Verteporfin Therapy of Subfoveal Choroidal Neovascularization in Age-related Macular Degeneration: Two-year Results of a Randomized Clinical Trial Including Lesions With Occult With No Classic Choroidal Neovascularization—Verteporfin In Photodynamic Therapy Report 2

VERTEPORFIN IN PHOTODYNAMIC THERAPY STUDY GROUP

• PURPOSE: To determine if photodynamic therapy with verteporfin (Visudyne; Novartis AG, Bülach, Switzerland), termed verteporfin therapy, can safely reduce the risk of vision loss compared with a placebo (with sham treatment) in patients with subfoveal choroidal neovascularization caused by age-related macular degeneration who were identified with a lesion composed of occult with no classic choroidal neovascularization, or with presumed early onset classic choroidal neovascularization with good visual acuity letter score.

• METHODS: This was a double-masked, placebo-controlled (sham treatment), randomized, multicenter clinical trial involving 28 ophthalmology practices in Europe and North America. The study population was patients with age-related macular degeneration, with subfoveal choroidal neovascularization lesions measuring no greater than 5400 μm in greatest linear dimension with either 1) occult with no classic choroidal neovascularization, best-corrected visual acuity score of at least 50 (Snellen equivalent approximately 20/100), and evidence of hemorrhage or recent disease progression; or 2) evidence of classic choroidal neovascularization with a best-corrected visual acuity score of at least 70 (better than a Snellen equivalent of approximately 20/40); assigned randomly (2:1) to verteporfin therapy or placebo therapy. Verteporfin (6 mg per square meter of body surface area) or placebo (5% dextrose in water) was administered by means of intravenous infusion of 30 ml over 10 minutes. Fifteen minutes after the start of the infusion, a laser light at 689 nm delivered 50 J/cm^2 by application of an intensity of 600 mW/cm^2 over 83 seconds using a spot size with a diameter 1000 μm larger than the greatest linear dimension of the choroidal neovascularization lesion on the retina. At follow-up examinations every 3 months, retreatment with the same regimen was applied if angiography showed fluorescein leakage. The main outcome measure was at least moderate vision loss, that is, a loss of at least 15 letters (approximately 3 lines), adhering to an intent-to-treat analysis with the last observation carried forward to impute for missing data.

• RESULTS: Two hundred ten (93%) and 193 (86%) of the 225 patients in the verteporfin group compared with 104 (91%) and 99 (87%) of the 114 patients in the placebo group completed the month 12 and 24 examinations, respectively. On average, verteporfin-treated patients received five treatments over the 24 months of follow-up. The primary outcome was similar for the verteporfin-treated and the placebo-treated eyes through the month 12 examination, although a number of secondary visual and angiographic outcomes significantly favored the verteporfin-treated group. Between the month 12 and 24 examinations, the treatment benefit

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A complete list of the participants in the Verteporfin In Photodynamic Therapy Study Group as of March 1, 2001, is at the end of the article.

