ORIGINAL ARTICLE

Ranibizumab versus Verteporfin for Neovascular Age-Related Macular Degeneration

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ABSTRACT

BACKGROUND

We compared ranibizumab — a recombinant, humanized, monoclonal antibody Fab that neutralizes all active forms of vascular endothelial growth factor A — with photodynamic therapy with verteporfin in the treatment of predominantly classic neovascular age-related macular degeneration.

METHODS

During the first year of this 2-year, multicenter, double-blind study, we randomly assigned patients in a 1:1:1 ratio to receive monthly intravitreal injections of ranibizumab (0.3 mg or 0.5 mg) plus sham verteporfin therapy or monthly sham injections plus active verteporfin therapy. The primary end point was the proportion of patients losing fewer than 15 letters from baseline visual acuity at 12 months.

RESULTS

Of the 423 patients enrolled, 94.3% of those given 0.3 mg of ranibizumab and 96.4% of those given 0.5 mg lost fewer than 15 letters, as compared with 64.3% of those in the verteporfin group (P<0.001 for each comparison). Visual acuity improved by 15 letters or more in 35.7% of the 0.3-mg group and 40.3% of the 0.5-mg group, as compared with 5.6% of the verteporfin group (P<0.001 for each comparison). Mean visual acuity increased by 8.5 letters in the 0.3-mg group and 11.3 letters in the 0.5-mg group, as compared with a decrease of 9.5 letters in the verteporfin group (P<0.001 for each comparison). Among 140 patients treated with 0.5 mg of ranibizumab, presumed endophthalmitis occurred in 2 patients (1.4%) and serious uveitis in 1 (0.7%).

CONCLUSIONS

Ranibizumab was superior to verteporfin as intravitreal treatment of predominantly classic neovascular age-related macular degeneration, with low rates of serious ocular adverse events. Treatment improved visual acuity on average at 1 year. (ClinicalTrials.gov number, NCT00061594.)

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AGE-RELATED MACULAR DEGENERATION is a leading cause of severe and irreversible vision loss in the developed world among people 50 years of age or older.[1-4] The neovascular form of the disease is characterized by the growth of abnormal, choroidal blood vessels beneath the macula, which causes severe loss of vision.[5] Two main patterns of choroidal neovascularization that are associated with age-related macular degeneration, as seen on fluorescein angiography, are classic (in which intensely bright fluorescence is seen in early phases of the angiogram and leaks in late phases) and occult (in which leakage is less intense and appears in the late phases of disease).[6] Choroidal neovascular lesions that are predominantly (50% or more) classic in composition cause more severe and more rapid loss of vision than do lesions that are minimally (less than 50%) classic or occult.[7,8]

Photodynamic therapy with verteporfin[9-12] and intravitreal administration of pegaptanib sodium are approved by the Food and Drug Administration (FDA) and the European Agency for the Evaluation of Medicinal Products for the treatment of neovascular age-related macular degeneration.[13] Neither treatment has resulted in clinically significant improvements in visual acuity.

Ranibizumab — a recombinant, humanized monoclonal antibody Fab that neutralizes all active forms of vascular endothelial growth factor A (VEGF-A) — was recently approved by the Food and Drug Administration for the treatment of this condition. Elsewhere in this issue of the *Journal*, Rosenfeld et al. report on a phase 3 study, called the Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration (MARINA),[14] which demonstrated that monthly intravitreal injections of ranibizumab prevented the loss of visual acuity in approximately 95% of patients and improved visual acuity in one quarter to one third of treated patients during 24 months of treatment. In a similar manner, the addition of ranibizumab to verteporfin photodynamic therapy in patients with predominantly classic choroidal neovascularization was associated with a reduction in the loss of visual acuity, as compared with verteporfin therapy alone, and with an improvement in visual acuity over baseline in many patients.[15] We report the first-year results of a 2-year, phase 3 study, which compared the efficacy and safety of repeated intravitreal injections of ranibizumab with that of photodynamic therapy with verteporfin in patients with predominantly classic lesions associated with neovascular age-related macular degeneration.

