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Ranibizumab Combined With Verteporfin Photodynamic Therapy in Neovascular Age-Related Macular Degeneration

Year 1 Results of the FOCUS Study

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Objective: : To investigate the safety and efficacy of intravitreal ranibizumab treatment combined with verteporfin photodynamic therapy (PDT) in patients with predominantly classic choroidal neovascularization secondary to age-related macular degeneration.

Methods: In this 2-year, phase I/II, multicenter, randomized, single-masked, controlled study, patients received monthly ranibizumab (0.5 mg) (n=106) or sham (n=56) injections. The PDT was performed 7 days before initial ranibizumab or sham treatment and then quarterly as needed.

Main Outcomes Measures: Proportion of patients losing fewer than 15 letters from baseline visual acuity at 12 months (primary efficacy outcome) and the incidence and severity of adverse events.

Results: At 12 months, 90.5% of the ranibizumab-treated patients and 67.9% of the control patients had lost fewer than 15 letters ($P<.001$). The most frequent ranibizumab-associated serious ocular adverse events were intraocular inflammation (11.4%) and endophthalmitis (1.9%; 4.8% if including presumed cases). On average, patients with serious inflammation had better visual acuity outcomes at 12 months than did controls. Key serious nonocular adverse events included myocardial infarctions in the PDT-alone group (3.6%) and cerebrovascular accidents in the ranibizumab-treated group (3.8%).

Conclusion/Application to Clinical Practice: Ranibizumab + PDT was more efficacious than PDT alone for treating neovascular age-related macular degeneration. Although ranibizumab treatment increased the risk of serious intraocular inflammation, affected patients, on average, still experienced visual acuity benefit.

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Group Information: A list of the FOCUS Study Group members appears on page 1542.

In the United States and other developed countries, age-related macular degeneration (AMD) is by far the most common cause of severe, irreversible vision loss in older adults.[1-4] In 2000, AMD was responsible for more than half of all cases of blindness in the United States.[1] The most common form of AMD resulting in severe vision loss is characterized by the development of choroidal neovascularization (CNV). Although this neovascular form accounts for only approximately 10% to 20% of AMD cases, it is responsible for 80% to 90% of AMD-associated vision loss.[5]

The CNV lesions in neovascular AMD are classified on the basis of fluorescein angiographic patterns into classic and occult types, which, in turn, are associated with different clinical courses and responses to treatment modalities.[6] For all types, the therapeutic options currently available are limited. Laser photocoagulation is used primarily to treat AMD-related CNV in the few patients whose lesions are 100% classic or well demarcated and do not involve the center of the fovea.[7] However, CNV recurs in approximately half of the treated patients within 3 years.[8] Verteporfin (Visudyne; Novartis AG, Basel, Switzerland) photodynamic therapy (PDT) currently is approved for use in the United States only for CNV lesions in which at least half of the lesion is classic (so-called predominantly classic CNV), having been shown to slow the progression of vision loss in patients with this lesion type.[9,10] Additional evidence[6,9,10] suggests that small, active, minimally classic or occult CNV lesions may also respond to PDT.

A recent approach to the treatment of neovascular AMD uses locally adminis-

tered antiangiogenic drugs that target the underlying pathogenesis by inhibiting the activity of vascular endothelial growth factor A (VEGF-A), which promotes the formation of new vessels and increases the permeability of existing vessels in the CNV lesion. The first such agent approved for use in the United States and Europe for the treatment of neovascular AMD is pegaptanib sodium, an RNA aptamer that binds only the most prevalent VEGF-A isoform (VEGF-A_{165}). In pivotal clinical trials, pegaptanib reduced vision loss.[11] However, only a small percentage of eyes treated with either pegaptanib or verteporfin PDT gained vision that was judged to be clinically relevant at 1 year, defined as an improvement of 15 or more letters as assessed using Early Treatment of Diabetic Retinopathy Study charts.

Ranibizumab (Lucentis; Genentech Inc, South San Francisco, Calif) is a recombinant, humanized antibody antigen-binding fragment (Fab) recently approved by the Food and Drug Administration for the treatment of neovascular AMD that neutralizes all active forms of VEGF-A.[12] Early development phase studies in which ranibizumab was administered intravitreally for up to 7 months to small numbers of patients with neovascular AMD showed encouraging signs of safety and activity.[13-15] Results for the first year of a larger, double-masked, sham injection–controlled, phase III trial in patients with minimally classic or occult without classic neovascular AMD (the MARINA study) show that ranibizumab produced statistically significant and clinically meaningful improvement in vision in one quarter to one third of treated eyes, with a low rate of serious ocular adverse events and no clear systemic safety concerns.[16]

This phase I/II study (FOCUS) was designed to evaluate the safety, tolerability, and efficacy of ranibizumab treatment in conjunction with verteporfin PDT compared with verteporfin PDT alone in patients with subfoveal, predominantly classic CNV secondary to AMD. The results for the first year of this 2-year study are reported herein. Another study in this patient population (the ongoing phase III ANCHOR trial[17]) directly compares ranibizumab monotherapy with PDT monotherapy; this comparison was not an objective of the FOCUS study.

METHODS

This ongoing study is being conducted in accordance with the International Conference on Harmonization E6 Guideline for Good Clinical Practice and with US and local requirements. Before the initiation of any study procedures, all the patients provided written informed consent for participation and were screened for eligibility.

STUDY DESIGN AND PATIENTS

FOCUS is a phase I/II, 2-year, single-masked (masked patient and visual acuity [VA] examiner, and unmasked investigator performing treatments and all other evaluations), multicenter study of intravitreally administered ranibizumab in conjunction with verteporfin PDT. Eligible patients had primary or recurrent subfoveal CNV that was secondary to AMD, determined by the investigator to be of the predominantly classic angiographic subtype, with total lesion size not exceeding 5400 μm in the greatest linear dimension, and that was suitable for PDT.[18] Predominantly classic CNV was defined as CNV exhibiting well-demarcated hyperfluorescent boundaries in the early phase of the fluorescein angiogram, with leakage in the later phases of the angiogram, and occupying 50% or more of the total lesion area. Additional patient inclusion criteria were age 50 years or older and best-corrected VA of 20/40 to 20/320 (Snellen equivalent, based on the lowest line on the Early Treatment Diabetic Retinopathy Study chart that the patient could read with ≥4 letters correct) in the study eye based on the ability to read Early Treatment Diabetic Retinopathy Study charts at a starting distance of 2 m. Patients were excluded if they had a history of any of the following in the study eye: verteporfin PDT in the preceding 3 months (or, for the nonstudy eye, in the preceding 7 days); more than 3 previous verteporfin PDT treatments in the preceding 12 months; juxtafoveal or extrafoveal laser photocoagulation within 1 month; previous subfoveal laser photocoagulation, external beam radiation therapy, or transpupillary thermotherapy at any time; or vitrectomy, submacular surgery, or other surgical intervention for AMD. Also excluded were patients who had previously participated in a clinical trial involving antiangiogenic treatment of either eye, had participated in a study of any investigational drug (except vitamins or minerals) in the preceding month, had permanent structural damage to the center of the fovea in the study eye, or had a concurrent ocular or systemic condition that could contraindicate administration of an investigational drug, verteporfin, or fluorescein, affect interpretation of the study results, or render the patient at high risk of treatment complications. Patients with retinal angiomatous proliferation were eligible if they had predominantly classic CNV lesions that otherwise qualified. Patients were prohibited from concomitantly using pegaptanib or from receiving other pharmacologic or surgical treatment for AMD in either eye during the study.