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grew so that by the month 24 examination, the verteporfin-treated eyes were less likely to have moderate or severe vision loss. Of the 225 verteporfin-treated patients, 121 (54%) compared with 76 (67%) of 114 placebo-treated patients lost at least 15 letters ($P = .023$). Likewise, 67 of the verteporfin-treated patients (30%) compared with 54 of the placebo-treated patients (47%) lost at least 30 letters ($P = .001$). Statistically significant results favoring verteporfin therapy at the month 24 examination were consistent between the total population and the subgroup of patients with a baseline lesion composition identified as occult choroidal neovascularization with no classic choroidal neovascularization. This subgroup included 166 of the 225 verteporfin-treated patients (74%) and 92 of the 114 placebo-treated patients (81%). In these patients, 91 of the verteporfin-treated group (55%) compared with 63 of the placebo-treated group (68%) lost at least 15 letters ($P = .032$), whereas 48 of the verteporfin-treated group (29%) and 43 of the placebo-treated group (47%) lost at least 30 letters ($P = .004$). Other secondary outcomes, including visual acuity letter score worse than 34 (approximate Snellen equivalent of 20/200 or worse), mean change in visual acuity letter score, development of classic choroidal neovascularization, progression of classic choroidal neovascularization and size of lesion, favored the verteporfin-treated group at both the month 12 and month 24 examination for both the entire study group and the subgroup of cases with occult with no classic choroidal neovascularization at baseline. Subgroup analyses of lesions composed of occult with no classic choroidal neovascularization at baseline suggested that the treatment benefit was greater for patients with *either* smaller lesions (4 disc areas or less) *or* lower levels of visual acuity (letter score less than 65, an approximate Snellen equivalent of $20/50^{-1}$ or worse) at baseline. Prospectively planned multivariable analyses confirmed that these two baseline variables affected the magnitude of treatment benefit. Of the 123 verteporfin-treated patients and 64 placebo-treated patients with either visual acuity score less than 65 or lesion size 4 disc areas or less at baseline, 60 (49%) and 48 (75%) lost at least 15 letters ($P < .001$), respectively, and 26 (21%) and 31 (48%) lost at least 30 letters ($P < .001$), respectively, at the month 24 examination. Conversely, treatment may not be beneficial for patients with *both* larger lesions *and* good visual acuity (both greater than 4 disc areas and letter score 65 or greater, an approximate Snellen equivalent of 20/50 or better). With respect to safety for the entire study group, 10 of 225 verteporfin-treated patients (4.4%) and none of the placebo-treated patients had a severe decrease of vision (at least 20 letters compared with the visual acuity just before the treatment) within 7 days after treatment, judged to be the result of the development of subretinal pigment epithelial blood, marked subretinal fluid associated with choroidal hypofluorescence, or no obvious cause. Five of these 10 patients had recovery of vision to less than a 20-letter loss compared with the pretreatment vision score at 3 months after this event. Photosensitivity reactions occurred in only one patient in each group.

• CONCLUSIONS: In this trial of patients with age-related macular degeneration and subfoveal choroidal neovascularization lesions composed of occult with no classic choroidal neovascularization, verteporfin therapy significantly reduced the risk of moderate and severe visual acuity loss. Subgroup analyses suggest that a greater benefit was achieved in patients presenting with *either* smaller lesions (4 disc areas or less) *or* lower levels of visual acuity (letter score less than 65, an approximate Snellen equivalent of $20/50^{-1}$ or less). The Verteporfin In Photodynamic Therapy Study Group recommends that this therapy should be considered for the treatment of patients with age-related macular degeneration with subfoveal lesions composed of occult with no classic choroidal neovascularization who are presumed to have recent disease progression. Patients to be treated should be aware of a small (4%) risk of acute, severe vision decrease. (Am J Ophthalmol 2001;131:541–560.

PHOTODYNAMIC THERAPY WITH VERTEPORFIN (VISUdyne; Novartis AG, Bülach, Switzerland), termed verteporfin therapy, caused short-term (1 to 4 week) cessation of fluorescein leakage from choroidal neovascularization resulting from age-related macular degeneration and other causes without angiographic damage to retinal blood vessels or loss of vision in a phase 1 and 2 investigation, even after multiple treatments.[1,2] Also, experience of verteporfin therapy showed no serious safety concerns when used within randomized clinical trials evaluating its role for selected cases of subfoveal choroidal neovascularization resulting from age-related macular degeneration with evidence of classic choroidal neovascularization (the Treatment of Age-related Macular Degeneration With Photodynamic Therapy Investigation[3]). Based on these investigations, this randomized clinical trial, called the Verteporfin In Photodynamic Therapy Trial was conducted in Europe and North America to evaluate the potential of this therapy in other situations. One part of the Verteporfin In Photodynamic Therapy Trial was to determine if verteporfin therapy could stabilize vision in people with subfoveal choroidal neovascularization caused by pathologic myopia, described in a separate report.[4] The other part of the Verteporfin in Photodynamic Therapy Trial was to determine if verteporfin therapy could reduce the risk of moderate visual acuity loss in selected cases of subfoveal choroidal neovascularization caused by age-related macular degeneration that were not included in the Treatment of Age-related Macular Degeneration With Photodynamic Therapy Investigation. Specifically, these cases included those with classic choroidal neovascularization presumed to be of early onset because of

