) were similar to those in patients who received monthly therapy (7–9 letters). Over 24 months, patients with PED present at baseline required slightly more injections (14.0 injections) than patients with PED absent at baseline in the ranibizumab 0.5-mg PRN group (12.5 injections), and patients in the ranibizumab 2.0-mg PRN group required a similar number of injections regardless of PED status at baseline (PED present, 11.6 injections; PED absent, 10.7 injections). There was a trend toward more injections being necessary in patients as PED height increased. These data suggest that patients with PEDs, especially larger PEDs, require close follow-up and more treatments, but still do well with regard to vision and OCT anatomic features with PRN therapy after 3 monthly loading doses. It is important to note that although the presence of PED was a re-treatment criterion in HARBOR, patients with complete resolution of PED did not necessarily see an additional vision benefit and were more likely to demonstrate macular atrophy at month 24. These data suggest that PRN treatment does not need to achieve complete resolution of the PED.

Previous small retrospective trials report mixed results of anti-VEGF therapy for PEDs. In a study of 125 consecutive patients with vascularized PED and neovascular AMD,
In 2 small investigations, anti-VEGF therapy was more beneficial in patients with serous or avascular PED than fibrovascular PED. In a prospective study of 32 patients with vascularized PED and 29 patients with serous PED, anti-VEGF therapy was effective in improving vision in both arms of the trial. These smaller investigations prompted larger more definitive prospective studies, such as this subanalysis of HARBOR.

Chan et al performed a prospective analysis similar to the current HARBOR subanalysis, but with a smaller number of patients (n = 36) and shorter study duration (12 months). Visual and anatomic outcomes of patients with neovascular AMD and PED at baseline treated with ranibizumab 0.5 mg (n = 6) or 2.0 mg (n = 12) monthly for 12 months or treated with ranibizumab 0.5 mg (n = 7) or 2.0 mg (n = 11) monthly for 4 months then PRN for 8 months were evaluated. In this study, 33.3%, 42.8%, 33.3%, and 18.2% of eyes had a gain of 15 letters or more at month 12 in the 0.5-mg monthly, 0.5-mg PRN, 2.0-mg monthly, and 2.0-mg PRN groups, respectively. Interestingly, the 0.5-mg PRN group showed the highest percentage of patients to demonstrate a gain in vision, but no statistically significant differences in visual or anatomic outcomes at 12 months were identified between patients treated with 0.5 mg or 2.0 mg ranibizumab. In an assessment of early response at weeks 4 and 8, there were more substantial improvements in vision and reductions of subretinal fluid in the 0.5-mg monthly group compared to the 0.5-mg PRN group.

Figure 1. The mean change in best-corrected visual acuity (BCVA) in patients by pigment epithelial detachment (PED) presence status at baseline by (A) ranibizumab (RBZ) treatment regimen group and (B) all treatment groups combined. Vertical bars represent 95% confidence intervals. ETDRS = Early Treatment Diabetic Retinopathy Study; PRN = pro re nata.
fluid in patients who received 2.0 mg ranibizumab relative to patients who received 0.5 mg ranibizumab. In this sub-analysis of HARBOR, greater early decreases (months 1 and 2) in PED height were noted in the 2.0-mg groups than in the 0.5-mg groups (notably 0.5 mg PRN), but visual acuity gains remained similar among 0.5-mg and 2.0-mg groups over the 24-month period, including months 1 and 2.

Another approved intravitreal anti-VEGF therapy for treatment of neovascular AMD, aflibercept, has been studied in patients with PED. In the VIEW (VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD) studies, patients with neovascular AMD were treated with aflibercept 2.0 mg every 4 weeks (n = 613; 75.3% had PED at baseline), aflibercept 2.0 mg every 8 weeks (n = 607; 75.8% had PED at baseline), or ranibizumab 0.5 mg every 4 weeks (n = 595; 73.3% had PED at baseline), although this study was limited by the use of time-domain OCT. At 1 year, complete resolution of PED occurred in 39.5% of patients in the group receiving aflibercept 2.0 mg every 4 weeks, 34.1% of patients in the group receiving aflibercept 2.0 mg every 8 weeks, and 33.5% of patients in the group receiving ranibizumab 0.5 mg every 4 weeks.