TREATMENT

After up to 28 days of screening, eligible patients were randomly assigned (day 0) in a 2:1 ratio to study treatment with either intravitreal injection of ranibizumab or sham injection in 1 eye. During the first 12 months of study, a lyophilized formulation of ranibizumab that required reconstitution before injection was used, as in the earlier phase I/II trials.[13-15] If both eyes qualified for study treatment, the eye with lower VA became the study eye, unless, for medical reasons, the investigator deemed the other eye more suitable. All the patients received verteporfin PDT on day 0. Starting on day 7 (±2 days), patients received a ranibizumab or sham injection monthly (30 days, ±7 days) for up to a total of 24 injections in 2 years. The rationale for the 7-day interval between verteporfin PDT and the study treatment was based on in vitro evidence that ranibizumab is unstable when combined with supratherapeutic verteporfin concentrations and exposed to red laser light (although ranibizumab was stable when exposed to the laser light alone) (Genentech Inc, unpublished data, 2003).

Only the verteporfin PDT administration on day 0, preceding the first ranibizumab or sham injection on day 7, was mandated by the study protocol. Repeated verteporfin PDT was permitted if fluorescein angiography revealed persistent or recurrent leakage from CNV lesions as determined by the investigator at any of 6 evaluation visits scheduled for months 3, 6, 9, 12, 18, and 21. The original study protocol specified that these evaluation visits were to occur 7 days (±2 days) before the next study treatment (mimicking the interval between the day 0 PDT and the initial study injection). However, the rate of serious intraocular inflammation in ranibizumab-treated patients after the initial verteporfin PDT was higher than expected based on previous studies,[13-15] and a longer interval between PDT and ranibizumab injection seemed advisable. The study protocol was, therefore, amended on March 19, 2004, to require that any re-

peated verteporfin PDT in the study eye occur at least 28 days before a ranibizumab or sham injection and no sooner than 21 days after an injection. Thus, if the study eye required verteporfin PDT, the ranibizumab or sham injection that was to occur at the monthly study treatment visit was held, but all scheduled assessments were performed. Timing of subsequent verteporfin PDT in the fellow (nonstudy) eye was restricted in the original and amended protocols to at least 5 days before ranibizumab or sham injection and no sooner than 21 days after injection.

Patients were instructed to self-administer prescribed antimicrobial drops 4 times daily for 3 days before each scheduled study injection. Just before injection, the eyelid, eyelashes, and periorbital area were thoroughly cleansed with povidone-iodine, and local anesthesia and antimicrobial agents were administered. For patients receiving ranibizumab, a 30-gauge, 1.27-cm (½-inch) needle attached to a low-volume (eg, tuberculin) syringe containing 50 µL of reconstituted study drug solution was inserted through the anesthetized conjunctiva and sclera, approximately 3.5 to 4.0 mm posterior to the limbus, avoiding the horizontal meridian and aiming toward the center of the globe. Antimicrobial drops were administered after injection in the clinic and then were self-administered by the patients for 3 days. Scleral sites of intravitreal injections were rotated during the study.

All preinjection and postinjection procedures were identical for patients receiving ranibizumab or sham injection. For ethical reasons, the sham-treated patients did not receive an actual intravitreal injection. Instead, the injecting physician used an empty syringe without a needle and mimicked an intraocular injection by making contact with the conjunctiva of an eye that was prepared and anesthetized and applying pressure without the needle.

To minimize bias, the patients, VA examiner, fundus photographer, and personnel at the Fundus Photograph Reading Center, University of Wisconsin–Madison, were masked to treatment assignment. The personnel responsible for mixing the drug, the physician administering the drug (typically the evaluating physician), and the personnel involved in patient randomization were unmasked to treatment assignment.

ASSESSMENTS

For efficacy outcomes based on VA assessments, unless otherwise noted, the values at 12 months were compared with baseline values obtained at randomization (day 0, before verteporfin PDT) and were derived from the VA score or Snellen equivalent obtained using Early Treatment Diabetic Retinopathy Study charts at a starting test distance of 2 m and a standardized refraction and VA testing protocol. The primary efficacy outcome measure was the proportion of patients whose study eye had lost fewer than 15 letters from the baseline VA score. Prespecified secondary VA-related efficacy outcomes measured in the first treatment year included mean change from baseline VA score, the proportion of patients whose VA score improved by at least 15 letters, and the proportion of patients whose VA Snellen equivalent was 20/200 or worse. Prespecified secondary efficacy outcomes based on retinal changes from screening to the month 12 evaluation visit (and documented in fluorescein angiograms and color fundus photographs assessed by the reading center) included the total areas of the CNV lesion; fluorescein leakage from the CNV lesion plus intense, progressive staining of the retinal pigment epithelium; and serous sensory retinal detachment/subretinal fluid. The number of verteporfin PDT repeated treatments of the study eye during the first treatment year (after day 0 and up to month 12) was another secondary efficacy measure.

The primary outcome measures for safety and tolerability were the incidence and severity of ocular and nonocular adverse events and the proportion of patients developing immunoreactivity to ranibizumab. All the patients were contacted 2 (±1) days after each injection to elicit reports of any vision reduction, eye pain, unusual redness, or any other new ocular symptom in the study eye and to ask about compliance with self-administration of postinjection antimicrobial drugs. Patients also returned to the clinic for safety assessments 7 and 14 days after their first study injection. Intraocular inflammation was assessed by means of adverse event reporting and slit-lamp examination. Intraocular pressure (IOP) was assessed by means of adverse event reporting and direct measurements.

STATISTICAL METHODS

The sample size per treatment group provided approximately 80% power to detect a difference between the 2 treatment groups in the proportion of patients losing fewer than 15 letters from baseline VA at the 12th month of treatment, assuming a rate of 86% for the ranibizumab + PDT group and 67% for the PDT-alone group (2-sided Pearson χ^2 test with $\alpha = .05$).

The randomization schedule was generated by a designee of Genentech Inc, using a static randomization method stratified by study site with an adequate block size to maintain the 2:1 ratio between ranibizumab + PDT and PDT alone. All the patients were randomized before receiving PDT on day 0.

