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Ranibizumab and Bevacizumab for Neovascular Age-Related Macular Degeneration

The CATT Research Group*

ABSTRACT

BACKGROUND

Clinical trials have established the efficacy of ranibizumab for the treatment of neovascular age-related macular degeneration (AMD). In addition, bevacizumab is used off-label to treat AMD, despite the absence of similar supporting data.

METHODS

In a multicenter, single-blind, noninferiority trial, we randomly assigned 1208 patients with neovascular AMD to receive intravitreal injections of ranibizumab or bevacizumab on either a monthly schedule or as needed with monthly evaluation. The primary outcome was the mean change in visual acuity at 1 year, with a noninferiority limit of 5 letters on the eye chart.

RESULTS

Bevacizumab administered monthly was equivalent to ranibizumab administered monthly, with 8.0 and 8.5 letters gained, respectively. Bevacizumab administered as needed was equivalent to ranibizumab as needed, with 5.9 and 6.8 letters gained, respectively. Ranibizumab as needed was equivalent to monthly ranibizumab, although the comparison between bevacizumab as needed and monthly bevacizumab was inconclusive. The mean decrease in central retinal thickness was greater in the ranibizumab-monthly group (196 μm) than in the other groups (152 to 168 μm, $P=0.03$ by analysis of variance). Rates of death, myocardial infarction, and stroke were similar for patients receiving either bevacizumab or ranibizumab ($P>0.20$). The proportion of patients with serious systemic adverse events (primarily hospitalizations) was higher with bevacizumab than with ranibizumab (24.1% vs. 19.0%; risk ratio, 1.29; 95% confidence interval, 1.01 to 1.66), with excess events broadly distributed in disease categories not identified in previous studies as areas of concern.

CONCLUSIONS

At 1 year, bevacizumab and ranibizumab had equivalent effects on visual acuity when administered according to the same schedule. Ranibizumab given as needed with monthly evaluation had effects on vision that were equivalent to those of ranibizumab administered monthly. Differences in rates of serious adverse events require further study. (Funded by the National Eye Institute; ClinicalTrials.gov number, NCT00593450.)

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In 2005, clinical trials established the efficacy of ranibizumab[1,2] (Lucentis, Genentech) for the treatment of neovascular age-related macular degeneration (AMD), the leading cause of legal blindness in the United States. While awaiting approval for ranibizumab from the Food and Drug Administration, ophthalmologists began treating neovascular AMD with off-label use of bevacizumab (Avastin, Genentech), since the drug had a target specificity similar to that of ranibizumab and was available at low cost.[3,4]

Because the intraocular safety of bevacizumab and the duration of its therapeutic effect were unknown, the drug was usually administered only when there were signs of active disease (i.e., as needed). Bevacizumab is the most commonly used drug in the United States for the treatment of neovascular AMD, despite the absence of large-scale clinical-trial data supporting its use.[5] Also, an as-needed regimen has been widely adopted for ranibizumab,[6] a departure from the monthly regimen that was used in the pivotal trials of this drug. In the randomized Comparison of Age-Related Macular Degeneration Treatments Trials (CATT), we set out to assess the relative efficacy and safety of ranibizumab and bevacizumab and to determine whether an as-needed regimen would compromise long-term visual acuity, as compared with a monthly regimen.[7]

METHODS

STUDY PATIENTS

From February 2008 through December 2009, we enrolled 1208 patients at 44 clinical centers in the United States. Eligibility criteria included an age of 50 years or more, the presence in the study eye (one eye per patient) of previously untreated active choroidal neovascularization due to AMD, and visual acuity between 20/25 and 20/320 on electronic visual-acuity testing.[8] To establish the presence of active choroidal neovascularization, we required the presence of leakage, as seen on fluorescein angiography, and of fluid, as seen on time-domain optical coherence tomography (OCT), located either within or below the retina or below the retinal pigment epithelium. Inclusion criteria were neovascularization, fluid, or hemorrhage under the fovea. The study was approved by the institutional review board at each clinical center. All patients provided written informed consent.

TREATMENT

A copy of the protocol and the statistical analysis plan (in the Supplementary Appendix) are available with the full text of this article at NEJM.org. Patients were randomly assigned to one of four study groups. Randomization schedules were stratified according to clinical center with the use of a permuted-block method with a randomly chosen block size. Study groups were defined according to the drug and the regimen of administration after the first mandatory intravitreal injection: ranibizumab every 28 days (ranibizumab monthly), bevacizumab every 28 days (bevacizumab monthly), ranibizumab only when signs of active neovascularization were present (ranibizumab as needed), and bevacizumab only when signs of active neovascularization were present (bevacizumab as needed).

The dose was 0.50 mg (in 0.05 ml of solution) for ranibizumab and 1.25 mg (in 0.05 ml of solution) for bevacizumab. Bevacizumab was used under an application for an investigational new drug. Commercially acquired bevacizumab was repackaged in glass vials in an aseptic filling facility, with all costs paid by study funds. Standard care for study patients, including the use of ranibizumab, was covered by Medicare and third-party insurers. Residual copayments for ranibizumab were made with the use of study funds after the patients' insurers had met their responsibilities for coverage.

