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Ranibizumab for Neovascular Age-Related Macular Degeneration

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ABSTRACT

BACKGROUND

Ranibizumab — a recombinant, humanized, monoclonal antibody Fab that neutralizes all active forms of vascular endothelial growth factor A — has been evaluated for the treatment of neovascular age-related macular degeneration.

METHODS

In this multicenter, 2-year, double-blind, sham-controlled study, we randomly assigned patients with age-related macular degeneration with either minimally classic or occult (with no classic lesions) choroidal neovascularization to receive 24 monthly intravitreal injections of ranibizumab (either 0.3 mg or 0.5 mg) or sham injections. The primary end point was the proportion of patients losing fewer than 15 letters from baseline visual acuity at 12 months.

RESULTS

We enrolled 716 patients in the study. At 12 months, 94.5% of the group given 0.3 mg of ranibizumab and 94.6% of those given 0.5 mg lost fewer than 15 letters, as compared with 62.2% of patients receiving sham injections ($P<0.001$ for both comparisons). Visual acuity improved by 15 or more letters in 24.8% of the 0.3-mg group and 33.8% of the 0.5-mg group, as compared with 5.0% of the sham-injection group ($P<0.001$ for both doses). Mean increases in visual acuity were 6.5 letters in the 0.3-mg group and 7.2 letters in the 0.5-mg group, as compared with a decrease of 10.4 letters in the sham-injection group ($P<0.001$ for both comparisons). The benefit in visual acuity was maintained at 24 months. During 24 months, presumed endophthalmitis was identified in five patients (1.0%) and serious uveitis in six patients (1.3%) given ranibizumab.

CONCLUSIONS

Intravitreal administration of ranibizumab for 2 years prevented vision loss and improved mean visual acuity, with low rates of serious adverse events, in patients with minimally classic or occult (with no classic lesions) choroidal neovascularization secondary to age-related macular degeneration. (ClinicalTrials.gov number, NCT00056836.)

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Age-related macular degeneration is a leading cause of irreversible blindness among people who are 50 years of age or older in the developed world.[1-3] The neovascular form of the disease usually causes severe vision loss and is characterized by the abnormal growth of new blood vessels under or within the macula, the central portion of the retina responsible for high-resolution vision.

Neovascularization in this disease is classified by fluorescein angiography into major angiographic patterns termed classic and occult, which may be associated with various degrees of aggressiveness of disease, vision loss, and response to various treatment options.[4] Pharmacologic therapies for neovascular disease that are available in the United States and Europe include verteporfin photodynamic therapy[5-8] — approved by the Food and Drug Administration only for predominantly classic lesions (in which 50% or more of the lesion consists of classic choroidal neovascularization) and by the European Agency for the Evaluation of Medicinal Products for both predominantly classic lesions and occult disease with no classic lesions — and pegaptanib sodium.[9] Both treatments can slow the progression of vision loss, but only a small percentage of treated patients show improvement in visual acuity.

The age-related changes that stimulate pathologic neovascularization are incompletely understood, but vascular endothelial growth factor A (VEGF-A) — a diffusible cytokine that promotes angiogenesis and vascular permeability — has been implicated as an important factor promoting neovascularization.[10-15] Multiple biologically active forms of VEGF-A are generated by alternative messenger RNA splicing and proteolytic cleavage,[16] and two isoforms have been detected in choroidal neovascular lesions.[15]

Ranibizumab — a recombinant, humanized monoclonal antibody Fab that neutralizes all active forms of VEGF-A — was recently approved by the Food and Drug Administration for the treatment of all angiographic subtypes of subfoveal neovascular age-related macular degeneration. In phase 1 and 2 clinical studies, ranibizumab demonstrated encouraging signs of biologic activity, with acceptable safety, when administered intravitreally for up to 6 months in patients with neovascular age-related macular degeneration.[17-19] In our phase 3 study, Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration (MARINA), we evaluated ranibizumab for the treatment of minimally classic or occult with no classic choroidal neovascularization associated with age-related macular degeneration.