METHODS

STUDY DESIGN

The Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration (ANCHOR) trial was an international, multicenter, randomized, double-blind, active-treatment–controlled study. Before the initiation of the study, we obtained approval from institutional review boards or ethics committees at all clinical centers. Patients provided written informed consent for study participation. Screening lasted as long as 28 days.

For inclusion in the study, patients had to be at least 50 years of age; have a lesion whose total size was no more than 5400 μm in greatest linear dimension in the study eye; have best-corrected visual acuity of 20/40 to 20/320 (Snellen equivalent), assessed with the use of Early Treatment Diabetic Retinopathy Study (ETDRS) charts; have no permanent structural damage to the central fovea; and have had no previous treatment (including verteporfin therapy) that might compromise an assessment of the study treatment. No patients were excluded because of preexisting cardiovascular, cerebrovascular, or peripheral vascular conditions.

STUDY TREATMENT

We randomly assigned eligible patients in a 1:1:1 ratio to receive either 0.3 or 0.5 mg of ranibizumab (Lucentis, Genentech) plus sham verteporfin therapy or sham intravitreal injections plus active verteporfin therapy. Randomization was stratified according to study center and to visual-acuity scores on day 0 (<45 letters vs. ≥45 letters, with a score of 45 letters as the approximate Snellen equivalent of 20/125 vision). In the group that received photodynamic therapy with verteporfin, intravenous administration of verteporfin (Visudyne, Novartis Pharmaceuticals) was followed by laser irradiation of the macula, according to instructions provided in the product package insert (www.visudyne.com). In the ranibizumab groups, sham verteporfin therapy was achieved by an intravenous infusion of saline rather than verteporfin, followed by laser

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Verteporfin (N=143)	0.3 mg of Ranibizumab (N=140)	0.5 mg of Ranibizumab (N=140)
Sex — no. (%)			
Male	64 (44.8)	73 (52.1)	75 (53.6)
Female	79 (55.2)	67 (47.9)	65 (46.4)
Race — no. (%)†			
White	140 (97.9)	137 (97.9)	136 (97.1)
Other	3 (2.1)	3 (2.1)	4 (2.9)
Age — yr			
Mean	77.7±7.8	77.4±7.5	76.0±8.6
Range	53–95	54–97	54–93
Age group — no. (%)			
50–64 yr	8 (5.6)	9 (6.4)	14 (10.0)
65–74 yr	35 (24.5)	28 (20.0)	41 (29.3)
75–84 yr	74 (51.7)	84 (60.0)	64 (45.7)
≥85 yr	26 (18.2)	19 (13.6)	21 (15.0)
Previous therapy — no. (%)			
Any treatment	64 (44.8)	63 (45.0)	58 (41.4)
Laser photocoagulation	19 (13.3)	23 (16.4)	20 (14.3)
Medication	1 (0.7)	1 (0.7)	1 (0.7)
Nutritional supplements	51 (35.7)	48 (34.3)	45 (32.1)
No. of letters read as a measure of visual acuity‡§			
Mean	45.5±13.1	47.0±13.1	47.1±13.2
<45 — no. (%)	66 (46.2)	63 (45.0)	60 (43.2)
≥45 — no. (%)	77 (53.8)	77 (55.0)	79 (56.8)

irradiation of the macula identical to that in the active verteporfin-therapy group.

Ranibizumab was injected into the study eye at a monthly interval (ranging from 23 to 37 days, for a total of 12 injections, excluding the injection at month 12) in the first year, beginning on day 0; sham injections were administered on the same schedule. Either verteporfin or sham verteporfin was administered on day 0 and then if needed on the basis of investigators' evaluation of angiography at months 3, 6, 9, or 12.

The study was designed and analyzed by a committee composed of Dr. Brown, representing the academic investigators, and representatives of Genentech. In analyzing the data and writing this manuscript, Dr. Brown had full and unrestricted access to the data, and all coauthors contributed to the interpretation of the data and the writing of the manuscript. The authors vouch for the accuracy and completeness of the reported data.