Data from patients who withdrew from the study after randomization but before the first ranibizumab or sham injection were excluded. Comparison of efficacy outcomes was based on the treatment groups as randomly assigned. Safety analyses included all the patients who received at least 1 ranibizumab or sham injection and were based on the actual treatment received. The pretreatment assessment on day 0 before verteporfin treatment was used as the baseline value for the analyses of VA outcomes; the baseline fluorescein angiogram was assessed at screening. All the statistical tests were 2-sided at the $\alpha = .05$ level. The last-observation-carried-forward approach was used to impute missing data. The Pearson χ^2 test was used to compare treatment groups for the primary efficacy outcome, the secondary VA outcomes involving numbers of letters lost or gained, and the number of PDT repeated treatments. Mean change in VA at each month was compared between treatment groups using the 2-sample *t* test. The proportion of patients with a VA Snellen equivalent of 20/200 or worse at 12 months was compared between treatment groups using the Cochran χ^2 test stratified by the baseline VA Snellen equivalent (20/200 or worse vs better than 20/200). Mean changes from baseline in lesion anatomical characteristics were compared between treatment groups using the Wilcoxon rank sum test. Post hoc analyses based on the Fisher exact test were performed to compare the treatment groups for incidences of key safety outcomes. However, the study was not powered to detect small differences in incidences, and no adjustments for multiplicity were made. All the *P* values based on these post hoc analyses should be interpreted with caution.

RESULTS

Between April 1, 2003, and January 14, 2004, 162 patients were enrolled and randomly assigned to study treatment with ranibizumab injection + PDT (n = 106) or sham injection + PDT (henceforth referred to as PDT alone; n = 56) at 25 investigative sites in the United States. Patient disposition is given in **Table 1**. More than 93% of the randomized patients in each treatment group remained in the study at the end of the first treatment year, and most (88.7% of the ranibizumab + PDT group and 91.1% of the PDT-alone group) continued study treatment through 12 months. The mean ± SD number of in-

Table 1. Patient Disposition in the FOCUS Trial

	Patients, No. (%)	
	PDT Alone (n = 56)	Ranibizumab + PDT (n = 106)
Enrolled	56 (100)	106 (100)
Randomly assigned to treatment	56 (100)	106 (100)
Received randomized treatment	56 (100)	105 (99.1)
Included in efficacy analyses*	56 (100)	105 (99.1)
Included in safety evaluation	56 (100)	105 (99.1)
Stayed in study at the end of the first treatment year	53 (94.6)	99 (93.4)
Discontinued study on or before month 12	3 (5.4)	7 (6.6)
Adverse event	1	3
Unavailable for follow-up	0	1
Patient's decision	1	3
Patient's condition mandated other therapeutic intervention	1	0
Remained on treatment at month 12	51 (91.1)	94 (88.7)
Discontinued treatment before month 12	5 (8.9)	12 (11.3)
Adverse event	2	7
Patient's decision	2	4
Physician's decision	0	1
Patient's condition mandated other therapeutic intervention	1	0

Abbreviation: PDT, verteporfin photodynamic therapy.
*All randomized patients who did not discontinue from the study before the initial study treatment (ranibizumab or sham injection) on day 7 were included in the efficacy evaluable population.

Table 2. Patient Demographics and Baseline Study Eye Characteristics

Characteristic	PDT Alone (n = 56)	Ranibizumab + PDT (n = 106)
Demographics		
Sex, No. (%)		
Male	30 (53.6)	46 (43.4)
Female	26 (46.4)	60 (56.6)
Race, No. (%)		
White	56 (100)	104 (98.1)
Other	0	2 (1.9)
Age, y		
Mean ± SD	73.0 ± 8.7	74.7 ± 7.2
Range	51-93	50-91
Age group, y, No. (%)		
50-64	11 (19.6)	8 (7.5)
65-74	19 (33.9)	36 (34.0)
75-84	23 (41.1)	56 (52.8)
≥85	3 (5.4)	6 (5.7)
Previous therapy for AMD, No. (%)		
Any	45 (80.4)	81 (76.4)
Photodynamic therapy	29 (51.8)	48 (45.3)
Laser photocoagulation	13 (23.2)	20 (18.9)
Medication	0	1 (0.9)
Supplements	22 (39.3)	48 (45.3)
Other	1 (1.8)	0
Visual acuity		
Letters, mean ± SD, No.*	48.5 ± 14.1	45.1 ± 13.8
Approximate Snellen equivalent, No. (%)*		
20/200 or worse	15 (26.8)	40 (37.7)
Better than 20/200	41 (73.2)	66 (62.3)
Lesion anatomical characteristics†		
CNV lesion subtype, No. (%)‡		
Predominantly classic	37 (66.1)	69 (65.7)
Minimally classic	15 (26.8)	32 (30.5)
Occult with no classic	4 (7.1)	2 (1.9)
Cannot classify	0	2 (1.9)
Total area of lesion, median (interquartile range), DA§	2.2 (1.1-3.6)	2.0 (1.1-3.9)
Total area of CNV, median (interquartile range), DA§	1.4 (0.7-2.7)	1.5 (0.7-2.9)
Leakage from CNV + RPE staining, median (interquartile range), DA§	3.0 (1.5-4.8)	2.8 (1.8-4.5)
Area of subretinal fluid, median (interquartile range), DA‖	4.0 (2.0-6.0)	4.0 (2.8-6.0)

Abbreviations: AMD, age-related macular degeneration; CNV, choroidal neovascularization; DA, disc areas; PDT, verteporfin photodynamic therapy; RPE, retinal pigment epithelium.
*Measured on day 0 using Early Treatment Diabetic Retinopathy Study charts at a starting distance of 2 m.
†Based on fluorescein angiography and fundus photography assessed at screening.
‡The sample size for the ranibizumab + PDT group is 105 for this variable.
§The sample size for the ranibizumab + PDT group is 103 for this variable.
‖The sample size for the PDT-alone group is 52 for this variable.

jections administered was 10.9±2.5 in the ranibizumab group and 10.4±1.9 in the sham-injected group. More than 85% of the patients in each group received the last planned injection.

Randomization produced treatment groups that were reasonably well balanced for demographics and baseline VA and highly similar in their lesion anatomical characteristics (**Table 2**). Nearly half of the patients had previously been treated with PDT in the study eye—mostly 3 or fewer treatments, although 5 patients in the ranibizumab + PDT arm had received more than 3 and 1 had received 9. Although eligibility for study enrollment was restricted to patients whose CNV lesion at screening was categorized by the investigator as being predominantly classic, subsequent analysis of fluorescein angiograms by a central reading center established that in each treatment group, approximately two thirds of the patients had predominantly classic lesions and approximately one third had minimally classic or occult without classic lesions. The mean area of the entire AMD lesion was approximately 2.5 optic disc areas (DA) in both groups, with a mean area of CNV of approximately 1.9 DA.

EFFICACY

Results for the primary outcome measure—the proportion of patients who at 12 months had lost fewer than 15 letters from baseline VA—favored the combination of ranibizumab + PDT over PDT alone. In the combination treatment group, 90.5% of the patients achieved this outcome vs 67.9% of the patients treated with PDT alone ($P<.001$).

