Ranibizumab versus Verteporfin Photodynamic Therapy for Neovascular Age-Related Macular Degeneration: Two-Year Results of the ANCHOR Study

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Objective: The 2-year, phase III trial designated *Anti*-vascular endothelial growth factor (VEGF) Antibody for the Treatment of Predominantly Classic *Choro*idal Neovascularization (CNV) in Age-related Macular Degeneration (ANCHOR) compared ranibizumab with verteporfin photodynamic therapy (PDT) in treating predominantly classic CNV.

Design: Multicenter, international, randomized, double-masked, active-treatment-controlled clinical trial.

Participants: Patients with predominantly classic, subfoveal CNV not previously treated with PDT or antiangiogenic drugs.

Intervention: Patients were randomized 1:1:1 to verteporfin PDT plus monthly sham intraocular injection or to sham verteporfin PDT plus monthly intravitreal ranibizumab (0.3 mg or 0.5 mg) injection. The need for PDT (active or sham) retreatment was evaluated every 3 months using fluorescein angiography (FA).

Main Outcome Measures: The primary, intent-to-treat efficacy analysis was at 12 months, with continued measurements to month 24. Key measures included the percentage losing <15 letters from baseline visual acuity (VA) score (month 12 primary efficacy outcome measure), percentage gaining ≥ 15 letters from baseline, and mean change over time in VA score and FA-assessed lesion characteristics. Adverse events were monitored.

Results: Of 423 patients (143 PDT, 140 each in the 2 ranibizumab groups), the majority ($\geq$77% in each group) completed the 2-year study. Consistent with results at month 12, at month 24 the VA benefit from ranibizumab was statistically significant ($P<0.0001$ vs. PDT) and clinically meaningful: 89.9% to 90.0% of ranibizumab-treated patients had lost <15 letters from baseline (vs. 65.7% of PDT patients); 34% to 41.0% had gained ≥ 15 letters (vs. 6.3% of PDT group); and, on average, VA was improved from baseline by 8.1 to 10.7 letters (vs. a mean decline of 9.8 letters in PDT group). Changes in lesion anatomic characteristics on FA also favored ranibizumab (all comparisons $P<0.0001$ vs. PDT). Overall, there was no imbalance among groups in rates of serious ocular and nonocular adverse events. In the pooled ranibizumab groups, 3 of 277 (1.1%) patients developed presumed endophthalmitis in the study eye (rate per injection = 3/5921 [0.05%]).

Conclusions: In this 2-year study, ranibizumab provided greater clinical benefit than verteporfin PDT in patients with age-related macular degeneration with new-onset, predominantly classic CNV. Rates of serious adverse events were low.

Financial Disclosure(s): Proprietary or commercial disclosure may be found after the references.
Ophthalmology 2009;116:57–65

Neovascular age-related macular degeneration (AMD) is the process of anomalous pathologic blood vessels arising from the choroid and disrupting the anatomy and function of the neurosensory retina. Choroidal neovascularization (CNV) can be classified on the basis of its appearance on fluorescein angiography (FA) as "occult" or "classic." The clinical course of vision loss associated with occult CNV, which is usually confined to the space beneath the retinal pigment epithelium (RPE), is typically indolent compared with "classic" CNV lesions, which often penetrate the RPE and grow in the subretinal space.[1–3] "Predominantly classic" CNV are lesions composed of at least 50% classic CNV. Before the approval of verteporfin (Visudyne; Novartis Pharmaceuticals Corp., East Hanover, NJ) in 2001, predominantly classic CNV typically led to permanent loss of the majority of central vision within 3 to 9 months after diagnosis.[4] The Treatment of Age-Related Macular Degeneration with Photodynamic Therapy (TAP) study demonstrated the efficacy and favorable adverse events profile of verteporfin photodynamic therapy (PDT) in patients with predominantly classic CNV over the natural history of the disease, with 59% of patients treated with PDT losing fewer

than 15 letters at 2 years (compared with 31% of patients treated with placebo).[5] On the basis of these findings, PDT became the standard of care for patients with this angiographic subtype of CNV.