METHODS

STUDY DESIGN

At 96 sites in the United States, we enrolled 716 patients in our 2-year, prospective, randomized, double-blind, sham-controlled study of the safety and efficacy of repeated intravitreal injections of ranibizumab among patients with choroidal neovascularization associated with age-related macular degeneration. We performed a prespecified primary efficacy analysis at 12 months. The primary efficacy end point was the proportion of patients who had lost fewer than 15 letters (approximately 3 lines) from baseline visual acuity, as assessed with the Early Treatment Diabetic Retinopathy Study (ETDRS) chart, with the use of standardized refraction and testing protocol at a starting test distance of 2 m. We obtained approval from the institutional review board at each study site before the enrollment of patients; all study sites complied with the requirements of the Health Insurance Portability and Accountability Act. The eligibility of lesions was confirmed by an independent central reading center with the use of standardized criteria and trained graders who were unaware of patients' treatment assignments. Patients provided written informed consent before determination of their full eligibility. Screening lasted as long as 28 days.

To be included in the study, patients had to be at least 50 years old; have a best corrected visual acuity of 20/40 to 20/320 (Snellen equivalent determined with the use of an ETDRS chart); have primary or recurrent choroidal neovascularization associated with age-related macular degeneration, involving the foveal center; have a type of lesion that had been assessed with the use of fluorescein angiography and fundus photography as minimally classic or occult with no classic choroidal neovascularization; have a maximum lesion size of 12 optic-disk areas (1 optic-disk area equals 2.54 mm^2 on the basis of 1 optic-disk diameter of 1.8 mm), with neovascularization composing 50% or more of the entire lesion; and have presumed recent progression of disease, as evidenced by observable blood, recent vision loss, or a recent increase in a lesion's greatest linear

diameter of 10% or more. (For a complete list of eligibility criteria, see Table 1 of the Supplementary Appendix, available with the full text of this article at www.nejm.org.) There were no exclusion criteria regarding preexisting cardiovascular, cerebrovascular, or peripheral vascular conditions.

STUDY TREATMENT

We randomly assigned eligible patients in a 1:1:1 ratio to receive ranibizumab (Lucentis, Genentech) at a dose of either 0.3 mg or 0.5 mg or a sham injection monthly (within 23 to 37 days) for 2 years (24 injections) in one eye. The evaluating physician was unaware of the patient's treatment assignment; the physician who administered the injection was aware of the patient's treatment assignment regarding ranibizumab or sham treatment but was unaware of the dose of ranibizumab. Other personnel at each study site (except for those assisting with injections), patients, and personnel at the central reading center were unaware of the patient's treatment assignment.

Verteporfin photodynamic therapy was allowed if the choroidal neovascularization in the study eye became predominantly classic. On the basis of a policy decision by the Centers for Medicare and Medicaid Services to reimburse photodynamic therapy for small, minimally classic, and occult lesions as of April 1, 2004, the study protocol was amended to allow photodynamic therapy for minimally classic or occult disease with no classic lesions that were no larger than 4 optic-disk areas and were accompanied by a loss of 20 letters or more from baseline visual acuity, as confirmed at consecutive study visits. (A score of 55 letters is approximately equal to a Snellen equivalent of 20/80 vision.)

The study was designed and analyzed by a committee composed of both academic investigators and representatives of the industry sponsor. In the analysis of the data and the writing of the manuscript, Dr. Rosenfeld had full and unrestricted access to the data, and all the coauthors contributed to the interpretation of the data and the final version of the manuscript. All the authors vouch for the accuracy and completeness of the reported data.

STATISTICAL ANALYSIS

We performed efficacy analyses on an intention-to-treat basis among all patients with the use of a last-observation-carried-forward method for missing data. For all pairwise comparisons, the statistical model adjusted for baseline score for visual acuity (<55 letters vs. ≥55 letters) and subtype of choroidal neovascularization (minimally classic vs. occult with no classic disease). Between-group comparisons for dichotomous end points were performed with the use of the Cochran chi-square test.[20] Change from baseline visual acuity was analyzed with the use of analysis-of-variance models. For end points for lesion characteristics, analysis-of-covariance models adjusting for the baseline value were used. The Hochberg–Bonferroni multiple-comparison procedure[21] was used to adjust for the two pairwise treatment comparisons for the primary end point. Safety analyses included all treated patients.

