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Twenty-four-Month Efficacy and Safety of 0.5 mg or 2.0 mg Ranibizumab in Patients with Subfoveal Neovascular Age-Related Macular Degeneration

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Objective: To evaluate the 24-month efficacy and safety of intravitreal ranibizumab 0.5 mg and 2.0 mg administered monthly or as needed (pro re nata [PRN]) in patients with neovascular age-related macular degeneration (wet AMD).

Design: Twenty-four-month, multicenter, randomized, double-masked, active treatment-controlled phase 3 trial.

Participants: Patients (n = 1098) ≥50 years of age with treatment-naïve subfoveal wet AMD.

Methods: Patients were randomized to receive intravitreal injections of ranibizumab 0.5 mg or 2.0 mg monthly or PRN after 3 monthly loading doses.

Main Outcome Measures: The primary efficacy end point was the mean change in best-corrected visual acuity (BCVA) from baseline at month 12. Key secondary end points included mean change in BCVA from baseline at month 24, proportion of patients who gained ≥15 letters in BCVA, mean number of ranibizumab injections, and mean change in central foveal thickness from baseline over time by spectral-domain optical coherence tomography. Ocular and systemic safety events also were evaluated through month 24.

Results: At month 24, the mean change from baseline in BCVA was (letters) +9.1 (0.5 mg monthly), +7.9 (0.5 mg PRN), +8.0 (2.0 mg monthly), and +7.6 (2.0 mg PRN). The change in mean BCVA from month 12 to 24 was (letters) −1.0, −0.3, −1.2, and −1.0, respectively. The proportion of patients who gained ≥15 letters from baseline in BCVA at month 24 was 34.5%, 33.1%, 37.6%, and 34.8%, respectively. The mean number of ranibizumab injections through month 24 was 21.4, 13.3, 21.6, and 11.2, respectively; 5.6 and 4.3 mean injections were required in year 2 in the 0.5 mg and 2.0 mg PRN groups, respectively. The average treatment interval in the 0.5 mg PRN group was 9.9 weeks after 3 monthly loading doses, and 93% of these patients did not require monthly dosing. Ocular and systemic safety profiles over 2 years were similar among all 4 treatment groups and were consistent with previous ranibizumab trials in AMD.

Conclusions: At month 24, mean BCVA improvements were clinically meaningful and similar among all 4 ranibizumab treatment groups. The 0.5 mg PRN group achieved a mean gain of 7.9 letters at month 24 with an average of 13.3 injections (5.6 injections in year 2). No new safety events were identified over 24 months. *Ophthalmology 2014;121:2181-2192 © 2014 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/3.0/).*

*Supplemental material is available at www.aaojournal.org.

Strategies to improve treatment effectiveness for neovascular age-related macular degeneration (wet AMD) aim to enhance visual function and reduce treatment burden, characterized by frequent intravitreal injections and patient encounters. Improved strategies are impactful because wet AMD affects approximately 1.75 million individuals in the United States and remains a leading cause of blindness among adults older than 50 years of age in many regions of the world.[1,2] Although the underlying disease pathogenesis has not been elucidated fully, vascular endothelial growth factor (VEGF) has been shown to play a key role in the development of choroidal neovascularization (CNV), which can lead to severe vision loss if left untreated.[2,3] Anti-VEGF agents have become the standard-of-care treatment option for the management of wet AMD.[4–12] Evidence from prospective, randomized clinical trials of intravitreal anti-VEGF therapy for the treatment of wet AMD demonstrate that visual outcomes are, on average, significantly improved from baseline after treatment, and the rates of serious ocular and systemic adverse events (AEs) are low and generally well tolerated.[4–13]

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The pivotal studies, Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration (ANCHOR)[4,5] and Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the treatment of Neovascular AMD (MARINA),[6] were the first phase 3 clinical trials to demonstrate that administration of 0.3 mg and 0.5 mg ranibizumab (Lucentis; Genentech, Inc., South San Francisco, CA)—a humanized, monoclonal anti-VEGF antigen binding fragment specifically designed for intraocular use that neutralizes all active isoforms of VEGF-A[14]—not only prevented vision loss associated with wet AMD, but also improved mean visual acuity (VA) over 2 years. Most of the functional and anatomic outcomes favored the 0.5 mg dose; in ANCHOR, the mean change from baseline in best-corrected VA (BCVA) at month 24 was +10.7 letters for ranibizumab 0.5 mg (n = 139) compared with +8.1 letters for ranibizumab 0.3 mg (n = 140) and −9.8 letters for verteporfin photodynamic therapy (n = 143). In MARINA, the mean change from baseline in BCVA at month 24 was +6.6 letters for ranibizumab 0.5 mg (n = 240) compared with +5.4 letters for ranibizumab 0.3 mg (n = 238) and −14.9 letters for sham injection (n = 238). An open-label, dose-ranging study demonstrated that ranibizumab doses up to 2.0 mg are well tolerated,[15] and the 2.0 mg dose has been shown to improve visual and anatomic outcomes significantly in wet AMD patients who were recalcitrant to ranibizumab 0.5 mg therapy.[16]