relatively good visual acuity upon entry into the trial (approximate Snellen equivalent better than 20/40) as well as lesions with occult with no classic choroidal neovascularization presumed to have recent disease progression. This article describes effects of verteporfin therapy compared with placebo therapy on all study visits through the month 24 examination for all patients with age-related macular degeneration participating in the Verteporfin In Photodynamic Therapy Trial.

METHODS

THE VERTEPORFIN IN PHOTODYNAMIC THERAPY TRIAL WAS A double-masked, placebo and sham treatment-controlled, randomized clinical trial. The trial included patients with age-related macular degeneration, presented in this report, as well as patients with subfoveal choroidal neovascularization caused by pathologic myopia (results on the patients with pathologic myopia are published elsewhere[4]). The protocol stipulated that Verteporfin In Photodynamic Therapy Trial patients with age-related macular degeneration were to be randomized and analyzed separately from Verteporfin In Photodynamic Therapy Trial patients enrolled with choroidal neovascularization lesions from pathologic myopia.

The Clinical Study Protocol BPD OCR 003 (originally dated December 19, 1997) and all protocol amendments are on file with regulatory agencies in the United States, Canada, and Europe. The highlights of the protocol relative to the patients enrolled in the Verteporfin In Photodynamic Therapy Trial with age-related macular degeneration are described below. The design was reviewed by a study advisory group (members of the Verteporfin In Photodynamic Therapy Study Group who advise the study sponsors of the scientific aspects of the investigation), the institutional review board of the participating clinical center, and a data and safety monitoring committee (identical in personnel and operations to the Treatment of Age-related Macular Degeneration With Photodynamic Therapy Investigation's Data and Safety Monitoring Committee[3]) independent of the study sponsors and the Verteporfin In Photodynamic Therapy Study Group. Certification of all clinical center study personnel and organization of the trial replicated procedures in the Treatment of Age-related Macular Degeneration With Photodynamic Therapy Investigation.[3] Clinic monitoring, Study Advisory Group work, Operations Committee work, and biannual safety reviews by the Data and Safety Monitoring Committee are described elsewhere.[3] Photographic grading also replicated procedures in the Treatment of Age-related Macular Degeneration With Photodynamic Therapy Investigation except that Reading Center evaluations were planned only at the baseline, month 12, and month 24 examinations unless a serious adverse event was noted with respect to visual acuity or retinal abnormalities that could be documented on color fundus photography or fluorescein angiography.

TABLE 1. Principal Eligibility Criteria for the Verteporfin In Photodynamic Therapy Trial of Age-related Macular Degeneration

Inclusion criteria
Choroidal neovascularization under the geometric center of the foveal avascular zone
Area of choroidal neovascularization at least 50% of the area of the total neovascular lesion
Greatest linear dimension no greater than 5400 μm (not including any area of prior laser photocoagulation)
If evidence of classic choroidal neovascularization, then visual acuity letter score more than 70
If no evidence of classic choroidal neovascularization, then presumed to have recent disease progression because of deterioration (visually or anatomically) within last 3 months or evidence of hemorrhage from choroidal neovascularization
Best-corrected protocol[7] visual acuity letter score of at least 50 (Snellen equivalent approximately 20/100 or better)
Willing and able to provide written informed consent
Exclusion criteria
Features of any condition other than age-related macular degeneration (such as pathologic myopia) associated with choroidal neovascularization in study eye
Tear (rip) of the retinal pigment epithelium
Any significant ocular disease (other than choroidal neovascularization) that has compromised or could compromise vision in the study eye and confound analysis of the primary outcome
Inability to obtain photographs to document choroidal neovascularization, including difficulty with venous access
History of treatment for choroidal neovascularization in study eye other than nonfoveal confluent laser photocoagulation
Participation in another ophthalmic clinical trial or use of any other investigational new drugs within 12 weeks before the start of study treatment
Active hepatitis or clinically significant liver disease
Porphyria or other porphyrin sensitivity
Prior photodynamic therapy for choroidal neovascularization
Intraocular surgery within last 2 months or capsulotomy within last month in study eye