Every 28 days, patients in the groups that received study drugs as needed underwent time-domain OCT and were evaluated for treatment. Time-domain OCT was performed with the use of macular thickness maps and fast macular thickness maps. Signs of active neovascularization were defined as fluid on OCT, new or persistent hemorrhage, decreased visual acuity as compared with the previous examination, or dye leakage or increased lesion size on fluorescein angiography. Ophthalmologists at each clinical center, who were unaware of study-group assignments, made retreatment decisions in the groups assigned to receive the study drugs as needed. Staff members who were aware of study-group assignments filled a syringe with the assigned drug and presented it to the ophthalmologist. Fluorescein angiography was performed at the discretion of the ophthalmologist to aid in retreatment decisions. The decisions whether to administer antibiotic drops

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Table 1. Baseline Characteristics of the Patients.*

Characteristic	Ranibizumab Monthly (N=301)	Bevacizumab Monthly (N=286)	Ranibizumab as Needed (N=298)	Bevacizumab as Needed (N=300)
Age — no. (%)				
50–59 yr	2 (0.7)	1 (0.3)	6 (2.0)	2 (0.7)
60–69 yr	33 (11.0)	28 (9.8)	31 (10.4)	34 (11.3)
70–79 yr	102 (33.9)	84 (29.4)	115 (38.6)	103 (34.3)
80–89 yr	142 (47.2)	150 (52.4)	126 (42.3)	142 (47.3)
≥90 yr	22 (7.3)	23 (8.0)	20 (6.7)	19 (6.3)
Mean — yr	79.2±7.4	80.1±7.3	78.4±7.8	79.3±7.6
Sex — no. (%)				
Female	183 (60.8)	180 (62.9)	185 (62.1)	184 (61.3)
Male	118 (39.2)	106 (37.1)	113 (37.9)	116 (38.7)
Race — no. (%)†				
White	297 (98.7)	281 (98.3)	296 (99.3)	294 (98.0)
Other	4 (1.3)	5 (1.7)	2 (0.7)	6 (2.0)
History of myocardial infarction — no. (%)	34 (11.3)	40 (14.0)	30 (10.1)	36 (12.0)
History of stroke — no. (%)	14 (4.7)	18 (6.3)	22 (7.4)	16 (5.3)
History of transient ischemic attack — no. (%)	12 (4.0)	25 (8.7)	12 (4.0)	19 (6.3)
Blood pressure — mm Hg				
Systolic	134±18	135±19	136±17	135±17
Diastolic	75±10	75±10	76±9	75±10
Visual-acuity score and Snellen equivalent				
68–82 letters, 20/25–40 — no. (%)	111 (36.9)	94 (32.9)	116 (38.9)	103 (34.3)
53–67 letters, 20/50–80 — no. (%)	98 (32.6)	118 (41.3)	108 (36.2)	119 (39.7)
38–52 letters, 20/100–160 — no. (%)	67 (22.3)	53 (18.5)	58 (19.5)	58 (19.3)
23–37 letters, 20/200–320 — no. (%)	25 (8.3)	21 (7.3)	16 (5.4)	20 (6.7)
Mean score	60.1±14.3	60.2±13.1	61.5±13.2	60.4±13.4
Total thickness at fovea — μm‡	458±184	463±196	458±193	461±175
Retinal thickness plus subfoveal-fluid thickness at fovea — μm	251±122	254±121	247±122	252±115
Foveal center involvement — no. (%)				
Choroidal neovascularization	176 (58.5)	153 (53.5)	176 (59.1)	183 (61.0)
Fluid	85 (28.2)	81 (28.3)	77 (25.8)	72 (24.0)
Hemorrhage	20 (6.6)	24 (8.4)	24 (8.1)	25 (8.3)
Other	18 (6.0)	20 (7.0)	15 (5.0)	18 (6.0)
No choroidal neovascularization or not possible to grade	2 (0.7)	8 (2.8)	6 (2.0)	2 (0.7)

* Plus–minus values are means ±SD.
† Race was self-reported.
‡ Total thickness at the fovea includes the retina, subretinal fluid, choroidal neovascularization, and retinal pigment epithelial elevation.

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before and after the intravitreal injections were made at the ophthalmologist's discretion.

OUTCOME MEASURES

The primary outcome was the mean change in visual acuity between baseline and 1 year. Secondary outcomes included the proportion of patients with a change in visual acuity of 15 letters or more, the number of injections, the change in fluid and foveal thickness on OCT (as measured by the OCT Reading Center), the change in lesion size on fluorescein angiography (as measured by the Fundus Photograph Reading Center), the incidence of ocular and systemic adverse events, and annual drug cost (per-dose cost, approximately $2,000 for ranibizumab and $50 for bevacizumab). Examiners of visual acuity and graders of OCT scans and angiograms were unaware of study-group assignments. Adverse events were ascertained through monthly questioning of patients by study coordinators who were aware of study-group assignments; events were coded according to the *Medical Dictionary for Regulatory Activities* (MedDRA) system, version 10. A medical monitor who was unaware of study-group assignments reviewed serious adverse events. Arteriothrombotic events (as defined by the Antiplatelet Trialists' Collaboration) were prespecified for monitoring.[9]

STATISTICAL ANALYSIS

This study was designed as a noninferiority trial among four study groups, with the ability to test for superiority if a treatment was found to be noninferior.[10,11] We used a Bonferroni approach to accommodate six pairwise treatment comparisons, which required the calculation of two-sided 99.2% confidence intervals. The noninferiority limit for the difference between study groups in the mean change in visual acuity at 1 year was 5 letters (i.e., one line on the Early Treatment Diabetic Retinopathy Study [ETDRS] visual-acuity chart).[11,12] Assuming a standard deviation for changes in visual acuity of 15 letters, we determined that a sample of 277 patients per group (which was increased to 300 to allow for a rate of death or dropout of 8%) would provide a power of 90%. This report includes all efficacy and safety data that were available by December 31, 2010, for the first 12 months of follow-up. In 40 cases in which the 12-month examination was missed, data from a later examination (up to 64 weeks) were used for the 12-month outcomes.