Results for the secondary VA-related efficacy outcomes were consistent with those for the primary outcome. Nearly one quarter of these patients (23.8%) had

Table 3. Summary of Efficacy Outcomes

Efficacy Outcome	PDT Alone (n = 56)	Ranibizumab + PDT (n = 105)	*P* Value*
Visual acuity at 12 months†			
Lost <15 letters from baseline, primary efficacy outcome, No. (%)	38 (67.9)	95 (90.5)	<.001
Gained ≥15 letters from baseline, No. (%)	3 (5.4)	25 (23.8)	.003
No. of letters, mean ± SD change from baseline	−8.2 ± 16.3	+4.9 ± 14.7	<.001
Lost ≥30 letters from baseline, No. (%)	5 (8.9)	1 (1.0)	.01
Snellen equivalent of 20/200 or worse, No. (%)	26 (46.4)	31 (29.5)	.006
Lesion anatomical characteristics at 12 months‡			
Total area of CNV lesion, DA§			<.001
Median (interquartile range)	3.6 (1.9-6.4)	1.9 (1.0-4.0)	
Mean (SD) change from baseline	+1.8 (2.3)	−0.02 (1.3)	
Total area of CNV, DA§			<.001
Median (interquartile range)	2.1 (1.1-4.4)	1.2 (0.2-2.4)	
Mean ± SD change from baseline	+1.3 ± 2.2	−0.1 ± 1.5	
Leakage from CNV + intense, progressive RPE staining (DA)§			<.001
Median (interquartile range)	2.3 (1.2-3.8)	0.1 (0.0-1.5)	
Mean ± SD change from baseline	−0.6 ± 2.8	−2.3 ± 2.4	
Area of serous sensory retinal detachment/subretinal fluid, DA‖			<.001
Median (interquartile range)	3.0 (0.0-6.0)	0.0 (0.0-3.0)	
Mean ± SD change from baseline	−0.6 ± 4.0	−2.9 ± 3.0	
Repeated PDT, No. (%)¶			<.001
Any repeated treatment	51 (91.1)	29 (27.6)	
No. of repeated treatments			
1	11 (19.6)	26 (24.8)	
2	12 (21.4)	2 (1.9)	
3	11 (19.6)	0	
4	17 (30.4)	1 (1.0)	

Abbreviations: CNV, choroidal neovascularization; DA, disc areas; PDT, verteporfin photodynamic therapy; RPE, retinal pigment epithelium.

*P values were based on the Cochran χ^2 test for the proportion of patients with Snellen equivalent 20/200 or worse and Pearson χ^2 tests for other binary outcomes. The t test was used for the change from baseline in visual acuity, and Wilcoxon rank sum tests were used for the mean changes from baseline in lesion anatomical characteristics.

†Measured using Early Treatment Diabetic Retinopathy Study charts at a starting distance of 2 m.

‡Based on fluorescein angiography and fundus photography. Data from patients without baseline values were excluded from the tabulation.

§The samples size for the ranibizumab + PDT group is 102 for this variable.

‖The sample size for the PDT-alone group is 52 and for the ranibizumab + PDT group is 104 for this variable.

¶The PDT treatments on day 0 were excluded from the tabulation.

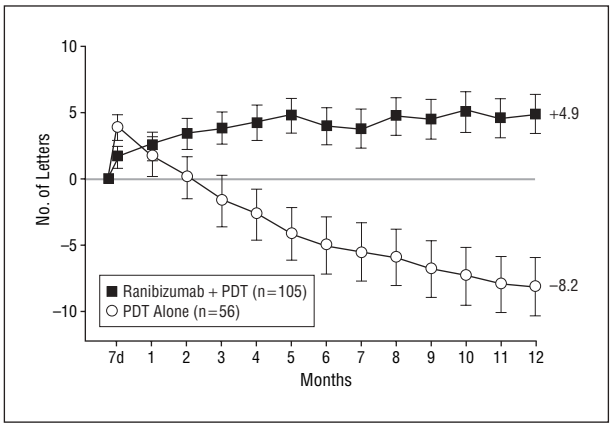

Figure 1. Mean visual acuity change from baseline across time. The last-observation-carried-forward approach was used for missing data imputation. For treatment comparison at each visit based on the 2-sample t test, P<.001 at months 5 to 12, P=.003 at month 4, and P=.01 at month 3. PDT indicates verteporfin photodynamic therapy. Error bars represent ±1 SEM.

gained 15 letters or more from their baseline VA score compared with only 5.4% of those who received PDT alone (P=.003). Also, whereas at baseline the study eye had a VA of 20/200 or worse in a higher percentage of patients in the ranibizumab + PDT group vs the PDT-alone group (37.7% vs 26.8%), this difference was reversed by 12 months (29.5% vs 46.4%; P=.006). Twenty percent of the patients in the ranibizumab + PDT group had a VA of 20/40 or better at 12 months compared with 7.1% of patients in the PDT-alone group. Conversely, the percentage of patients who had severe VA loss (≥30 letters) in the study eye at 12 months was significantly smaller in the ranibizumab + PDT group than in the PDT-alone group (1.0% vs 8.9%; P=.01) (**Table 3**).

For mean change from baseline VA, the clinical benefit achieved in the ranibizumab + PDT group compared with the PDT-alone group was evident as early as the third month of treatment (P=.01 for the difference between groups at 3 months and significant at each subsequent monthly assessment) (**Figure 1**). By 12 months, the difference between the 2 groups had reached 13.1 letters (ie, a mean gain from baseline of 4.9 letters in the ranibizumab + PDT group vs a mean loss from baseline of 8.2 letters in the PDT-alone group; P<.001). Detailed distributions for VA change from baseline at each visit for each treatment group are shown in **Figure 2**.