We determined the number of patients in each group on the basis of a 1:1:1 randomization ratio, Pearson's 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 (adjusting for the three planned safety interim analyses before the primary efficacy analysis). Monte Carlo simulations were used to evaluate the power of the study. We estimated that the enrollment of 720 patients would provide the study with a statistical power of 95% to detect a significant difference between one or both ranibizumab groups and the sham-injection group in the proportion of patients losing fewer than 15 letters at 12 months, assuming a proportion of 65% in each ranibizumab group and 50% in the sham-injection group. (For more details, see the Methods section of the Supplementary Appendix.)

RESULTS

STUDY PATIENTS

Between March 2003 and December 2003, 716 patients were enrolled and randomly assigned to study treatment. Groups were balanced for demographic and baseline ocular characteristics (Table 1).

More than 90% of patients in each treatment group remained in the study at 12 months, and approximately 80 to 90% remained at 24 months (Table 2 of the Supplementary Appendix). The percentages who were still receiving study treatment were similarly high at 12 months and at the end of the study. After the unmasking of first-year results and discussion with the data and safety monitoring committee, ranibizumab was

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Sham Injection (N=238)	0.3 mg of Ranibizumab (N=238)	0.5 mg of Ranibizumab (N=240)
Sex — no. (%)			
Male	79 (33.2)	85 (35.7)	88 (36.7)
Female	159 (66.8)	153 (64.3)	152 (63.3)
Race — no. (%)†			
White	231 (97.1)	229 (96.2)	232 (96.7)
Other	7 (2.9)	9 (3.8)	8 (3.3)
Age — yr			
Mean	77±7	77±8	77±8
Range	56–94	52–95	52–93
Age group — no. (%)			
50–64 yr	11 (4.6)	13 (5.5)	16 (6.7)
65–74 yr	67 (28.2)	64 (26.9)	64 (26.7)
75–84 yr	132 (55.5)	130 (54.6)	124 (51.7)
≥85 yr	28 (11.8)	31 (13.0)	36 (15.0)
Previous therapy for age-related macular degeneration — no. (%)			
Any treatment	135 (56.7)	140 (58.8)	139 (57.9)
Laser photocoagulation	22 (9.2)	13 (5.5)	14 (5.8)
Medication‡	3 (1.3)	1 (0.4)	3 (1.2)
Nutritional supplements	121 (50.8)	134 (56.3)	127 (52.9)
Other	8 (3.4)	3 (1.3)	3 (1.2)
No. of letters as measure of visual acuity§			
Mean	53.6±14.1	53.1±12.9	53.7±12.8
<55 — no. (%)	109 (45.8)	115 (48.3)	117 (48.8)
≥55 — no. (%)	129 (54.2)	123 (51.7)	123 (51.2)

offered to all patients in October 2005, 2 months before the end of the last patient's final study visit at 24 months. Of the patients in the sham-injection group, 12 were switched to receive 0.5 mg of ranibizumab: 5 patients (2.1%) at 22 months and 7 (2.9%) at 23 months, the last possible injection visit. During the 2-year treatment period, 38 patients in the sham-injection group (16.0%), 2 patients in the group receiving 0.3 mg of ranibizumab (0.8%), and none in the group receiving 0.5 mg of ranibizumab received verteporfin photodynamic therapy at least once. In the second year, 13 patients (5.5%) in the sham-injection group and none in the ranibizumab groups chose to discontinue study treatment and receive pegaptanib sodium, which was approved in the United States in December 2004 for the treatment of neovascular age-related macular degeneration. Of these 13 patients, 8 remained in the follow-up group at 24 months.