Figure 1 (facing page). Findings on Optical Coherence Tomography.

Panel A shows an optical coherence tomogram of a normal retina, with a multilayered neurosensory retina, normal central foveal depression, and retinal pigment epithelial (RPE) cell layer. Panel B shows the results for a typical study patient at baseline, with a marked increase in retinal thickness caused by intraretinal fluid, subretinal fluid, and sub-RPE fluid. Panel C shows a small area of intraretinal fluid, approximately equal to the median amount of fluid that was present in patients assigned to treatment as needed who did not receive treatment even though the reading-center graders identified fluid. Panel D shows the retinal thickness at 12 months in a patient treated with ranibizumab monthly. The retinal thickness, approximately equal to the mean thickness in the ranibizumab-monthly group, and the morphologic features of the retina are similar to normal retinal anatomy. Panel E shows the 12-month results for a patient who was treated with bevacizumab monthly. The retinal thickness, approximately equal to the mean for the bevacizumab-monthly group, and the morphologic features of the retina are also similar to normal retinal anatomy. Panel F shows the mean change in total retinal thickness at the fovea during the first year of follow-up.

All analyses were performed on the basis of the intention-to-treat principle. To compare the study groups, we used exact chi-square tests for categorical variables and analysis of variance for continuous variables, except as otherwise noted. The primary analyses did not include adjustment for covariates. Adjustment for covariates and three alternative approaches for handling missing data from the 52-week examination were performed as sensitivity analyses.[13] These three approaches were the inclusion of data only from patients who completed the 52-week visit or the use of multiple imputation for missing data on the basis of either propensity scoring or regression modeling. Quarterly measurements of change in visual acuity from baseline were summarized by means of a longitudinal analysis.[14] We used a modified version of the Wilcoxon rank-sum test to compare median areas of fluid between groups that received the study drug as needed.[15] Person-specific rates of adverse events were compared according to study group and drug group. The time to the first serious adverse event was analyzed with the use of the Cox model that included age, sex, use or nonuse of dietary supplements, and status with respect to patient-reported history of 13 conditions associated ($P<0.10$) with the incidence of

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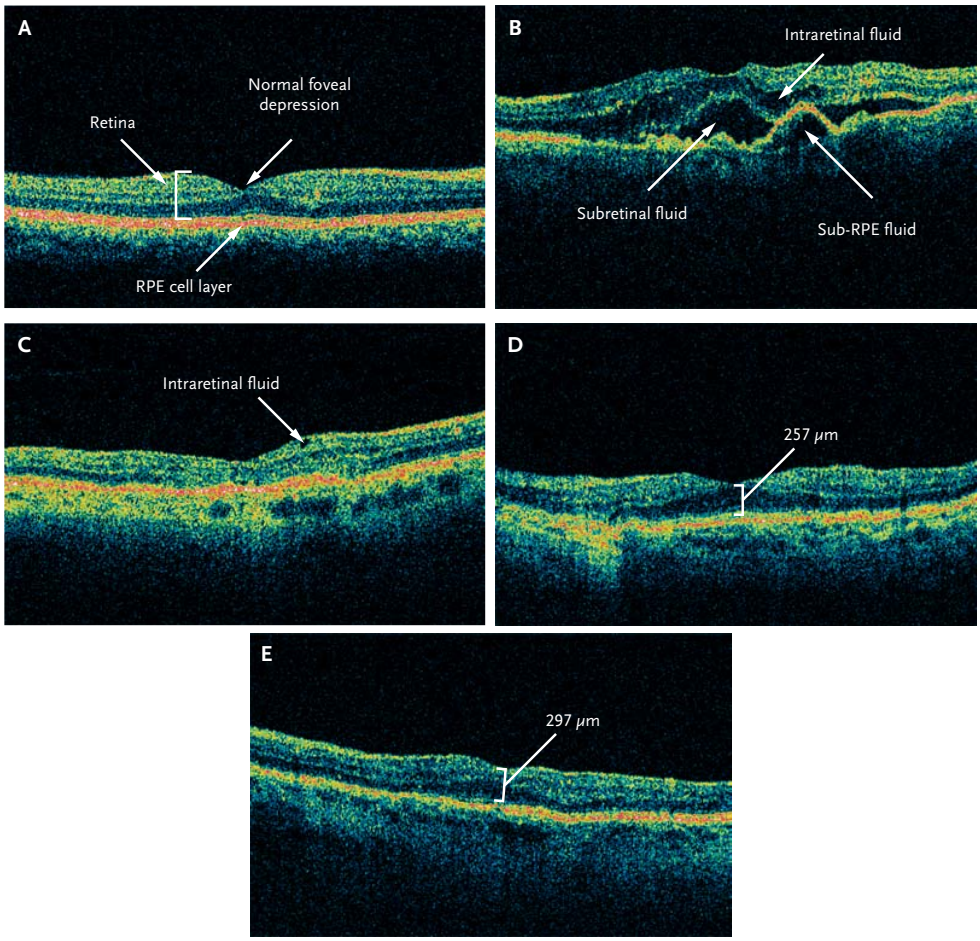