The 2-year, phase III trial designated *An*ti-vascular endothelial growth factor (VEGF) Antibody for the Treatment of Predominantly Classic *Chor*oidal Neovascularization in Age-related Macular Degeneration (ANCHOR) compared the recombinant, humanized anti-VEGF monoclonal antibody antigen-binding fragment (Fab) ranibizumab (Lucentis; Genentech, Inc., South San Francisco, CA) with PDT in patients with predominantly classic, subfoveal CNV secondary to AMD. At 12 months (the prespecified primary efficacy analysis), ranibizumab had superior efficacy to PDT as indicated by both visual acuity (VA) measures and changes in CNV lesion characteristics.[6] The percentage of patients who had lost fewer than 15 letters from baseline VA (primary efficacy end point) was 94.3% and 96.4% in the 0.3-mg and 0.5-mg ranibizumab groups, respectively, compared with 64.3% of patients in the PDT group. Also, ranibizumab-treated patients, on average, had improved VA compared with baseline at month 12, whereas VA declined in the PDT group. This was the first demonstration that a therapy could not only prevent further VA loss but also provide clinically meaningful improvement of VA in a substantial proportion of patients with predominantly classic CNV. Serious ocular events associated with treatment were uncommon. These first-year results, together with positive 2-year results in a similarly designed, sham-injection-controlled phase III trial in patients with minimally classic or occult with no classic CNV lesions (the Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab In the Treatment of Neovascular Age-Related Macular Degeneration (MARINA) study[7]), led to United States Food and Drug Administration approval of ranibizumab for treatment of all angiographic subtypes of CNV secondary to AMD in June 2006. The ANCHOR study is completed, and the 2-year results are reported here.

Materials and Methods

The methods for the ANCHOR study have been reported[6] and are summarized briefly below.

ANCHOR was a multicenter (83 sites), international, randomized, double-masked, active-treatment-controlled phase III trial evaluating the efficacy and adverse events profile of ranibizumab in treating predominantly classic subfoveal CNV secondary to AMD that, on the basis of FA and fundus photography, was confirmed by an independent central reading center (the University of Wisconsin Fundus Photograph Reading Center) to be predominantly classic in composition and suitable for treatment with PDT. Predominantly classic lesions were defined as those where the classic component made up 50% or more of the total lesion area, which could include, in addition to CNV, components such as contiguous subretinal hemorrhage, blocked fluorescence not from hemorrhage, serous detachment of the RPE, and fibrosis.

Patients provided written, informed consent for study participation. Institutional Review Board, National Competent Authority, or Ethics Committee approval was obtained at each participating clinical center before the start of the study. All US study sites complied with the Health Insurance Portability and Accountability Act of 1996. Patients were excluded if they had permanent structural damage to the central fovea or a history of treatment for subfoveal neovascular AMD (including any prior PDT) that by its nature or timing might compromise valid assessment of the effects of the study treatment. There were no exclusion criteria regarding preexisting cardiovascular, cerebrovascular, or peripheral vascular conditions.

Only 1 eye per patient (the study eye) received the study treatment. Eligible patients were randomized 1:1:1 to either verteporfin PDT plus monthly sham ocular injection or sham verteporfin PDT plus monthly intravitreal ranibizumab (0.3 mg or 0.5 mg) injection. Ranibizumab was injected into the study eye every 30±7 days for a total of 24 injections beginning on day 0; sham injections were administered on the same dosing schedule. Patients' CNV lesions were evaluated using FA at screening and then every 3 months to assess the need for additional PDT (active or sham intravenous verteporfin injection). The central reading center assessed all images, but the decision to retreat with PDT (active or sham) was based on the evaluating physician's assessment of CNV leakage on the FA images. Active PDT treatment was administered according to the Visudyne prescribing information[8] (i.e., the physician should reevaluate the patient every 3 months, and if CNV leakage is detected on FA then standard fluence PDT should be repeated). After careful review of the 12-month data, the study protocol was amended to allow all patients to receive active ranibizumab injections if they had not yet completed their month 23 visit (the last possible injection visit). Double-masking was maintained. Patients in the active PDT/sham ocular injection arm who participated in the amendment received monthly injections of 0.3 mg ranibizumab for the remainder of the trial, whereas patients in the ranibizumab groups who participated continued to receive ranibizumab according to their original randomization (0.3 or 0.5 mg). Active or sham PDT was no longer administered to patients who participated in the amendment but was continued (if needed) per randomization in patients who did not.