This was a multicenter trial involving patients referred to 28 ophthalmology practices in Europe and North America. Patients were enrolled from March 1998 through September 1998. Vision testing, color photographs, fluorescein angiography, medical histories, and ocular examinations were completed within 7 days before enrollment into the trial. Patients had to fulfill eligibility criteria determined by an ophthalmologist certified to enroll and treat study participants. The principal eligibility criteria are shown in Table 1. The primary criteria included a best-corrected visual acuity letter score (as measured in

previous trials[3]) of at least 50 (Snellen equivalent approximately 20/100 or better).

Fluorescein angiographic criteria, using definitions previously described,[3,5] included evidence of choroidal neovascularization caused by age-related macular degeneration that extended under the center of the foveal avascular zone. Furthermore, if the lesion had evidence of classic choroidal neovascularization, the visual acuity letter score had to be better than 70 (better than a Snellen equivalent of approximately 20/40). If the lesion had occult choroidal neovascularization without evidence of classic choroidal neovascularization, the lesion had to have evidence of "presumed deterioration." This was defined as either hemorrhage associated with choroidal neovascularization at the baseline examination, a loss of at least five letters (approximately 1 line) following a Treatment of Age-related Macular Degeneration With Photodynamic Therapy protocol refraction and visual acuity measurement within 3 months of the baseline examination, or a growth in the greatest linear dimension of the lesion of at least 10% within 3 months of the baseline examination. The lesion could include features that may obscure the identification of classic or occult choroidal neovascularization on fluorescein angiography, including blood, hypofluorescence not from visible blood, or a serous detachment of the retinal pigment epithelium. These obscuring features had to occupy an area less than 50% of the entire lesion's area. The greatest linear dimension of the entire lesion had to be 5400 μm or less on the retina.

Vision testing, stereoscopic color fundus photographs, fluorescein angiograms, and other medical aspects replicated procedures followed in the Treatment of Age-related Macular Degeneration With Photodynamic Therapy Investigation.[4] After reviewing and signing a written informed consent form accompanied by an oral consent process with a certified investigator (ophthalmologist), patients who were judged by a Verteporfin In Photodynamic Therapy—certified enrolling ophthalmologist to satisfy all eligibility criteria were assigned to placebo or verteporfin infusion.

Randomized treatment assignments were prepared as described elsewhere.[4] Masking was done also in a manner identical to procedures followed in the Treatment of Age-related Macular Degeneration With Photodynamic Therapy Investigation.[3]

Verteporfin therapy, placebo therapy, and patient follow-up were performed in all clinical centers according to the standard protocol followed in the Treatment of Age-related Macular Degeneration With Photodynamic Therapy Investigation.[3] Fluorescein angiographic assessment at follow-up was graded at the Photograph Reading Center in a masked fashion, as described for the Treatment of Age-related Macular Degeneration With Photodynamic Therapy Investigation.[3] Assessment of adverse events was done at each visit every 3 months and by telephone contact 2 to 4 days after each treatment.

• **STATISTICAL METHODS:** It was estimated that 40% of the placebo-treated patients and 20% of the verteporfin-treated patients would lose at least 15 letters by the month 12 examination. This difference was judged to be clinically relevant. In order to detect this difference statistically with 90% power, a sample size of 290 patients (193 assigned to verteporfin and 97 assigned to placebo) would be required. This assumed a two-sided significance level (α) of .05 and a 7% dropout rate by the month 12 examination. In the month when the sample size was attained, enrollment was allowed to continue through the end of that month, accounting for an additional 49 patients enrolled beyond the total sample size.