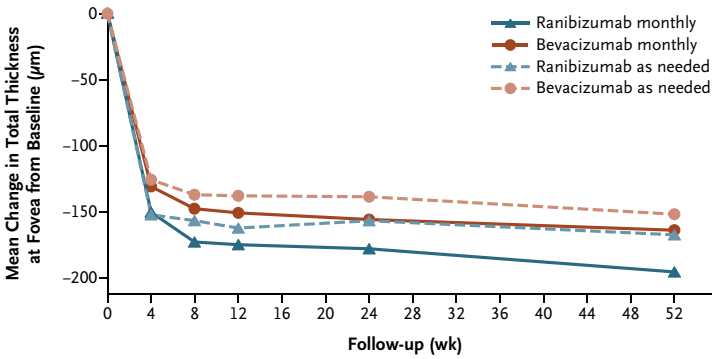

Mean (±SE) Change in Thickness at Fovea from Baseline (μm)	Wk 4	Wk 8	Wk 12	Wk 24	Wk 52
Ranibizumab monthly	−151±9	−173±9	−175±10	−178±10	−196±11
Bevacizumab monthly	−131±9	−147±9	−151±10	−156±11	−164±11
Ranibizumab as needed	−153±9	−157±10	−163±11	−157±11	−168±11
Bevacizumab as needed	−126±8	−137±9	−138±10	−139±10	−152±11

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serious adverse events.[16] Analyses were performed with the use of SAS software, version 9.2.

The data and safety monitoring committee recommended that data for all 23 patients at one study center be excluded because of serious protocol noncompliance. Unless otherwise specified, we included only the 1185 patients who were enrolled at the remaining 43 centers in the analyses.

RESULTS

PATIENTS AND TREATMENT

There were no substantial imbalances in the demographic or ocular characteristics of the study groups at baseline (Table 1, and Section 2 in the Supplementary Appendix). Fulfillment of eligibility criteria was confirmed by central review of images for 1143 of 1185 patients (96.5%). All but 3 patients had evidence of choroidal neovascularization on OCT or fluorescein angiography and continued with the assigned treatment. Among the 1161 patients who were alive 1 year after enrollment, visual-acuity scores were available for 1105 (95.2%), with proportions ranging from 93.8% to 97.3% among the four study groups.

After completion of the review of OCT scans by the reading center, treatment decisions by study ophthalmologists were consistent with the retreatment protocol for 2336 of 3268 examinations (71.5%) in the group assigned to ranibizumab as needed and for 2328 of 3133 examinations (74.3%) in the group assigned to bevacizumab as needed. Detection of fluid on OCT scans in patients who were not treated accounted for most cases of a discrepancy between OCT findings and treatment decisions (865 of 932 cases [92.8%] in the group assigned to ranibizumab as needed and 733 of 805 cases [91.1%] in the group assigned to bevacizumab as needed). In a random sample of 400 cases of discrepancies between OCT findings and treatment decisions, the median area of fluid was 0.007 mm^2 in the group that received ranibizumab as needed and 0.008 mm^2 in the group that received bevacizumab as needed ($P=0.20$) (Fig. 1). During 22,138 visits by patients, the identity of the drug that was being administered was known to the treating ophthalmologist in only 46 instances (0.2%).

MEAN CHANGE IN VISUAL ACUITY

Visual acuity improved from baseline to 1 year in all four study groups. Most of the improvement occurred during the first 6 months (Fig. 2A). At 1 year, bevacizumab was equivalent to ranibizumab (99.2% confidence interval for the difference in the mean change in visual-acuity score within –5 to +5 letters) both when the drugs were given monthly and when the drugs were given as needed (Fig. 2B). Ranibizumab given as needed was equivalent to ranibizumab given monthly. The comparison between bevacizumab given as needed and bevacizumab given monthly was inconclusive, so neither noninferiority nor inferiority was established between the two study groups. Ranibizumab given as needed was equivalent to bevacizumab given monthly. The comparison between bevacizumab given as needed and ranibizumab given monthly was also inconclusive.

The outcomes for the pairwise comparisons between study groups did not change after adjustment for clinical center, age, baseline visual acuity, and baseline lesion size; after the application of alternative methods for handling missing data on visual acuity; or after the inclusion of data from all 44 centers. When inclusion criteria from two pivotal clinical trials of ranibizumab were applied to patients given ranibizumab monthly, the mean increases in visual acuity for the two subgroups were similar to those in the pivotal trials. These increases were 9.8 letters in CATT versus 7.2 letters in the Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular AMD (MARINA; ClinicalTrials.gov number, NCT00056836)[1] and 10.8 letters in CATT versus 11.3 letters in the Anti-VEGF Antibody for the Treatment of Pre-

Figure 2 (facing page). Change in Visual-Acuity Score from Baseline to 1 Year.

Panel A shows the mean change in the visual-acuity score during the first year of follow-up. Panel B shows differences between pairs of study groups in the mean change from baseline to 1 year in the visual-acuity score. The red vertical lines indicate means, and the gray bars 99.2% confidence intervals. Negative values reflect a greater mean increase in group 2. Confidence intervals within –5 and +5 letters (dashed vertical lines) indicate that the two groups are equivalent. Confidence intervals extending beyond the noninferiority limit of –5 letters indicate that the comparison of the two groups is inconclusive with respect to noninferiority. Panel C shows the proportions of patients in each group with a decrease of 15 letters or more, a change within 14 letters, or an increase of 15 letters or more from baseline values during the first study year.