STATISTICAL ANALYSIS

We performed efficacy analyses on an intention-to-treat basis with the use of a last-observation-carried-forward method for missing data. Pairwise treatment comparisons were performed with the use of statistical methods adjusting for baseline scores of visual acuity (<45 letters vs. ≥45 letters) and, for lesion morphologic end points, the baseline value of the lesion characteristic. Binary end points were analyzed with the use of the Cochran chi-square test.[16] Mean changes from baseline were analyzed with the use of analysis of variance for end points with respect to visual acuity and an analysis of covariance for morphologic end points. The Hochberg–Bonferroni multiple-comparison procedure[17] was used to adjust for the two pairwise treatment comparisons of the primary end point. Safety analyses included all treated patients.

The number of patients required for statistical

Table 1. (Continued.)

Characteristic	Verteporfin (N=143)	0.3 mg of Ranibizumab (N=140)	0.5 mg of Ranibizumab (N=140)
Visual acuity (approximate Snellen equivalent) — no. (%)‡§			
20/200 or worse	46 (32.2)	35 (25.0)	32 (23.0)
Better than 20/200 but worse than 20/40	97 (67.8)	103 (73.6)	101 (72.7)
20/40 or better	0	2 (1.4)	6 (4.3)
Type of choroidal neovascularization — no. (%)			
Predominantly classic lesion	141 (98.6)	134 (95.7)	135 (96.4)
Minimally classic lesion	2 (1.4)	5 (3.6)	5 (3.6)
Occult with no classic lesion	0	1 (0.7)	0
Size of lesion — optic-disk area¶			
Mean	1.88±1.40	1.89±1.44	1.79±1.54
Range	0.07–5.75	0.12–7.20	0.05–10.00
Size of choroidal neovascularization — optic-disk area¶			
Mean	1.48±1.25	1.48±1.33	1.31±1.24
Range	0.07–5.55	0.11–6.80	0.05–7.50
Size of classic choroidal neovascularization — optic-disk area¶			
Mean	1.36±1.13	1.28±1.05	1.21±1.12
Range	0.07–5.55	0.00–6.40	0.05–5.30
Size of leakage from choroidal neovascularization plus staining of retinal pigment epithelium — optic-disk area¶			
Mean	3.06±1.81	3.00±1.92	2.92±2.08
Range	0.20–8.20	0.20–11.00	0.25–9.0

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding.
† Race was determined by the investigators.
‡ Visual acuity was measured with the use of Early Treatment Diabetic Retinopathy Study charts at a starting distance of 2 m. A score of 45 letters is the approximate Snellen equivalent of 20/125.
§ For the group that received 0.5 mg of ranibizumab, 139 patients were observed.
¶ One optic-disk area is equal to 2.54 mm^2 on the basis of one optic-disk diameter of 1.8 mm.

significance was determined on the basis of a 1:1:1 randomization ratio, the Pearson chi-square test for the two pairwise comparisons of the primary end point, and the Hochberg–Bonferroni multiple-comparison procedure at an overall type I error of 0.0497. We estimated that the enrollment of 426 patients would provide the study with a statistical power of 96% to detect a significant difference between one or both ranibizumab groups and the verteporfin group in the percentage of patients losing fewer than 15 letters at 12 months, assuming a rate of 84% in each ranibizumab group and 67% in the sham verteporfin group. (See the Supplementary Appendix, available with the full text of this article at www.nejm.org, for additional information on the study design and analysis.)

RESULTS

STUDY PATIENTS

Between June 2003 and September 2004, 423 patients were enrolled and randomly assigned to a study treatment (143 to the verteporfin group and 140 to each of the ranibizumab groups). The disposition of the patients is summarized in Table 1 of the Supplementary Appendix. Three patients in the group receiving 0.3 mg of ranibizumab did not receive any treatment: one because of the patient's decision and two because of an investigator's decision. More than 90% of patients in each group (91.5% overall) were receiving treatment at 12 months. Of a possible 12 injections of ranibizumab or sham injections, the mean number administered was 11.1 in the verteporfin group,

11.0 in the 0.3-mg group, and 11.2 in the 0.5-mg group. Including the required administration on day 0 and excluding month 12, active verteporfin therapy was administered a mean of 2.8 times in the verteporfin group, and sham verteporfin was administered a mean of 1.7 times in each of the ranibizumab groups.