Although patients in the ANCHOR and MARINA trials received monthly ranibizumab injections, many retina specialists in clinical practice individualize treatment regimens in an effort to reduce patient burden.[17] Variable dosing regimens, such as treat-and-extend and pro re nata (PRN; as needed) administration, are used frequently and may reduce treatment burden.[17,18] Nonmonthly treatment approaches with VEGF inhibitors have been investigated in several clinical trials.[7–12,19–21] Visual outcomes were most favorable when optical coherence tomography (OCT) was used—in addition to VA decline criteria—to initiate PRN treatment for recurrent macular fluid.[22,23] For example, in the 2-year Prospective Optical Coherence Tomography Imaging of Patients with Neovascular AMD Treated with Intra-Ocular Lucentis (PRONTO) study, 40 patients received 3 monthly loading doses of ranibizumab 0.5 mg and were monitored monthly and re-treated based on time-domain OCT and VA criteria.[22,23] At month 24, patients treated with ranibizumab 0.5 mg PRN achieved comparable VA gains (+11.1 letters), as did the fixed monthly ranibizumab 0.5 mg dosing arms in ANCHOR (+10.7 letters) and MARINA (+6.6 letters), but with fewer injections over 2 years (on average, 9.9 injections in the PRONTO study versus the 24 scheduled injections in both ANCHOR and MARINA).[22,23] Pro re nata therapy was adopted by many retina specialists after the results of the PRONTO study. In the past few years, OCT technology has advanced, with practices now routinely using higher-resolution spectral-domain OCT (SD-OCT), which is more sensitive than time-domain OCT for the detection of fluid.[24]

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) evaluated over 2 years the potential beneficial effects of both a higher dose and PRN dosing of ranibizumab after 3 monthly loading doses compared with 0.5 mg ranibizumab monthly on functional and anatomic outcomes in patients with treatment-naïve subfoveal wet AMD.[7] At 12 months (the primary end point), the ranibizumab 2.0 mg monthly dose was not superior to the 0.5 mg monthly dose and did not offer any incremental improvements in efficacy outcomes (model-adjusted mean difference, −1.1 letters; 95.1% confidence interval, −3.4 to 1.3; $P = 0.8145$).[7] Additionally, the ranibizumab 0.5 mg PRN and 2.0 mg PRN groups failed to meet the prespecified 4-letter noninferiority margin compared with the 0.5 mg monthly group (noninferiority comparison between 0.5 mg PRN and 0.5 mg monthly: model-adjusted mean difference, −2.0 letters [97.5% confidence interval, −4.5 to 0.6]; noninferiority comparison between 2.0 mg PRN and 0.5 mg monthly: model-adjusted mean difference, −1.6 letters [98.4% confidence interval, −4.4 to 1.1]).[7]

Despite not meeting prespecified superiority and noninferiority comparisons, the HARBOR year 1 results demonstrated that PRN dosing with ranibizumab using VA and SD-OCT–guided re-treatment criteria decreased treatment burden and provided similar VA gains as monthly dosing for the treatment of wet AMD. The mean change in BCVA from baseline at month 12 was +8.2 and +8.6 letters in the ranibizumab 0.5 mg and 2.0 mg PRN groups, respectively, compared with +10.1 and +9.2 letters in ranibizumab 0.5 mg and 2.0 mg monthly groups, respectively. Over the first year, the ranibizumab 0.5 mg and 2.0 mg PRN groups required approximately 4 fewer injections, on average, than the 0.5 mg and 2.0 mg monthly groups (7.7 and 6.9 injections vs. 11.3 and 11.2 injections, respectively).[7] No new safety events were identified in year 1 of the HARBOR study. In particular, there was no difference in the safety profile regardless of dose group (0.5 vs. 2.0 mg) or treatment regimen (monthly vs. PRN).[7] The HARBOR study has been completed, and the 2-year efficacy and safety results are reported herein.

Methods

The methods for the HARBOR study have been published previously[7] and are summarized below.

Study Design and Eligibility

The HARBOR study was a 24-month, phase 3, randomized, multicenter, double-masked, active treatment-controlled study (ClinicalTrials.gov identifier NCT00891735) with 100 investigator sites across the United States. The HARBOR 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. Institutional review boards approved the study protocol before the start of the study, and all participants provided written informed consent for study participation.