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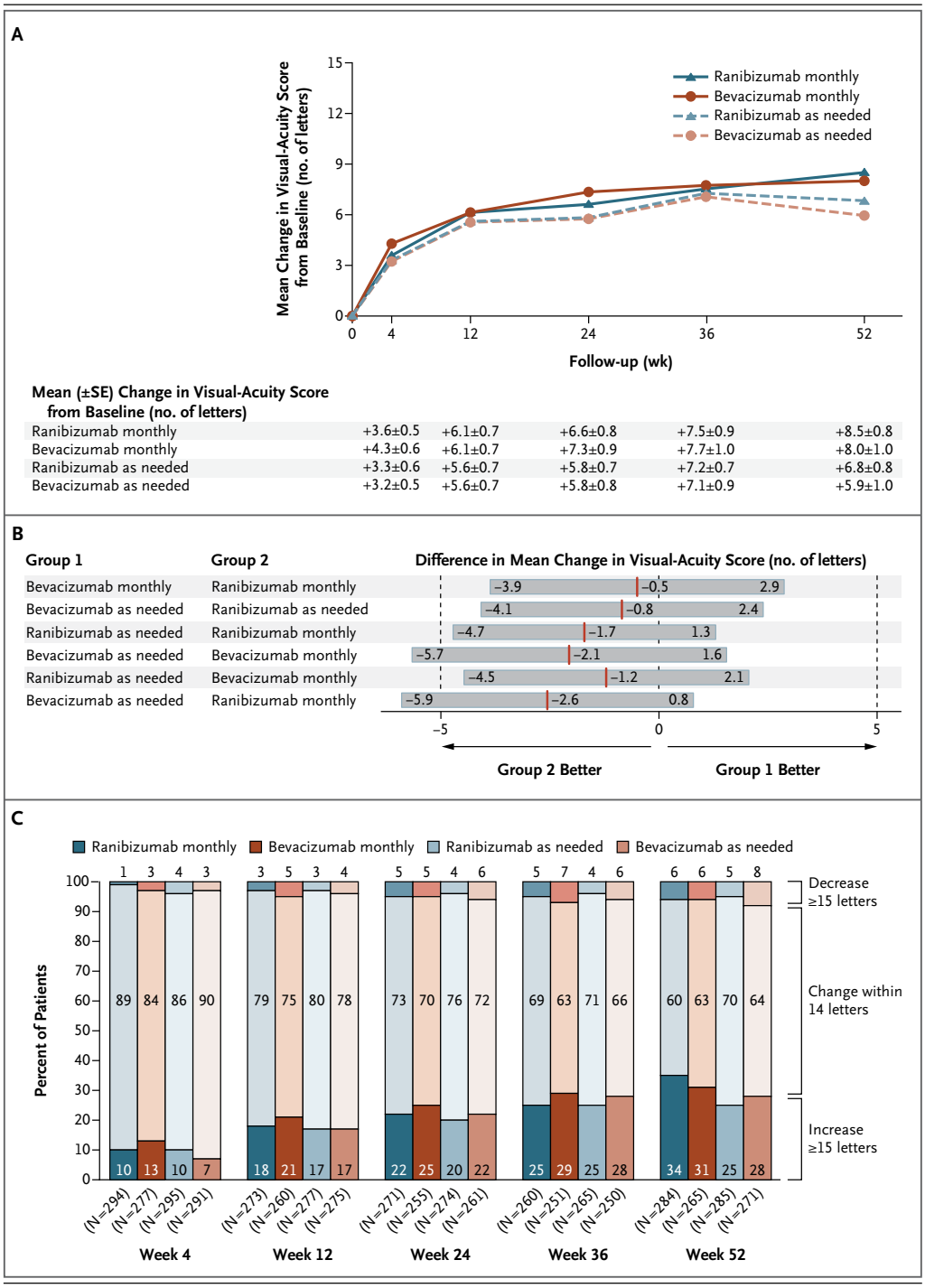

dominantly Classic Choroidal Neovascularization in AMD (ANCHOR, NCT00061594).[2]

In a longitudinal regression model of changes in visual acuity, the estimated mean (±SE) increase in the number of letters from baseline was 7.2±0.7 in the ranibizumab-monthly group, 7.3±0.8 in the bevacizumab-monthly group, 6.4±0.6 in the ranibizumab-as-needed group, and 6.1±0.7 in the

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bevacizumab-as-needed group (P=0.53). In all pairwise comparisons of the groups, with and without covariate adjustment, there were equivalent mean changes in visual acuity averaged over the 1-year period.

SECONDARY OUTCOMES

At 1 year, the proportion of patients who did not have a decrease in visual acuity of 15 letters or more from baseline was 94.4% in the ranibizumab-monthly group, 94.0% in the bevacizumab-monthly group, 95.4% in the ranibizumab-as-needed group, and 91.5% in the bevacizumab-as-needed group (P=0.29 by the chi-square test) (Fig. 2C). The proportion of patients who gained at least 15 letters increased during the first 36 weeks in all four study groups and at 1 year did not differ significantly among the groups, ranging from 24.9% in the group that received ranibizumab as needed to 34.2% in the group that received ranibizumab