Best-corrected VA measured per the study protocol (i.e., measured with Early Treatment Diabetic Retinopathy Study charts at a starting distance of 2 m and using a standardized refraction and testing protocol) and CNV lesion characteristics (based on FA and fundus photography) were assessed at the regularly scheduled study visits. Key FA evaluations were the area of classic CNV, total lesion area, total area of CNV, and total area of leakage from CNV.

Intraocular pressure measurement (before and 60±10 minutes after each study treatment) and indirect ophthalmoscopy and slit-lamp examination (before each study treatment) were performed. The incidence and severity of ocular and nonocular (systemic) adverse events and systemic immunoreactivity (i.e., the presence of serum antibodies against ranibizumab) were assessed.

Efficacy end points were evaluated using an intent-to-treat analysis for randomized patients on the basis of their original treatment assignment. Missing data were imputed using the last-observation-carried-forward method and compared for consistency with those obtained using observed data. All available data were included in analyses of efficacy end points for year 2, including those that occurred after ranibizumab treatment initiation in patients randomized to PDT who crossed over to ranibizumab as part of the protocol amendment.

The primary efficacy end point was the proportion of patients who at 12 months lost fewer than 15 letters (~3 lines) from baseline VA in the study eye. The proportion of patients who lost fewer than 15 letters from baseline at 24 months was a secondary efficacy end point. Other prespecified secondary VA end points assessed at 12 months and 24 months included the mean change from baseline (letters), proportion of patients who gained 15 or more letters from baseline, and proportion of patients with a

Snellen equivalent of 20/200 or worse. Severe VA loss (30 letters [~6 lines] or more from baseline) was an exploratory efficacy end point. Prespecified secondary end points involving characteristics of the CNV lesion at months 12 and 24 were mean changes from baseline in the area of the classic CNV component and the total area of leakage from CNV (including leakage and intense progressive RPE staining). Mean changes in the area of CNV and the area of the entire lesion were exploratory efficacy end points.

Visual acuity outcomes were compared between each ranibizumab dose group and the control group with stratification by baseline VA score (<45 letters vs. ≥45 letters). Binary VA end points were analyzed using the Cochran chi-square test,[9] and the mean change from baseline was analyzed using the *t* test from an analysis of variance model. The mean changes from baseline to month 24 in the CNV lesion characteristics were compared between each ranibizumab dose group and the control group using the *t* test from a stratified, covariate-adjusted analysis of covariance model, with baseline VA score as the stratification variable and baseline value of the corresponding end point as a covariate. The percentage of patients with CNV leakage was compared between groups at month 24 using the Pearson chi-square test.

The main analyses comparing adverse events in the treatment groups were performed using all data for the entire study period, except for patients randomized to PDT who crossed over to ranibizumab as part of the protocol amendment. For these patients, adverse events data collected after their crossover were excluded from the main summaries and summarized separately.

Results

Patient Disposition

Patient disposition is summarized in Table 1 (available at http://aaojournal.org). Of 423 patients enrolled and randomized, 143 were assigned to active PDT and 140 each were assigned to the 2 ranibizumab dose levels. Three patients assigned to 0.3 mg ranibizumab withdrew before starting study treatment, and 1 patient in the 0.5-mg group did not have a baseline VA score. The study was completed by 110 patients (76.9%) in the PDT group, 117 patients (83.6%) in the 0.3-mg ranibizumab group, and 116 patients (82.9%) in the 0.5-mg ranibizumab group. Of those patients who discontinued early from the study, only 3 patients (2.1%), 1 patient (0.7%), and 3 patients (2.1%) from the PDT, 0.3-mg, and 0.5-mg groups, respectively, were reported as having been discontinued because of "loss to follow-up." Other reasons for early discontinuation as reported by investigators on the case report form (i.e., death, adverse event, patient's decision, physician's decision, patient noncompliance, patient's condition mandated other therapeutic intervention) were similarly distributed among the treatment groups, with the exception of discontinuation because of "patient's decision," which was more frequent among patients in the PDT group (17/143, 11.9%) than in the 0.3-mg (6/140, 4.3%) and 0.5-mg (8/140, 5.7%) ranibizumab groups.