The primary efficacy variable was the proportion of eyes that had fewer than 15 letters lost compared with the baseline examination. There were two prospectively planned efficacy analysis time points, at the month 12 examination and the month 24 examination. To be consistent with previous publications evaluating vision outcomes in patients with choroidal neovascularization resulting from age-related macular degeneration, the vision outcomes are expressed as the proportion with at least 15 letters lost (approximately 3 or more lines of visual acuity loss) or at least 30 letters lost (approximately 6 or more lines of visual acuity loss) compared with the baseline examination. Other secondary efficacy variables include the mean change from baseline in visual acuity, proportion of eyes with a letter score less than 34 (approximate Snellen equivalent 20/200 or worse), changes in contrast threshold, and angiographic outcomes (evidence of classic choroidal neovascularization, progression of occult choroidal neovascularization, absence of leakage from occult choroidal neovascularization, and size of lesion). Prospectively planned subgroup analyses of the primary efficacy variable (proportion with at least 15-letter loss) were performed on the following baseline variables: age, gender, systemic hypertension, smoking history, evidence of prior laser photocoagulation, presence of blood as a lesion component, visual acuity score, and lesion size. Additional exploratory subgroup analyses using the secondary efficacy variable of the proportion with at least a 30-letter loss at the month 24 examination were also performed on the same baseline variables.

The primary efficacy analyses were based on a strict intent-to-treat analysis; patients were analyzed within the group to which they were randomized. All 339 randomized patients were included in the primary efficacy analyses. The proportions of eyes that lost at least 15 or 30 letters from baseline to 1 and 2 years and that had a visual acuity score less than 34 (an approximate Snellen equivalent of 20/200 or worse) were analyzed using a Pearson chi-squared test.[6] The frequency distributions of changes in visual acuity from baseline and visual acuity score were compared between groups using a Wilcoxon rank sum test.[7] Mean changes in visual acuity were analyzed using a two-sample *t* test.[7] Assessments of fluorescein leakage and

lesion size were compared between groups using a Pearson chi-squared test.[6]

To explore the possible effects that various baseline variables had on the primary efficacy variable and assess whether the treatment effect was consistent across different levels of any variable, logistic regression analyses were performed. Because of the number of baseline variables to be evaluated, each variable was included separately in a simple logistic regression model that included treatment. A second logistic regression model, which included treatment, the baseline variable, and its interaction with treatment, was also evaluated. Variables and interactions with treatment found to be statistically significant in the simple logistic models were then incorporated into a multiple logistic regression model. A backward, step-wise elimination procedure was then used to eliminate nonsignificant terms. Main effects were not removed unless the interaction term involving the main effect had been removed.

The intent-to-treat analysis included all patients who were randomized; missing values were imputed using the method of last observation carried forward. Outcomes described at specific time points, for example, at the month 12 examination, imply that the outcomes are at that time point with the last observation carried forward. To confirm results, a secondary analysis was done on observed values with no imputation of missing values.

• **DATA MONITORING AND REPORTING:** Independent monitoring was performed by the same Data and Safety Monitoring Committee as in the Treatment of Age-related Macular Degeneration With Photodynamic Therapy Investigation.[3] No prospectively defined stopping rules were employed. The randomization code was not broken for any patient, and there were no major protocol deviations that required exclusion from the primary analysis through the month 24 examination. On March 22, 2000, data through the month 12 examination, analyzed by the sponsors, were reviewed by the Data and Safety Monitoring Committee along with an independent analysis of the month 12 efficacy analyses conducted by the Jaeb Center for Health Research to verify the accuracy of the sponsors' data analyses. Based on this review of the data and to comply with Securities and Exchange Commission policies in Canada and the United States, the top-line results of these analyses were shared with the public by means of a news release from the sponsors on March 27, 2000. On February 6, 2001, data through the month 24 examination, analyzed by the sponsors, were reviewed by the Data and Safety Monitoring Committee along with an independent analysis of the month 24 efficacy analyses conducted by the Jaeb Center. Based on this more recent review of the data, the top-line results of these 2-year analyses were shared with the public by means of a news release from the sponsors on February 7, 2001. The data on which this public announcement were based were reviewed by the Verteporfin In Photodynamic Therapy Study Advisory Group and the Verteporfin in Photodynamic Therapy Study Group investigators on March 3, 2001, and are presented in this report.