Table 2. Outcome Measures at 1 Year.*

Outcome	Ranibizumab Monthly (N=284)	Bevacizumab Monthly (N=265)	Ranibizumab as Needed (N=285)	Bevacizumab as Needed (N=271)	P Value†
Visual-acuity score and Snellen equivalent					
83–97 letters, 20/12–20 — no. (%)	42 (14.8)	45 (17.0)	38 (13.3)	40 (14.8)	
68–82 letters, 20/25–40 — no. (%)	149 (52.5)	134 (50.6)	141 (49.5)	127 (46.9)	
53–67 letters, 20/50–80 — no. (%)	52 (18.3)	47 (17.7)	66 (23.2)	57 (21.0)	
38–52 letters, 20/100–160 — no. (%)	23 (8.1)	21 (7.9)	23 (8.1)	24 (8.9)	
≤37 letters, ≤20/200 — no. (%)	18 (6.3)	18 (6.8)	17 (6.0)	23 (8.5)	
Mean no. of letters	68.8±17.7	68.4±18.2	68.4±16.4	66.5±19.0	0.45
Change from baseline visual-acuity score					
Increase of ≥15 letters — no. (%)	97 (34.2)	83 (31.3)	71 (24.9)	76 (28.0)	
Increase of 5–14 letters — no. (%)	90 (31.7)	98 (37.0)	103 (36.1)	90 (33.2)	
Change of ≤4 letters — no. (%)	62 (21.8)	50 (18.9)	75 (26.3)	59 (21.8)	
Decrease of 5–14 letters — no. (%)	19 (6.7)	18 (6.8)	23 (8.1)	23 (8.5)	
Decrease of ≥15 letters — no. (%)	16 (5.6)	16 (6.0)	13 (4.6)	23 (8.5)	
Mean no. of letters	8.5±14.1	8.0±15.8	6.8±13.1	5.9±15.7	0.16
Mean no. of treatments	11.7±1.5	11.9±1.2	6.9±3.0	7.7±3.5	<0.001
Average cost of drug/patient — $	23,400	595	13,800	385	
Total thickness at fovea — μm‡					
Mean§	266±125	300±149	294±139	308±127	0.002
Mean change from baseline¶	−196±176	−164±181	−168±186	−152±178	0.03
Retinal thickness plus subfoveal-fluid thickness at fovea — μm					
Mean§	152±57	172±81	166±66	172±68	0.001
Mean change from baseline¶	−100±130	−79±132	−81±134	−79±123	0.18
Fluid on optical coherence tomography — no. (%)					
Absent	124 (43.7)	69 (26.0)	68 (23.9)	52 (19.2)	<0.001
Present	151 (53.2)	188 (70.9)	203 (71.2)	214 (79.0)	
Data missing	9 (3.2)	8 (3.0)	14 (4.9)	5 (1.8)	
Dye leakage on angiogram — no. (%)					
Absent	167 (58.8)	153 (57.7)	133 (46.7)	111 (41.0)	<0.001
Present	97 (34.2)	100 (37.7)	137 (48.1)	145 (53.5)	
Data missing	20 (7.0)	12 (4.5)	15 (5.3)	15 (5.5)	

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Table 2. (Continued).

Outcome	Ranibizumab Monthly (N=284)	Bevacizumab Monthly (N=265)	Ranibizumab as Needed (N=285)	Bevacizumab as Needed (N=271)	P Value†
Area of lesion — optic-disk area					
Mean‖	2.6±2.7	2.5±2.6	2.9±2.6	2.8±3.0	0.56
Mean change from baseline**	0.0±2.1	0.1±1.9	0.2±2.5	0.5±2.6	0.047
Change in blood pressure from baseline — mm Hg††					
Systolic	−2.1±22.4	−5.4±18.2	−5.2±20.3	−4.5±20.0	0.27
Diastolic	−0.9±11.9	−1.4±11.2	−1.9±10.2	−2.1±10.8	0.63

* Plus–minus values are means ±SD.
† P values are for the test of the hypothesis of equality among the four study groups.
‡ The total thickness at the fovea includes the retina, subretinal fluid, choroidal neovascularization, and retinal pigment epithelial elevation.
§ Data were missing for 4 patients in the ranibizumab-monthly group, 4 patients in the bevacizumab-monthly group, 4 patients in the ranibizumab-as-needed group, and 5 patients in the bevacizumab-as-needed group.
¶ Data were missing for 4 patients in the ranibizumab-monthly group, 5 patients in the bevacizumab-monthly group, 7 patients in the ranibizumab-as-needed group, and 6 patients in the bevacizumab-as-needed group.
‖ Data were missing for 28 patients in the ranibizumab-monthly group, 22 patients in the bevacizumab-monthly group, 20 patients in the ranibizumab-as-needed group, and 22 patients in the bevacizumab-as-needed group.
** Data were missing for 34 patients in the ranibizumab-monthly group, 27 patients in the bevacizumab-monthly group, 26 patients in the ranibizumab-as-needed group, and 30 patients in the bevacizumab-as-needed group. At follow-up, the area being measured included the same lesion components as those measured at baseline plus atrophy contiguous with or in the area of the baseline lesion.
†† Data were missing for 45 patients in the ranibizumab-monthly group, 39 patients in the bevacizumab-monthly group, 35 patients in the ranibizumab-as-needed group, and 39 patients in the bevacizumab-as-needed group.

monthly (P=0.09). The mean (±SD) number of a maximum of 13 treatments was 6.9±3.0 for ranibizumab given as needed and 7.7±3.5 for bevacizumab given as needed (P=0.003). Among patients who were examined at 4 and 8 weeks, 145 of 288 patients (50.3%) given ranibizumab as needed and 166 of 282 patients (58.9%) given bevacizumab as needed received injections at both times (P=0.04). The average cost of a study drug per patient for the first year was $23,400 in the ranibizumab-monthly group, $13,800 in the ranibizumab-as-needed group, $595 in the bevacizumab-monthly group, and $385 in the bevacizumab-as-needed group.