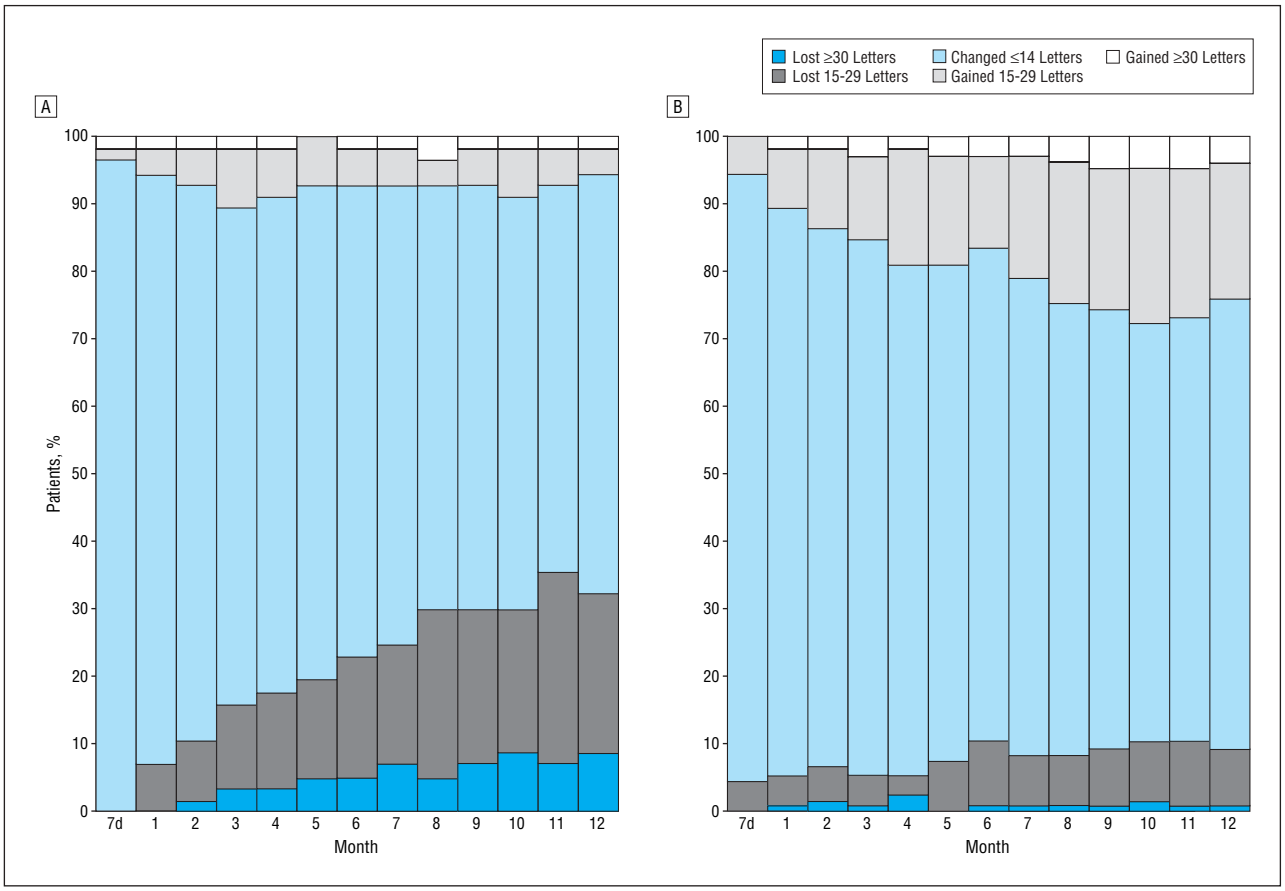

Figure 2. Distribution of visual acuity change from baseline across time in the verteporfin photodynamic therapy (PDT)–alone group (A) and in the ranibizumab + PDT group (B). The last-observation-carried-forward approach was used for missing data imputation.

Key VA end points, including the percentage of patients losing fewer than 15 letters, the percentage of patients gaining at least 15 letters, and the mean change in VA, were compared between treatment groups descriptively in each of the subgroups defined by PDT history (previous PDT vs no previous PDT), baseline lesion type (predominantly classic vs minimally classic or occult), and baseline VA Snellen equivalent (20/200 or worse vs better than 20/200). A favorable treatment effect of ranibizumab was observed in each subgroup (**Figure 3**).

Differences between treatment groups for the VA outcomes were reflected in differences in lesion characteristics observed by using fluorescein angiography (Table 3). Compared with PDT alone, ranibizumab + PDT was more effective in arresting the growth of CNV lesions, as indicated by mean change from baseline in total lesion area (+1.82 vs –0.02 DA) and area of CNV (+1.34 vs –0.12 DA) ($P<.001$ for both). Ranibizumab + PDT also produced significantly greater improvement from baseline in the area of CNV leakage and staining of the retinal pigment epithelium (–0.56 DA for PDT alone vs –2.30 DA for ranibizumab + PDT) and the area of subretinal fluid (–0.60 vs –2.87 DA) ($P<.001$ for both).

Use of ranibizumab with PDT reduced the need for repeated PDT of the study eye. Of 56 study eyes receiving PDT alone, 51 (91.1%) required repeated PDT compared with only 29 (27.6%) of 105 ranibizumab + PDT study eyes ($P<.001$). Of the retreated study eyes, most in the ranibizumab + PDT group required only 1 additional PDT, whereas nearly a third of the retreated eyes in the PDT-alone group required 4 PDTs. A marked difference in the proportion of study eyes requiring repeated PDT was evident by 3 months (80.4% of the PDT-alone study eyes vs 16.2% of the ranibizumab + PDT study eyes) and was also observed at each subsequent 3-month interval (**Figure 4**).

OCULAR SAFETY

Ocular adverse events that occurred in 10% or more of the study eyes are summarized in **Table 4**. Most ocular adverse events that were more common in the ranibizumab + PDT group than in the PDT-alone group are attributable to the injection procedure and to intraocular inflammation.

The most common serious ocular adverse events reported by investigators were endophthalmitis in 2 patients (1.9%) and a total of 13 episodes of serious intraocular inflammation (iritis, iridocyclitis, uveitis, or vitritis) in 12 patients (11.4%) in the ranibizumab + PDT group vs none in the PDT-alone group for both adverse events ($P=.54$ for the treatment comparison of endophthalmitis incidences and $P=.009$ for serious intraocular inflammation incidences) (Table 4). Intraocular inflammation was defined as serious if it was associated either with an observation of 4+ aqueous or vitreous cells[19,20] or with