Randomized treatment groups were balanced for demographic and baseline ocular and morphologic characteristics (Table 1). The independent reading center subtyped the choroidal neovascularization as predominantly classic in all patients during the expedited screening evaluation. Subsequent reevaluation confirmed the initial classification in 96.9% of patients, and 3.1% were reclassified. In each group, the mean total lesion area was slightly less than 2 optic-disk areas (1 optic-disk area equals 2.54 mm^2 on the basis of 1 optic-disk diameter of 1.8 mm).

PRIMARY AND SECONDARY END POINTS

All end points with respect to visual acuity in the study eye at 12 months favored ranibizumab treatment over verteporfin therapy. With respect to the primary efficacy end point, 94.3% of patients in the 0.3-mg group and 96.4% in the 0.5-mg group lost fewer than 15 letters from baseline visual acuity, as compared with 64.3% in the verteporfin group (P<0.001 for each comparison) (Fig. 1A). In addition, the proportion of patients whose visual acuity improved from baseline by 15 or more letters was significantly greater among those receiving ranibizumab treatment (35.7% in the 0.3-mg group and 40.3% in the 0.5-mg group, as compared with 5.6% in the verteporfin group; P<0.001 for each comparison) (Fig. 1B). Significantly greater proportions of ranibizumab-treated patients than patients in the verteporfin group had visual acuity of 20/40 or better (P<0.001 for the comparison of each ranibizumab group with the verteporfin group) (Fig. 1C), and smaller proportions had visual acuity of 20/200 or worse (P<0.001 for each comparison) (Fig. 1D). A severe loss of visual acuity (defined as a decrease of 30 letters or more) did not occur in any patient in the ranibizumab groups but occurred in 13.3% of patients in the verteporfin group (P<0.001 for each comparison) (Fig. 1E). Although no patient had baseline visual acuity of 20/20 or better, at 12 months 7.1% of the patients in the 0.3-mg group and 6.4% in the 0.5-mg group had visual acuity of 20/20 or better, as compared with 0.7% of patients in the verteporfin group.

Figure 1 (facing page). Visual Acuity Scores and Snellen Equivalents at 12 Months.

Panel A shows the percentage of patients who lost fewer than 15 letters (moderate loss) from baseline visual acuity at 12 months (the primary efficacy end point). Panel B shows the percentage of patients who gained 15 or more letters (moderate gain) from baseline at 12 months. Panels C and D show the percentage of patients with vision of the Snellen equivalent of 20/40 or better and of those with vision of 20/200 or worse, respectively, at both baseline and 12 months. (For the group that received 0.5 mg of ranibizumab, 139 patients were observed at baseline and 140 patients were observed at 12 months in Panels C and D.) Panel E shows the percentage of patients who lost 30 or more letters (severe loss) from baseline at 12 months. Treatment comparisons were based on the Cochran chi-square test stratified according to the visual-acuity score on day 0 (<45 letters vs. ≥45 letters). Confidence intervals, denoted by I bars, were based on the normal approximation and the simple (unstratified) estimates of the percentages and their standard errors. The last-observation-carried-forward method was used to impute missing data. All statistical tests were two-sided. P<0.001 for all comparisons of each dose of ranibizumab with verteporfin.

The tracking of mean changes in visual-acuity scores over time showed that the values in each of the ranibizumab groups were significantly superior to those in the verteporfin group at each month during the first year (P<0.001) (Fig. 2). On average, visual acuity of ranibizumab-treated patients increased by 5.9 letters in the 0.3-mg group and 8.4 letters in the 0.5-mg group at 1 month after the first treatment and increased further over time to a gain of 8.5 letters in the 0.3-mg group and 11.3 letters in the 0.5-mg group by 12 months. In contrast, the verteporfin group had an average loss in visual acuity at each month after the first month, with a mean loss of 9.5 letters by 12 months. Results for all end points with respect to visual acuity at 12 months were similar when the analyses used the observed data with no imputation of missing values (data not shown).

Results for prespecified secondary end points related to the morphologic characteristics of lesions are summarized in Table 2. At 12 months, the area occupied by classic choroidal neovascularization decreased by a mean of 0.52 optic-disk area in the 0.3-mg group and 0.67 optic-disk area in the 0.5-mg group, as compared with a mean increase of 0.54 optic-disk area in the verteporfin group (P<0.001 for each comparison). The area of leakage from choroidal neovascularization plus

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