Baseline Patient Characteristics

Demographic and baseline characteristics of the patients, summarized in Table 2 (available at http://aaojournal.org), were well balanced among the treatment groups. Although only patients with predominantly classic CNV, based on initially expedited assessment by the central reading center, were to be enrolled, the central reading center subsequently categorized a few patients in each treatment arm (2 in the PDT group, 6 in the 0.3-mg group, and 5 in the 0.5-mg group) as having minimally classic or occult with no classic CNV lesions; these patients were included in all analyses.

Study Treatment Exposure

The mean number of ranibizumab injections administered during the 2-year treatment period was 21.5 in the 0.3-mg group and 21.3 in the 0.5-mg group. Patients in the PDT group received a mean of 19.2 sham ocular injections. Including the required administration on day 0, active PDT was administered a mean of 3.8 times in the PDT group and sham PDT was administered a mean of 2.2 and 1.9 times in the 0.3-mg and 0.5-mg ranibizumab groups, respectively, during the 24-month study period. This calculation for the active PDT group includes patients who crossed over to ranibizumab (and thus became ineligible for further PDT) as part of the protocol amendment. Ranibizumab exposure and treatment results for the patients in the PDT group who crossed over are discussed below.

Starting as early as month 18, 50 of the 143 patients randomized to the PDT group (35%) crossed over to receive monthly injections of 0.3 mg ranibizumab for the remainder of the treatment period. Patients could receive up to 6 ranibizumab injections if crossover occurred at month 18 or 1 injection if crossover occurred at month 23. The 50 patients who crossed over received a mean of 3.3 ranibizumab injections.

Visual Acuity End Points

Visual acuity outcomes results, which include data from those patients who crossed over (but analyzed according to their randomized treatment assignment) are summarized in Table 3. (An additional table, Table 4 available at http://aaojournal.org, provides a frequency distribution of changes in VA relative to baseline in the study eye at month 24.) As previously reported by Brown et al,[6] the study met its objectives for the primary VA efficacy end point and all secondary VA and FA end points at the end of the first treatment year (i.e., each of the ranibizumab groups was superior to the PDT group for each end point). All second-year efficacy objectives (both VA and FA) concerning secondary end points were also met (the primary analysis for VA end points was at the end of the first year). A statistically significant and clinically meaningful effect of ranibizumab on VA was seen in all VA end points at month 24. Statistical analyses performed using observed data were consistent with the results using the last-observation-carried-forward method described above (i.e., $P<0.0001$ for all treatment comparisons vs. PDT using either method).

At month 24, 90.0% of patients in the 0.3-mg ranibizumab group and 89.9% of patients in the 0.5-mg ranibizumab group had lost <15 letters from baseline VA, compared with 65.7% of patients in the PDT group. A gain of 15 or more letters from baseline VA was seen in 34.3% of patients in the 0.3-mg ranibizumab group and 41.0% of patients in the 0.5-mg ranibizumab group, compared with 6.3% of patients in the PDT group. The mean change in VA over the 24-month treatment period is shown in Figure 1. On average, VA had improved from baseline by 8.1 letters in the 0.3-mg group and 10.7 letters in the 0.5-mg group at month 24, compared with a mean decline of 9.8 letters in the PDT group. The superior VA benefit of ranibizumab compared with PDT was statistically significant as early as month 1.

At month 24, the percentage of patients with a VA Snellen equivalent of 20/200 or worse was significantly higher in the PDT group (60.8%) than in the ranibizumab groups (22.9% in the 0.3-mg group and 20.0% in the 0.5-mg group; $P<0.0001$ vs. PDT). Only 1.4% of patients in the 0.3-mg group and none of the patients in the 0.5-mg group experienced severe vision loss (loss ≥30 letters; an exploratory end point) compared with baseline, whereas 16.1% of patients in the PDT group had severe vision loss at month 24.