The two drugs resulted in a substantial reduction in total retinal thickness at the fovea after the first injection (Fig. 1F). At 4 weeks, no fluid was seen on OCT for 161 of 586 patients (27.5%) who were treated with ranibizumab and for 98 of 567 patients (17.3%) who were treated with bevacizumab (P<0.001). At 1 year, the mean decrease in thickness at the foveal center ranged from 152±178 μm in the group given bevacizumab as needed to 196±176 μm in the group given ranibizumab monthly (P=0.03) (Table 2 and Fig. 1D and 1E). The proportion of patients with no fluid on OCT ranged from 19.2% among patients who received bevacizumab as needed to 43.7% among those who received ranibizumab monthly (P<0.001). The mean lesion size on fluorescein angiography was unchanged from baseline in the two groups that received monthly treatment. However, lesions were slightly larger in the two groups that were treated as needed (P=0.047). Dye leakage was absent on angiography in 58.8% of patients in the ranibizumab-monthly group, 57.7% in the bevacizumab-monthly group, 46.7% in the ranibizumab-as-needed group, and 41.0% in the bevacizumab-as-needed group (P<0.001 by the chi-square test).

ADVERSE EVENTS

At 1 year, 24 of the 1185 patients (2.0%) had died: 4 of 301 patients (1.3%) in the ranibizumab-monthly group, 4 of 286 patients (1.4%) in the bevacizumab-monthly group, 5 of 298 patients (1.7%) in the ranibizumab-as-needed group, and 11 of 300 patients (3.7%) in the bevacizumab-as-needed group (P=0.18 for all groups, P=0.22 for the bevacizumab groups vs. the ranibizumab groups) (Table 3). The proportions of patients with arteriothrombotic events were similar among the groups, at 2 to 3% (P=0.97 for all groups, P=0.85 for the bevacizumab groups vs. the ranibizumab

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Table 3. Adverse Events within 1 Year after Enrollment.*

Adverse Event	Ranibizumab Monthly (N=301)	Bevacizumab Monthly (N=286)	Ranibizumab as Needed (N=298)	Bevacizumab as Needed (N=300)	P Value	
					Among Groups	Between Drugs
	number of patients (percent)					
Serious systemic event						
Death from any cause	4 (1.3)	4 (1.4)	5 (1.7)	11 (3.7)	0.18	0.22
Arteriothrombotic event	7 (2.3)	6 (2.1)	6 (2.0)	8 (2.7)	0.97	0.85
Nonfatal myocardial infarction	2 (0.7)	2 (0.7)	3 (1.0)	1 (0.3)	0.78	0.73
Nonfatal stroke	3 (1.0)	2 (0.7)	1 (0.3)	2 (0.7)	0.88	1.00
Death from vascular causes†	2 (0.7)	2 (0.7)	2 (0.7)	5 (1.7)	0.57	0.38
Venous thrombotic event	0	4 (1.4)	2 (0.7)	1 (0.3)	0.08	0.28
Transient ischemic attack	1 (0.3)	0	2 (0.7)	3 (1.0)	0.48	1.00
Hypertension	0	2 (0.7)	0	0	0.06	0.24
≥1 Serious systemic event	53 (17.6)	64 (22.4)	61 (20.5)	77 (25.7)	0.11	0.04
MedDRA system organ class‡						
Cardiac disorder	10 (3.3)	16 (5.6)	12 (4.0)	13 (4.3)	0.61	0.32
Infection	6 (2.0)	11 (3.8)	12 (4.0)	18 (6.0)	0.09	0.10
Nervous system disorder	6 (2.0)	9 (3.1)	12 (4.0)	9 (3.0)	0.54	1.00
Injury or procedural complication	7 (2.3)	11 (3.8)	8 (2.7)	9 (3.0)	0.76	0.39
Benign or malignant neoplasm	7 (2.3)	5 (1.7)	10 (3.4)	9 (3.0)	0.62	0.71
Surgical or medical procedure	4 (1.3)	6 (2.1)	4 (1.3)	8 (2.7)	0.57	0.20
Gastrointestinal disorder	3 (1.0)	6 (2.1)	2 (0.7)	9 (3.0)	0.11	0.02
Any other system organ class	18 (6.0)	26 (9.1)	16 (5.4)	28 (9.3)	0.14	0.03
Ocular event in the study eye						
Endophthalmitis	2 (0.7)	4 (1.4)	0	0	0.03	0.45
Pseudoendophthalmitis	1 (0.3)	0	0	0	1.00	1.00

* Multiple events in the same category were counted only once. MedDRA denotes *Medical Dictionary for Regulatory Activities.*
† Included in this category are deaths after myocardial infarction, stroke, or cardiac arrest.
‡ Data are listed only for system organ classes with 20 or more events.

groups). Venous thrombotic events occurred infrequently (in approximately 1.0% of patients), with the highest number (4, or 1.4%) in the bevacizumab-monthly group (P=0.08 for all groups, P=0.28 for the bevacizumab groups vs. the ranibizumab groups).