![Figure 2. The mean change in best-corrected visual acuity (BCVA) over 24 months in patients treated with ranibizumab (RBZ) by treatment group and all treatment groups combined. Vertical bars represent 95% confidence intervals. ETDRS = Early Treatment Diabetic Retinopathy Study; PED = pigment epithelial detachment; PRN = pro re nata.](image)

![Figure 3. The resolution of pigment epithelial detachment (PED) in patients treated with ranibizumab (RBZ) over 24 months. Vertical bars represent 95% confidence intervals. PRN = pro re nata.](image)
mg every 8 weeks, and 28.1% of patients in the group receiving ranibizumab 0.5 mg every 4 weeks. In this HARBOR analysis, 42% to 71% of patients treated with ranibizumab 0.5 mg or 2.0 mg had complete resolution of PED at 1 year. In a multivariate model in VIEW, presence of PED at baseline demonstrated a -1.88-letter impact on change in BCVA at week 52 from baseline compared with absence of PED in all treatment groups (afibercept and ranibizumab) combined. This is similar to what was seen in the current analysis of HARBOR at 2 years in which patients with PED at baseline had a -1.8-letter impact on BCVA change from baseline compared with patients without PED at baseline. In a further analysis of VIEW2, the vision decline seen in eyes with PED at baseline was increased by the occurrence of intraretinal cystoid edema during the PRN period. In smaller retrospective studies of patients with PED who were considered refractory to ranibizumab or bevacizumab therapy and switched to afibercept therapy, afibercept demonstrated reductions in anatomic measurements, such as PED height, and either a stabilization or decline in vision over the course of the study, suggesting that although switching to afibercept had an impact on anatomic features, there was either no impact or a negative impact on vision outcomes.

In this exploratory analysis of HARBOR data, there was an approximately 3-fold higher rate of macular atrophy development in patients with complete flattening of PED compared with patients with persistent PED at month 24 (44% vs. 17%), but no difference in rates of macular atrophy at month 24 between patients with and without PED at baseline (32% vs. 29%). These data further support the idea that treatment to resolve PEDs completely may not be necessary because more macular atrophy is seen when the PED resolved completely. It is unclear from the data whether macular atrophy preceded or followed PED resolution, and further analysis is required to elucidate this association. An association between PEDs and macular atrophy was observed previously in the Inhibit VEGF in Age-Related Choroidal Neovascularization study. In 12 of 18 eyes with PED at baseline that were treated with anti-VEGF therapy and that showed macular atrophy at a follow-up visit, the area of atrophy was localized to the site of the PED.

Figure 4. The change in mean pigment epithelial detachment (PED) height in patients treated with ranibizumab (RBZ) over 24 months. Vertical bars represent 95% confidence intervals. PRN = as needed.

Figure 5. The mean change in pigment epithelial detachment (PED) height by baseline PED height group over 24 months in patients treated with ranibizumab (RBZ). Graph axes have been scaled to best show each PED height group. Vertical bars represent 95% confidence intervals. PRN = pro re nata.
of PED.\textsuperscript{31} In a natural history study of patients with PED and central serous chorioretinopathy, complete resolution of PED was associated with atrophy development in 19 of 22 patients (86%).\textsuperscript{32} Additionally, in a study of the natural history of drusenoid PEDs, a higher proportion of patients with drusenoid PED demonstrated atrophy at 5 years than patients without PED (18\% vs. 7\%; $P < 0.001$).\textsuperscript{33} These data suggest that the pathophysiology and association between PEDs and macular atrophy should be explored further.