Table 3. Key Visual Acuity Outcomes Relative to Baseline in the Study Eye at Month 12 and Month 24

Efficacy Outcome	Verteporfin PDT (n = 143)	Ranibizumab 0.3 mg (n = 140)	Ranibizumab 0.5 mg (n = 140)
Lost <15 letters—n (%)*			
Month 12†	92 (64.3)	132 (94.3)	134 (96.4)
Month 24	94 (65.7)	126 (90.0)	125 (89.9)
Lost ≥30 letters—n (%)*			
Month 12	19 (13.3)	0	0
Month 24	23 (16.1)	2 (1.4)	0
Snellen VA 20/200 or worse—n (%)			
Baseline*	46 (32.2)	35 (25.0)	32 (23.0)
Month 12	86 (60.1)	31 (22.1)	23 (16.4)
Month 24	87 (60.8)	32 (22.9)	28 (20.0)
Gained ≥0 letters—n (%)*			
Month 12	43 (30.1)	104 (74.3)	108 (77.7)
Month 24	41 (28.7)	109 (77.9)	108 (77.7)
Gained ≥15 letters—n (%)*			
Month 12	8 (5.6)	50 (35.7)	56 (40.3)
Month 24	9 (6.3)	48 (34.3)	57 (41.0)
Gained ≥30 letters—n (%)*			
Month 12	0	9 (6.4)	17 (12.2)
Month 24	3 (2.1)	12 (8.6)	20 (14.4)
Change from baseline (letters)*			
Month 12			
Mean (SD)	−9.5 (16.4)	8.5 (14.6)	11.3 (14.6)
Month 24			
Mean (SD)	−9.8 (17.6)	8.1 (16.2)	10.7 (16.5)

PDT = photodynamic therapy; SD = standard deviation; VA = visual acuity.
NOTE: $P<0.0001$ for all comparisons of each ranibizumab dose group with the verteporfin PDT group with the exception of Gained ≥30 letters, where at month 12 $P = 0.0018$ for the 0.3-mg ranibizumab group, and at month 24 $P = 0.0132$ and $P=0.0001$ for the 0.3-mg and 0.5-mg ranibizumab groups, respectively.
*For ranibizumab 0.5-mg group, the number of patients with observations is 139.
†Primary efficacy endpoint.

Angiographic End Points

Persistent, statistically significant beneficial effects of ranibizumab on FA-assessed lesion characteristics were also demonstrated at the end of the second study year (Table 5). At month 24, the total area of lesion, on average, remained essentially stable in the ranibizumab groups, increasing from baseline by 0.52 disc areas (DA) and 0.39 DA in the 0.3-mg and 0.5-mg groups, respectively. However, in the PDT group, the area increased by 2.89 DA ($P<0.0001$ for each dose group vs. PDT). At month 24, the total area of CNV, on average, also remained essentially stable in the ranibizumab groups, increasing from baseline by 0.33 DA and 0.27 DA in the 0.3-mg and 0.5-mg groups, respectively. In contrast, in the PDT group, the area increased by 1.60 DA ($P<0.0001$ for each dose group vs. PDT). At month 24, the mean area of classic CNV had decreased from baseline by 0.57 DA and 0.72 DA in the 0.3-mg and 0.5-mg groups, respectively; in the PDT group, it had increased by 0.41 DA ($P<0.0001$, vs. PDT). On average, although the area of classic CNV decreased from baseline in the ranibizumab groups, the area of occult CNV with no classic component increased (by 0.91 DA in the 0.3-mg group and by 0.99 DA in the 0.5-mg group), resulting in small mean increases in the total area of CNV. The total area occupied by other lesion components showed small mean increases in the ranibizumab groups, reflecting mean increases in the area of subretinal fibrous tissue (or fibrin) or disciform scar and area of atrophic scar, mean changes in the area of blood that was part of the lesion, and negligible mean changes in the area of serous pigment epithelial detachment (data not shown). These changes in the total area of CNV and the area of other lesion components with no CNV account for the small overall mean increase from baseline in the total area of the entire neovascular lesion.