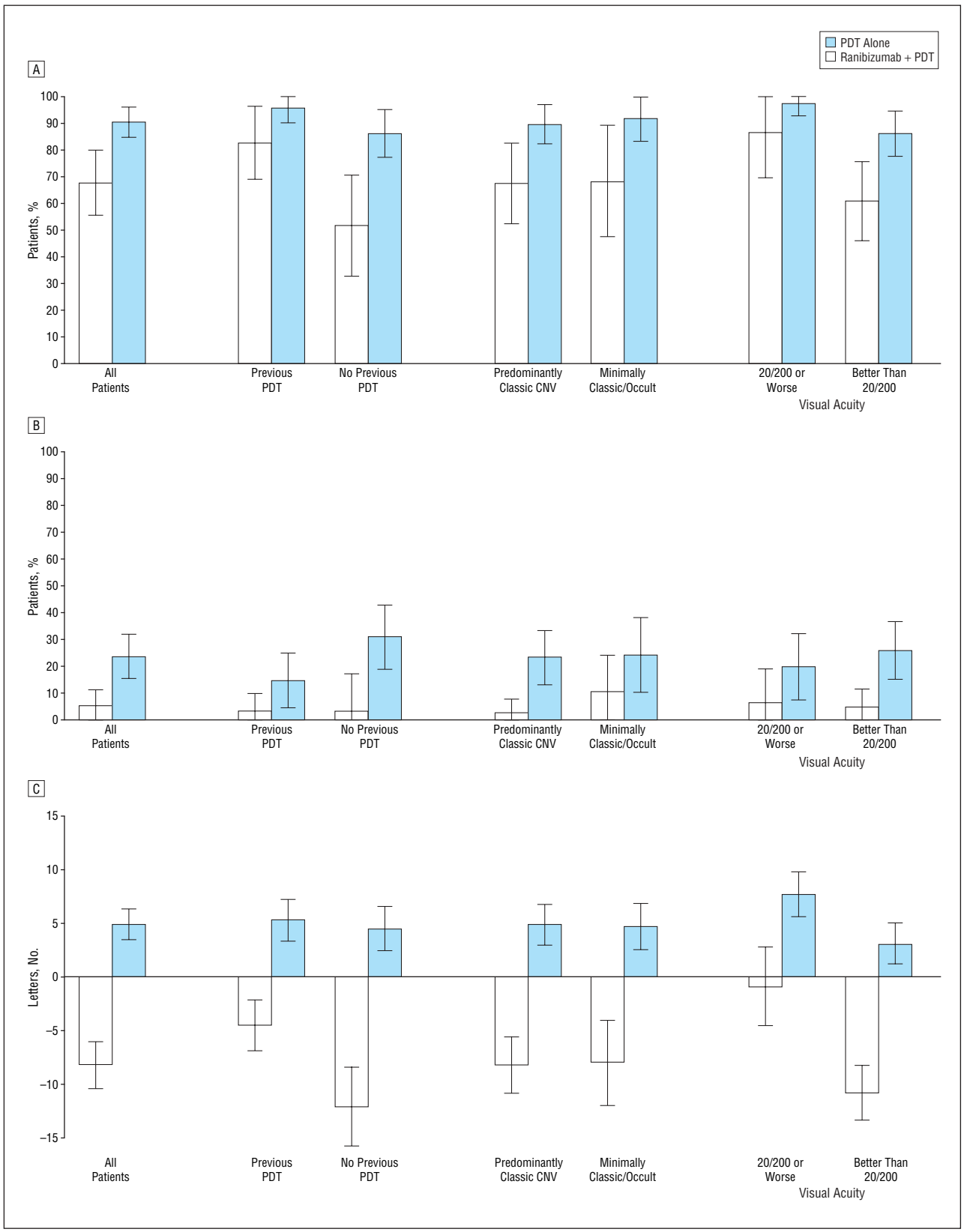

Figure 3. Subgroup analyses of visual acuity change from baseline. A, Percentage of patients losing fewer than 15 letters at 12 months. Error bars represent 95% confidence intervals. B, Percentage of patients gaining 15 letters or more at 12 months. Error bars represent 95% confidence intervals. C, Mean change in visual acuity at 12 months. Error bars represent ±1 SEM. The sample sizes for the PDT alone and ranibizumab + PDT groups, respectively, are 65 and 105 for all patients, 29 and 27 for previous PDT, 27 and 58 for no previous PDT, 37 and 68 for predominantly classic choroidal neovascularization (CNV), 19 and 37 for minimally classic or occult CNV, 14 and 40 for visual acuity 20/200 or worse, and 41 and 65 for visual acuity better than 20/200. PDT indicates verteporfin photodynamic therapy.

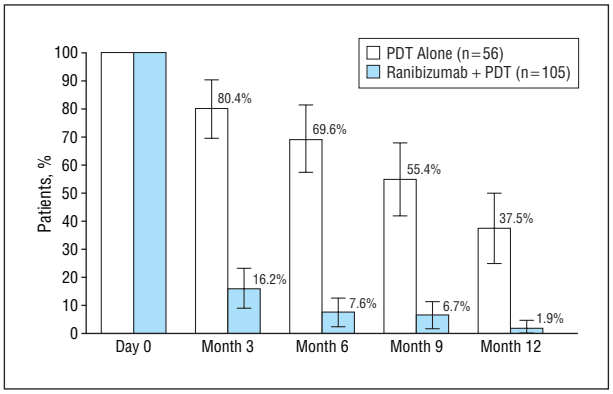

Figure 4. Percentage of patients receiving verteporfin photodynamic therapy (PDT) in the study eye across time. Error bars represent 95% confidence intervals.

a 30-letter or greater decrease in the VA score between consecutive visits. Because 3 of the patients with serious intraocular inflammation were treated with injections of intravitreal antibiotic agents, we defined any case in which intraocular antibiotics were injected as "presumed" endophthalmitis, resulting in a total of 5 (4.8%) presumed endophthalmitis cases (vs none in the PDT-alone group; $P=.16$). The culture from 1 of the presumed endophthalmitis cases was positive (aqueous humor culture positive for *Staphylococcus epidermidis*); culture results from the other 4 endophthalmitis cases (including the 2 other presumed cases) were negative. The mean VA outcomes at 12 months for the 5 presumed endophthalmitis cases (–4.8 letters) and for the 9 remaining cases with reported serious intraocular inflammation (+3.0 letters) were better than those for the PDT-alone group (–8.2 letters). Only 1 of these patients had a VA loss of more than 15 letters: a patient with presumed endophthalmitis (culture negative; reported as serious intraocular inflammation) lost 27 letters.

The incidence of all types of intraocular inflammation adverse events (reported as iritis, iridocyclitis, uveitis, vitritis, or anterior chamber inflammation), nonserious and serious, was 38% in the ranibizumab + PDT group compared with 5% in the PDT-alone group ($P<.001$). Slitlamp findings corresponded with the adverse event reports, with 39% of the ranibizumab + PDT group experiencing trace or more inflammation vs 7% in the PDT-alone group ($P<.001$). Inflammation that was graded as 2+ or above at any time during the 12-month study was reported for 22 (21.0%) of 105 ranibizumab-treated patients compared with 1 (1.8%) of 56 patients treated with PDT alone ($P<.001$).

Increased IOP adverse events were reported in 16.2% of the ranibizumab + PDT group vs 1.8% of the PDT-alone group ($P=.007$). These increases were typically transient events that followed injection. Intraocular pressure was measured before and 1 hour after injections. No increase in mean preinjection IOP was observed across time in either group. An occurrence of postinjection IOP of 30 mm Hg or greater was reported in 13.3% of the ranibizumab + PDT group and in 3.6% of the PDT-alone group ($P=.06$), whereas any occurrence of a predose (postbaseline) IOP of this magnitude was reported in approximately 2% of patients in each group. The likelihood of experiencing a transient postdose increase in IOP did not change significantly with repeated injections. There was no notable increased incidence of cataract adverse events in the ranibizumab + PDT group (12.4%) relative to the PDT-alone group (10.7%; $P>.99$).