PRIMARY AND SECONDARY END POINTS

The primary and key secondary efficacy results at 12 months (prespecified primary analysis) and 24 months are summarized in Figures 1 and 2. The study met its primary end point (Fig. 1A) at 12 months. Of the patients who were treated with ranibizumab, 94.5% of the patients receiving 0.3 mg and 94.6% of those receiving 0.5 mg had lost fewer than 15 letters from baseline visual acuity, as compared with 62.2% in the sham-injection group ($P<0.001$ for the comparison of each dose with the sham-injection group). At 24 months, this end point was met by 92.0% of the patients receiving 0.3 mg of ranibizumab and 90.0% of those receiving 0.5 mg, as compared with 52.9%

Table 1. (Continued.)

Characteristic	Sham Injection (N=238)	0.3 mg of Ranibizumab (N=238)	0.5 mg of Ranibizumab (N=240)
Visual acuity (approximate Snellen equivalent) — no. (%)§			
20/200 or worse	32 (13.4)	35 (14.7)	31 (12.9)
Better than 20/200 but worse than 20/40	170 (71.4)	176 (73.9)	173 (72.1)
20/40 or better	36 (15.1)	27 (11.3)	36 (15.0)
Type of choroidal neovascularization — no. (%)			
Occult with no classic lesion	151 (63.4)	151 (63.4)	149 (62.1)
Minimally classic lesion	87 (36.6)	86 (36.1)	91 (37.9)
Predominantly classic lesion	0	1 (0.4)	0
Missing data	1 (0.4)	0	0
Size of lesion — optic-disk area¶			
Mean	4.4±2.5	4.3±2.5	4.5±2.6
Range	0.0–11.8	0.1–11.8	0.3–12.0
Size of choroidal neovascularization — optic-disk area¶			
Mean	4.3±2.4	4.1±2.5	4.3±2.5
Range	0.0–11.8	0.0–11.8	0.1–12.0
Size of leakage from choroidal neovascularization plus staining of retinal pigment epithelium — optic-disk area¶			
Mean	3.5±2.5	3.6±2.5	3.5±2.6
Range	0.0–12.9	0.0–12.0	0.0–13.5

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding.
† Race was determined by the investigators.
‡ Medications included triamcinolone acetonide, prednisolone ophthalmic, and diclofenac sodium.
§ Visual acuity was measured with the use of ETDRS charts at a starting distance of 2 m. A score of 55 letters is approximately equal to a Snellen equivalent of 20/80.
¶ One optic-disk area is equal to 2.54 mm^2 on the basis of one optic-disk diameter of 1.8 mm.

in the sham-injection group (P<0.001 for each comparison). The visual-acuity benefit associated with ranibizumab was independent of the size of the baseline lesion, the lesion type, or baseline visual acuity (Fig. 1B and 1C).

At 12 and 24 months, approximately one quarter of patients treated with 0.3 mg of ranibizumab and one third of patients treated with 0.5 mg of ranibizumab had gained 15 or more letters in visual acuity, as compared with 5.0% or less of those in the sham-injection group (P<0.001 for each comparison) (Fig. 1D).

At both doses of ranibizumab, the mean improvement from baseline in visual-acuity scores was evident 7 days after the first injection (P=0.006 for the 0.3-mg dose and P=0.003 for the 0.5-mg dose), whereas mean visual acuity in the sham-injection group declined steadily over time at each monthly assessment (P<0.001 for both comparisons) (Fig. 2A). At 12 months, mean increases in visual acuity were 6.5 letters in the 0.3-mg group and 7.2 letters in the 0.5-mg group, as compared with a decrease of 10.4 letters in the sham-injection group (P<0.001 for both comparisons). The benefit in visual acuity was maintained at 24 months. The average benefit associated with ranibizumab over that of sham injection was approximately 17 letters in each dose group at 12 months and 20 to 21 letters at 24 months.

At baseline, the percentages of patients with 20/40 vision or better were similar among the three groups (Fig. 2B). At 12 months, approximately 40% of patients receiving ranibizumab had 20/40 vision or better, as compared with 11.3% in the sham-injection group (P<0.001). At 24 months, of the patients receiving ranibizumab, 34.5% of

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