At month 24, the total area of leakage from CNV plus intense progressive RPE staining, on average, had decreased from baseline by 2.23 DA and 2.37 DA in the 0.3-mg and 0.5-mg groups, respectively, and had decreased by 0.78 DA in the verteporfin PDT group ($P<0.0001$, vs. PDT). The percentage of patients with leakage from CNV plus intense progressive RPE staining declined in all 3 treatment groups from month 12 to month 24, but the percentage of patients whose lesions were still leaking at month 24 was significantly smaller in the ranibizumab-treated groups ($P<0.0001$, vs. PDT). Both the mean and standard deviation for the total area of leakage from CNV were identical (to 2 decimal places) with those for the total area of leakage from CNV plus intense progressive RPE staining, indicating that the mean area of intense progressive RPE staining was small.

Patients Who Crossed Over to Ranibizumab

Demographic and baseline characteristics of patients in the PDT group who switched to ranibizumab treatment were comparable to those of patients in the PDT group who did not switch to ranibizumab treatment (Table 2, available at http://aaojournal.org). Efficacy outcomes for patients who did and did not cross over are summarized in Table 6 (available at http://aaojournal.org). After 18 months or longer in the PDT group, patients who switched to ranibizumab treatment, on average, maintained the VA measured just before crossover. The overall mean change in VA was +0.2 letters (median change, 0 letters; range, −20 to +24 letters) at month 24. The 33 patients who received 3 or more ranibizumab injections after crossover had a mean change in VA of −0.6 letters (median change, 0 letters; range, −20 to +24 letters). At month 24, patients who crossed over to ranibizumab had a mean decrease of 5.7 letters compared with a mean decrease of 12.1 letters for patients who did not cross over. There were no notable differences between these PDT groups in the mean changes in total area of lesion, total area of CNV, and area of classic CNV at month 24. However, patients who crossed over had better control of leakage from CNV at month 24 (mean decrease of 1.9 DA in the total area of leakage from CNV plus intense progressive RPE staining and 40% of patients with leakage from CNV plus intense progressive RPE staining) compared with patients who did not cross over (mean decrease of 0.2 DA and 79% of patients with leakage). Patients randomized to PDT who crossed over to ranibizumab as part of the amendment were, on average, doing better on their original treatment regimen both in VA measures and in control of leakage from CNV than were patients who did not cross over (see month 12 and month 18 outcomes in Table 6, available at http://aaojournal.org).

Adverse Events

The cumulative rates of key ocular and nonocular adverse events during the 2-year study period are summarized in Table 7. Overall, there was no imbalance among the 3 treatment groups in the rates of serious and nonserious ocular adverse events in the study eye. The percentages of patients with any serious ocular adverse event in the study eye were similar among the PDT (7.7%), 0.3-mg ranibizumab (7.3%), and 0.5-mg ranibizumab (9.3%) groups.