Table 4. Patients With Adverse Events

Adverse Event Category Preferred Term	Patients, No. (%) PDT Alone (n = 56)	 Ranibizumab + PDT (n = 105)
Ocular Adverse Events in Study Eye in ≥10% of Patients, Either Group		
Any ocular adverse event*	56 (100)	105 (100)
Intraocular inflammation*	3 (5.4)	40 (38.1)
Iritis	3 (5.4)	20 (19.0)
Vitritis	2 (3.6)	20 (19.0)
Iridocyclitis	0	21 (20.0)
Vision-related adverse event*	18 (32.1)	47 (44.8)
Vision blurred	5 (8.9)	21 (20.0)
Visual acuity reduced	9 (16.1)	14 (13.3)
Visual disturbance	4 (7.1)	16 (15.2)
Photopsia	7 (12.5)	2 (1.9)
AMD-related adverse event*	43 (76.8)	54 (51.4)
Macular degeneration	28 (50.0)	29 (27.6)
Retinal hemorrhage	22 (39.3)	16 (15.2)
Retinal detachment†	9 (16.1)	11 (10.5)
Subretinal fibrosis	8 (14.3)	9 (8.6)
Other ocular symptoms and signs*	56 (100)	105 (100)
Conjunctival hemorrhage	54 (96.4)	102 (97.1)
Eye pain	11 (19.6)	34 (32.4)
Vitreous floaters	3 (5.4)	30 (28.6)
Eye irritation	13 (23.2)	15 (14.3)
Foreign body sensation in eyes	8 (14.3)	15 (14.3)
Intraocular pressure increased	1 (1.8)	17 (16.2)
Blepharitis	1 (1.8)	16 (15.2)
Vitreous detachment	3 (5.4)	14 (13.3)
Serious Ocular Adverse Events in the Study Eye, All		
Any serious ocular adverse event	4 (7.1)	16 (15.2)
Endophthalmitis	0	2 (1.9)
Intraocular inflammation	0	12 (11.4)
Iridocyclitis	0	7 (6.7)
Uveitis	0	4 (3.8)
Iritis	0	1 (1.0)
Vitritis	0	1 (1.0)
Vision-related adverse event	0	1 (1.0)
Visual acuity reduced	0	1 (1.0)
Other ocular symptoms and signs	2 (3.6)	3 (2.9)
Vitreous hemorrhage	2 (3.6)	2 (1.9)
Retinal tear	0	1 (1.0)
AMD-related adverse event	2 (3.6)	0
Choroidal hemorrhage	1 (1.8)	0
Choroidal neovascularization	1 (1.8)	0
Macular degeneration	1 (1.8)	0

(continued)

SYSTEMIC SAFETY

Overall, there was no notable imbalance between the 2 treatment groups in the incidence of serious nonocular adverse events: 16.2% of patients in the ranibizumab + PDT group vs 19.6% in the PDT-alone group had such

Table 4. Patients With Adverse Events (cont)

Adverse Event Category Preferred Term	Patients, No. (%) PDT Alone (n = 56)	 Ranibizumab + PDT (n = 105)
Serious Nonocular Adverse Events, All		
Any serious nonocular adverse event	11 (19.6)	17 (16.2)
Vascular system serious adverse events	3 (5.4)	9 (8.6)
Cerebrovascular accident	0	4 (3.8)
Myocardial infarction	2 (3.6)	0
Atrial fibrillation	0	1 (1.0)
Coronary artery disease	0	1 (1.0)
Coronary artery occlusion	0	1 (1.0)
Coronary artery stenosis	0	1 (1.0)
Transient ischemic attack	0	1 (1.0)
Unstable angina	0	1 (1.0)
Thrombosis	1 (1.8)	0
Other systemic serious adverse event	8 (14.3)	10 (9.5)
Hip fracture	2 (3.6)	1 (1.0)
Osteoarthritis	0	2 (1.9)
Pneumonia	2 (3.6)	0
Acute renal failure	0	1 (1.0)
Abdominal pain	0	1 (1.0)
Cholelithiasis	0	1 (1.0)
Chronic renal failure	0	1 (1.0)
Dementia	0	1 (1.0)
Postoperative infection	0	1 (1.0)
Rotator cuff syndrome	0	1 (1.0)
Sinusitis	0	1 (1.0)
Thyroid gland cancer	0	1 (1.0)
Urinary tract infection	0	1 (1.0)
Viral upper respiratory tract infection	0	1 (1.0)
Dehydration	1 (1.8)	0
Depression	1 (1.8)	0
Gastroenteritis	1 (1.8)	0
Intestinal obstruction	1 (1.8)	0
Malignant lung neoplasm	1 (1.8)	0
Spinal compression fracture	1 (1.8)	0
Varicella	1 (1.8)	0

Abbreviations: AMD, age-related macular degeneration; PDT, verteporfin photodynamic therapy.

*Represents the number of patients with any adverse event of the indicated category, including those not listed in the table.

†There were no rhegmatogenous retinal detachments.

events ($P=.66$) (Table 4). No deaths occurred in the first year of this study. Three nonocular adverse events were reported more commonly in the ranibizumab + PDT group than in the PDT-alone group: hypertension (12.4% vs 7.1%; $P=.42$), anxiety (6.7% vs 1.8%; $P=.26$), and pain in an extremity (7.6% vs 3.6%; $P=.50$).

Nonocular adverse events potentially associated with systemic VEGF inhibition, based on clinical trials of intravenously administered anti-VEGF therapy in patients with colorectal cancer,[21,22] include arterial thromboembolic events, hypertension, bleeding events, and proteinuria. Analysis of arterial thromboembolic events can be challenging because of variable definitions, assessments, and reporting. The Antiplatelet Trialists' Collaboration[23] classification addresses these issues by focusing on a limited but clearly defined spectrum of serious adverse events: nonfatal myocardial infarctions, nonfatal cerebrovascular accidents, and vascular deaths (including deaths of unknown cause). The Antiplatelet Trialists' Collaboration arterial thromboembolic event rate was 3.8% for the ranibizumab + PDT group and 3.6% for the PDT-alone group ($P>.99$). Categorization of nonocular serious adverse events into "vascular system adverse events" and "other" led to rates for the ranibizumab + PDT group that were slightly higher for vascular system adverse events (8.6% vs 5.4%; $P=.54$) and slightly lower for other adverse events (9.5% vs 14.3%; $P=.43$) compared with the rate for the PDT-alone group (Table 4).

As noted previously, treatment-emergent hypertension was reported at a higher rate in ranibizumab-treated patients. There were no protocol-defined criteria for what constituted a hypertension adverse event, but except for 2 patients in the ranibizumab + PDT group (1.9%) whose hypertension was described as moderate, all episodes in both treatment groups were described as mild. There were no imbalances between treatment groups for proteinuria (none reported during the first treatment year) or bleeding adverse events.

Systemic immunoreactivity to ranibizumab was present in both treatment groups at baseline and throughout the 12-month study. The percentage of ranibizumab-treated patients with positive test results in the assay did not exceed that in the PDT-alone group. Review of the VA data and adverse events revealed nothing clinically relevant in patients with positive immunoreactivity results.

COMMENT

In this randomized, multicenter, sham injection–controlled, single-masked study, we compared treatment of neovascular AMD with verteporfin PDT alone and PDT plus multiple intravitreal injections of the anti–VEGF-A agent ranibizumab. The efficacy outcomes after 12 months show that the addition of ranibizumab to PDT is superior to PDT alone as assessed by VA, the anatomical characteristics of the lesions, and the need for repeated PDT.