One or more serious systemic adverse events occurred in 255 patients (21.5%), with 53 (17.6%) in the ranibizumab-monthly group, 64 (22.4%) in the bevacizumab-monthly group, 61 (20.5%) in the ranibizumab-as-needed group, and 77 (25.7%) in the bevacizumab-as-needed group (P=0.11 by the chi-square test). Hospitalizations accounted for 298 of the 370 individual serious systemic adverse events (80.5%). When dosing-regimen groups were combined, the proportions of patients with serious systemic adverse events were 24.1% for bevacizumab and 19.0% for ranibizumab (P=0.04). After adjustment for demographic features and coexisting illnesses at baseline, the risk ratio for bevacizumab, as compared with ranibizumab, was 1.29 (95% confidence interval, 1.01 to 1.66; P=0.04). No one MedDRA system organ class accounted for the difference between drugs; differences in rates were largest for hospitalizations for infections (e.g., pneumonia and urinary tract

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infections) and gastrointestinal disorders (e.g., hemorrhage and nausea and vomiting).

Endophthalmitis developed after 2 of 5449 injections (0.04%) in 599 patients treated with ranibizumab and after 4 of 5508 injections (0.07%) in 586 patients treated with bevacizumab (P=0.49). Uveitis, retinal detachment, ocular-vessel occlusion or embolism, retinal tear, and vitreous hemorrhage each occurred in less than 1% of patients. (Additional details regarding serious and nonserious adverse events are provided in the Supplementary Appendix.)

DISCUSSION

In each of the head-to-head comparisons of ranibizumab with bevacizumab, the drugs had equivalent effects on visual acuity at all time points throughout the first year of follow-up. The mean number of letters gained, the proportion of patients in whom visual acuity was maintained (<15 letters lost), and the proportion of those who had a gain of at least 15 letters were nearly the same for each drug when the regimen was the same (Table 2 and Fig. 2A, 2B, and 2C).

We also found that excellent results for visual acuity could be achieved with less-than-monthly regimens for both drugs. Ranibizumab given as needed was equivalent to ranibizumab given monthly, with a mean difference of 1.7 letters. Bevacizumab given as needed was equivalent to bevacizumab given monthly at all time points through 36 weeks (with mean differences all within 1.6 letters); at 52 weeks, the difference of 2.1 letters yielded an inconclusive comparison. The mean gains of 5.9 letters with bevacizumab given as needed and of 6.8 letters with ranibizumab given as needed are the best outcomes observed with less-than-monthly regimens in any large, multicenter clinical trial of ranibizumab.[17-19] There are several possible explanations. Previous studies had retreatment guidelines that were set according to time or retinal thickness. The protocol for our study specified treatment whenever there was evidence of disease activity (e.g., fluid on OCT), with no minimum threshold for retinal thickness. This strategy allowed therapy to be more responsive to disease activity. During the first year, patients assigned to ranibizumab as needed received a mean of seven injections, which was more than the mean number of injections received in previous studies.[17-19] We primarily assessed disease activity by means of time-domain OCT. In the second year of this ongoing study, we are investigating whether the use of high-resolution spectral-domain OCT results in increased detection of fluid and subsequent treatment.

Both bevacizumab and ranibizumab substantially and immediately reduced the amount of fluid in or under the retina (Fig. 1F). The proportion of patients who had complete resolution of fluid was greater with ranibizumab than with bevacizumab. This difference was evident after the first injection, with no fluid seen at 4 weeks in 27.5% of patients receiving ranibizumab and 17.3% of those receiving bevacizumab, and the difference persisted throughout the first year. The absolute between-drug difference in the amount of residual fluid was small (Fig. 1D and 1E), and in the majority of patients, neither drug eliminated all fluid. The greater prevalence of fluid in the group given bevacizumab as needed led to an average of 0.8 more injections during the first year than in the group given ranibizumab as needed. Monthly injections of either drug resulted in no increase in the mean lesion area, whereas there was a small increase with injections given as needed (Table 2). On the basis of data from the 2-year analysis, we will evaluate the cumulative effect of the presence of fluid and change in lesion size on visual acuity.

One of the many factors that contribute to selection of a drug for a patient is cost. A single dose of ranibizumab costs 40 times as much as a single dose of bevacizumab. This cost differential has important economic implications when extrapolated to the more than 250,000 patients who are treated for neovascular AMD annually in the United States.

Clinical trials of intravenous bevacizumab in patients with cancer have identified associations with arteriothrombotic events, venous thrombotic events, gastrointestinal perforation and hemorrhage, wound-healing complications, and hypertension.[20,21] With a limited statistical power to detect important adverse events, we found no significant differences between the two drugs in rates of death, arteriothrombotic events, or venous thrombotic events, findings that are consistent with the results of a study of Medicare claims involving more than 145,000 treated patients.[22] However, in our study, the rate of serious systemic adverse events, primarily hospitalizations, was higher among bevacizumab-treated patients than among

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ranibizumab-treated patients (24.1% vs. 19.0%, P=0.04). The excess numbers of these events were distributed over many different types of conditions, most of which were not identified in cancer trials involving patients who were receiving intravenous doses of bevacizumab that were 500 times those used in intravitreal injections. We also did not observe increased rates of adverse events with increased exposure to the study drugs; rates were higher for the two drugs when given as needed than when given monthly. The difference in rates may be attributable to chance, imbalances in baseline health status that were not included in the medical history or multivariate models, or a true difference in risk. Resolving this issue will require many more patients than were available for this study. Results from the second year of this study and from other comparative trials will provide more information regarding the relative risks of serious adverse events.

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