Among patients with PED and no RPE tear at baseline in HARBOR, 28 patients experienced an RPE tear by month 24; this occurred more often in the largest PEDs, with no association by treatment group. A previous small prospective analysis by Sarraf et al\textsuperscript{34} evaluated 37 eyes with vascularized PED and neovascular AMD treated with ranibizumab 0.5 mg or 2.0 mg either monthly or PRN for 12 months. Five eyes (14\%) demonstrated an RPE tear. Four of the 5 tears occurred in patients treated with ranibizumab 2.0 mg. Additionally, an increased risk of tear development was seen in patients with a PED height more than 550 \(\mu\)m (4 of 13 patients [31\%]). The rate of RPE tears was lower in HARBOR, occurring in 5\% of patients with a PED at baseline; however, this rate increased to 14\% (a rate very similar to the overall RPE tear rate in the study by Sarraf et al\textsuperscript{34}) in the group with larger PEDs. Unlike the previous analysis, which identified more tears in patients treated with ranibizumab 2.0 mg, a similar number of tears were seen across treatment groups. Similar to the previous analysis, most tears occurred in patients with larger PEDs at baseline (\(\geq 352\ \mu\)m; mean PED height in this group, 515.6 \(\mu\)m). These data suggest that patients with larger PEDs, especially greater than 500 \(\mu\)m, receiving anti-VEGF experience a higher rate of RPE tears compared with patients with smaller PEDs and confirms the results of previous smaller studies.\textsuperscript{34,35}

There are a few limitations of this HARBOR subanalysis study. This was an exploratory post hoc subgroup analysis and the results should be interpreted with caution because they may be the result of chance. The PED type (i.e., serous, fibrovascular) at baseline was not assessed, and therefore the effect of PED type on outcomes could not be evaluated at this time. Only the height of the PED was measured in HARBOR; 3-dimensional assessments of the PED volume may give more information than height.\textsuperscript{36} Additionally, height categories were not predetermined and were defined by quartile assignment of the entire cohort with PED. Although this allows for an approximately equal comparison between PED height groups, it may not demonstrate accurately the effect of ranibizumab on PEDs of any specific height. In terms of the atrophy analysis, this study lacked fundus autofluorescence imaging, which is used routinely for evaluation of macular atrophy. Despite these limitations, this subanalysis still provides previously unavailable data on the efficacy of ranibizumab therapy in approximately 600 patients with PEDs.

In conclusion, ranibizumab 0.5 mg given monthly or PRN effectively managed PEDs in patients with neovascular AMD, and significant vision gains of +7.9 to +9.0 letters were achieved regardless of PED height at baseline in this analysis of 598 patients with PED. Similar vision gains were observed with ranibizumab treatment regardless of PED status at baseline; despite the perception that PEDs are a more difficult anatomic subtype to treat, patients with a PED started and completed the study with better average vision than those without a PED. In this analysis, although
there was a higher rate of resolution of PED with a higher dose of ranibizumab (2.0 mg), no additional vision was gained. The rate of on-study RPE tears was low in HAR-BOR (5%), with most tears occurring in patients with extra-large PEDs.

References


Figure 8. The development of macular atrophy (MA) at 24 months by pigment epithelial detachment (PED) status (A) at baseline and (B) at month 24 in patients with PED at baseline. Data are from study eyes with no detectable atrophy at baseline; ranibizumab treatment groups pooled. Data excludes eyes for which atrophy status could not be determined at month 24 (A, 32 eyes; B, 17 eyes).

Figure 9. The development of retinal pigment epithelium (RPE) tears during the study in the extra-large pigment epithelial detachment group. PRN = pro re nata.


Footnotes and Financial Disclosures

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Abbreviations and Acronyms:

AMD = age-related macular degeneration; BCVA = best-corrected visual acuity; CNV = choroidal neovascularization; ETDRS = Early Treatment Diabetic Retinopathy Study; HARBOR = Phase III, Double-Masked, Multicenter, Randomized, Active Treatment-Controlled Study of the Efficacy and Safety of 0.5 mg and 2.0 mg Ranibizumab Administered Monthly or on an As-Needed Basis (PRN) in Patients with Subfoveal Neovascular Age-Related Macular Degeneration; OCT = optical coherence tomography; PED = pigment epithelial detachment; PRN = pro re nata (as needed); RPE = retinal pigment epithelium; SD = standard deviation; VEGF = vascular endothelial growth factor.

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Pictures & Perspectives

Antimony Intraocular Foreign Body with an Intact Electroretinogram

A 65-year-old man with a history of trauma to the right eye 60 years previously presented with a metallic intraocular foreign body (Fig 1A, B). The object was removed via pars plana vitrectomy (Fig 1C, arrow) and found to be composed of antimony. A postoperative maximum combined scotopic white 0-decibel electroretinogram demonstrated normal amplitude and implicit times, 209 μV and 52 ms, respectively (Fig 1D). Antimony is well-tolerated within the eye with no indications of metallosis.

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