At 12 months, the most notable VA benefits of the combination treatment included a greater proportion of patients losing fewer than 15 letters, a greater proportion of patients (nearly one quarter) gaining 15 letters or more, a mean improvement in VA, and smaller proportions of patients with severe (≥30 letters) VA loss or VA 20/200 or worse in the study eye.

Although only patients who were judged by the investigator at screening to have predominantly classic CNV were enrolled into the study, subsequent standardized gradings of fluorescein angiograms by a central reading center revealed that approximately one third of the patients in this trial actually had minimally classic or occult without classic CNV lesions. This level of discordance is consistent with that in previous studies.[24,25] The VA benefits of ranibizumab + PDT in patients with minimally classic or occult CNV lesions were comparable in this study to those in patients with predominantly classic lesions.

Anatomically, the addition of ranibizumab to verteporfin PDT resulted, on average, in greater arrest of lesion growth (total and CNV component) and a greater reduction in CNV leakage and subretinal fluid than oc-

curred with PDT alone. Furthermore, the decreased need for repeated PDT was marked.

Adverse events related to the injection procedure were common and expected. Intraocular inflammation was the most common serious ocular adverse event in the ranibizumab + PDT group. Investigators reported 12 (11.4%) of 105 patients experiencing a total of 13 episodes of serious intraocular inflammation, with 10 of the 12 patients experiencing these events with the first ranibizumab dose a week after the initial PDT treatment. Reasons for this high rate are not obvious. The rate of serious intraocular inflammation was much higher than that observed in earlier clinical trials of ranibizumab, which used the same formulation,[13-15] and in the phase III MARINA study of ranibizumab treatment of minimally classic/occult without classic neovascular AMD,[16] in which a different formulation of ranibizumab was used. The impact of the protocol amendment increasing the spacing between PDT and subsequent ranibizumab treatments is also unclear. No episodes of serious intraocular inflammation occurred in the ranibizumab + PDT group after the protocol amendment, but only 7 patients required a total of 8 additional PDT treatments after the amendment, and none of the 7 patients had a previous serious intraocular inflammatory event. Although the cause of serious intraocular inflammation could not be identified in this study, the average visual outcome in patients in whom it occurred was better than the average outcome in the PDT only group.

The risk of endophthalmitis is a concern with any drug that is injected into the eye. Although the rate of investigator-reported endophthalmitis (1.9%) was comparable to that seen in studies with other intravitreally injected antiangiogenic treatments for AMD (eg, the pivotal study of pegaptanib[11]), the rate of presumed endophthalmitis was higher (4.8%). However, only 1 of these patients had lost 15 or more letters (–27 letters) in VA score at the end of the first year of treatment.

Overall, there was no notable imbalance between treatment groups in nonocular adverse events in this study. Concerning adverse events that have been associated with intravenously administered anti-VEGF therapy in patients with cancer, there was no overall imbalance in Antiplatelet Trialists' Collaboration arterial thromboembolic events (nonfatal myocardial infarctions, nonfatal cerebrovascular accidents, and vascular deaths). Two patients treated with verteporfin PDT alone (3.6%) had a nonfatal myocardial infarction during the study, and 4 patients treated with ranibizumab + PDT (3.8%) had a nonfatal cerebrovascular accident. Because arterial thromboembolic events have been observed to increase in general with systemic anti-VEGF therapy,[26,27] the overall lack of imbalance suggests that such events are not a frequent serious systemic effect of intravitreal ranibizumab treatment. Patients in the ranibizumab + PDT group had a higher incidence of treatment-emergent hypertension (mostly mild, none severe), despite being well matched at baseline for an existing diagnosis of hypertension, use of antihypertensive agents, and mean systolic and diastolic blood pressure. The routine monthly blood pressure measurements (vital signs data) revealed no differences between the ranibizumab + PDT and PDT-alone groups in mean systolic or diastolic blood pressure, although this may be due to treatment of observed blood pressure elevations with antihypertensive drugs. Given the lack of protocol-defined criteria for hypertension adverse event reporting, the impact of unmasked investigators on the rate of reporting is unknown. Verteporfin PDT alone is not known to cause hypertension. Longer-term follow-up in this study and results from larger, double-masked, phase III ranibizumab trials will help better define the systemic safety profile of ranibizumab. In the MARINA and ANCHOR studies through 2 and 1 years, respectively, no imbalance between the ranibizumab and control groups in the rate of hypertension adverse events was observed.[16,17] In the present study, there was no imbalance in proteinuria or bleeding adverse events, which have also been associated with systemic anti-VEGF therapy at much higher doses administered intravenously.

The systemic immunoreactivity seen in both treatment groups at baseline and throughout the study may reflect detection of preexisting antibodies to endogenous Fabs rather than specific antibodies to ranibizumab. Although similar findings were observed in both the MARINA and ANCHOR studies at 12 months, final 24-month results for MARINA demonstrated higher rates of immunoreactivity in the ranibizumab groups than in the sham injection control group. The clinical significance of observed immunoreactivity is unclear.[16,17]

In conclusion, monthly injection of ranibizumab administered in conjunction with verteporfin PDT was shown at 12 months to be superior to verteporfin PDT alone for all primary and secondary efficacy outcomes, including those based on VA, lesion characteristics, and the need for PDT retreatment. Although intraocular inflammation was reported in more than a third of the patients who received combination treatment, and was serious in up to 11%, patients who experienced serious intraocular inflammation events typically had good VA outcomes and did not experience long-term harm. Limitations of this phase I/II study include the relatively small sample sizes, the absence of a control group treated with ranibizumab alone (allowing assessment of the contribution of ranibizumab vs that of PDT in the efficacy and safety outcomes), and the use of a single-masked study design with no formal evaluation of compliance with masking. The phase III ANCHOR trial will provide information that may help elucidate the relative efficacy of ranibizumab monotherapy and verteporfin PDT monotherapy.

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Author Contributions: Dr Heier had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
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aera Corp. He is also a researcher, consultant, and/or advisor for each of these companies. Dr Boyer has financial interest in and is a consultant for Genentech Inc, Novartis, QLT, Eyetech, and Alcon. Drs Ferrone and Gentile have financial interest in Genentech and Novartis; in addition, Dr Gentile is a consultant for and stockowner in Genentech. Ms Kotlover and Drs Chung and Kim have financial interest in Genentech Inc; in addition, they are employees of and/or stockholders in Genentech.

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Correction

Error in Figure and Omission of Clinical Trial Registration Number. In the Clinical Trials article by Heier et al titled "Ranibizumab Combined With Verteporfin Photodynamic Therapy in Neovascular Age-Related Macular Degeneration," published in the November issue of the ARCHIVES (2006;124:1532-1542), Figure 3A contained an error. In the key, the boxes should have been reversed so that the white bars corresponded to "PDT Alone" and the blue bars to "Ranibizumab + PDT." In addition, the Clinical Trial Registration number should have been listed in the abstract. It is NCT00056823. The ARCHIVES regrets the error.