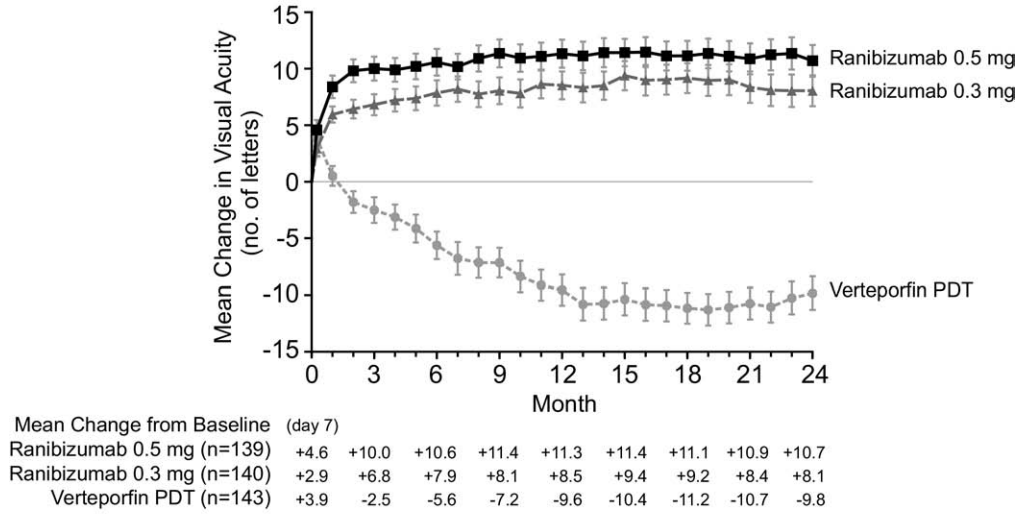

Figure 1. Mean change from baseline visual acuity (VA) score (letters) over time. Vertical bars represent ±1 standard error of the mean. The mean change at some visits in the first year differed slightly from those previously reported[6] because the present analysis is based on the final data. $P<0.001$ for all comparisons versus verteporfin photodynamic therapy (PDT) at each month. Pairwise analysis of variance models adjusting for VA score at day 0 (<45 letters vs. ≥45 letters) were used to analyze mean VA change from baseline at each monthly assessment. The last-observation-carried-forward method was used to impute missing data. All tests were 2-sided.

Serious ocular adverse events considered to be potentially related to intravitreal ranibizumab treatment include endophthalmitis, uveitis, vitreous hemorrhage, rhegmatogenous retinal detachment, retinal tear, and lens damage. In the combined ranibizumab groups, "presumed" endophthalmitis (i.e., including the patient in Table 7 whose adverse event was reported as "serious uveitis," but was treated with systemic antibiotics) in the study eye occurred in 3 of 277 patients (1.1%) in the pooled ranibizumab groups and in no patients in the PDT group. The rate of presumed endophthalmitis in the study eye per injection was 3 of 5921 injections (0.05%) in the pooled ranibizumab groups; all 3 of these patients had gains in VA at month 24 compared with baseline (+13, +26, and +32 letters, respectively). No patient other than the one mentioned above experienced uveitis classified as serious. Vitreous hemorrhage was reported in 2 of 277 patients (0.7%) in the pooled ranibizumab groups versus 0 of 143 patients in the PDT group. Rhegmatogenous retinal detachment occurred in 2 patients (0.7%) in the pooled ranibizumab groups and 1 patient (0.7%) in the PDT group; the rates per ocular injection were 2 of 2571 (0.07%) in the PDT group (sham injection) and 2 of 5921 (0.03%) in the pooled ranibizumab groups.

The percentage of patients who experienced any serious or nonserious adverse event of intraocular inflammation (i.e., iritis, iridocyclitis, vitritis, uveitis, anterior-chamber inflammation, or

Table 5. Anatomical Characteristics in the Study Eye at Month 24

Month 24 Outcome Measure	Verteporfin PDT (n = 143)	Ranibizumab	
		0.3 mg (n = 140)	*0.5 mg (n = 140)*
Change in total area of lesion (DA)			
Mean (SD)	2.89 (3.33)	0.52 (1.34)	0.39 (1.34)
95% CI of the mean	(2.34, 3.44)	(0.30, 0.75)	(0.16, 0.61)
Change in total area of CNV (DA)			
Mean (SD)	1.60 (2.42)	0.33 (1.21)	0.27 (1.28)
95% CI of the mean	(1.20, 2.00)	(0.13, 0.54)	(0.05, 0.48)
Change in area of classic CNV (DA)			
Mean (SD)	0.41 (2.30)	−0.57 (1.12)	−0.72 (1.12)
95% CI of the mean	(0.03, 0.79)	(−0.76, −0.39)	(−0.91, −0.54)
Change in total area of leakage from CNV + intense progressive RPE staining (DA)			
Mean (SD)	−0.78 (3.44)	−2.23 (2.09)	−2.37 (2.14)
95% CI of the mean	(−1.35, −0.21)	(−2.58, −1.88)	(−2.72, −2.01)
Patients with leakage from CNV + intense progressive RPE staining	65.0%	37.9%	39.3%

CI = confidence interval; CNV = choroidal neovascularization; DA = disc areas; PDT = photodynamic therapy; SD = standard deviation; RPE = retinal pigment epithelium.
NOTE: $P<0.0001$ for all comparisons of each ranibizumab dose group with the verteporfin PDT group.

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