RESULTS

THREE HUNDRED THIRTY-NINE EYES IN 339 PATIENTS WERE randomly assigned to verteporfin therapy (225 eyes) or placebo treatment (114 eyes). One hundred sixty-six of the 225 eyes (74%) in the verteporfin-treated group and 92 of the 114 eyes (81%) in the placebo-treated group had evidence of occult choroidal neovascularization with no classic choroidal neovascularization. In 38 cases where the presence of either classic or occult choroidal neovascularization was questionable or photographic quality precluded a conclusive lesion component assessment by the Photograph Reading Center, the classification of the lesion composition was based on the interpretation of the enrolling ophthalmologist. Twenty-seven of these 38 cases were interpreted by the enrolling ophthalmologist to be occult with no classic choroidal neovascularization.

The baseline characteristics for the entire study population as well as for the subgroup with occult with no classic choroidal neovascularization appeared balanced (Table 2). Only 16 eyes (7%) of the verteporfin-treated group and three eyes (3%) of the placebo-treated group had evidence of predominantly classic choroidal neovascularization (area of classic choroidal neovascularization 50% or greater area of entire lesion) at the baseline examination. An additional 38 eyes (17%) in the verteporfin-treated group and 18 eyes (16%) in the placebo-treated group had minimally classic choroidal neovascularization (area of classic choroidal neovascularization less than 50% but greater than 0% area of the entire lesion).

Two hundred ten (93%) and 193 (86%) of the 225 patients in the verteporfin group compared with 104 (91%) and 99 (87%) of the 114 patients in the placebo group completed the month 12 and 24 examinations, respectively (Figure 1). At the month 12 examination, 138 of the verteporfin-treated cases (61%) compared with 83 of the placebo-treated cases (73%) received retreatment (Figure 1). By the month 21 examination, these numbers had decreased to 75 (33%) and 51 (45%), for the verteporfin-treated and placebo-treated groups, respectively.

For the subgroup of cases with occult with no classic choroidal neovascularization, 157 (95%) and 143 (86%) in the verteporfin-treated group compared with 83 (90%) and 81 (88%) in the placebo-treated group completed the month 12 and 24 examinations, respectively. At the month 12 examination, 99 of the verteporfin-treated cases (60%) compared with 69 of the placebo-treated cases (75%) in this subgroup received retreatment. By the month 21 examination, these numbers had decreased to 55 (33%) and 41 (45%) for the verteporfin-treated and placebo-treated groups, respectively. For this subgroup, an

TABLE 2. Baseline Characteristics by Treatment Group*

Characteristic	Entire Study Group		Occult With No Classic	
	Verteporfin (%)	Placebo (%)	Verteporfin (%)	Placebo (%)
Patients	225	114	166	92
Gender				
Women	131 (58)	71 (62)	101 (61)	59 (64)
Men	94 (42)	43 (38)	65 (39)	33 (36)
Race				
White	222 (99)	112 (98)	164 (99)	90 (98)
Other	3 (1)	2 (2)	2 (1)	2 (2)
Age (years)				
49–64	17 (8)	14 (12)	11 (7)	7 (8)
65–74	87 (39)	37 (33)	63 (38)	33 (36)
75–84	96 (43)	54 (47)	72 (43)	45 (49)
≥85	25 (11)	9 (8)	20 (12)	7 (7)
Mean	75	74	75	75
Definite hypertension†	105 (47)	56 (49)	80 (48)	43 (47)
Letter score (visual acuity‡) in study eye				
>73 (>20/40)	45 (20)	18 (16)	39 (23)	14 (15)
73–53 (20/40–20/80)	163 (72)	88 (77)	110 (66)	71 (77)
52–34 (20/100–20/200)	17 (8)	8 (7)	17 (10)	7 (8)
Mean	66 (20/50+1)	65 (20/50)	66 (20/50+1)	65 (20/50)
Letter score (visual acuity‡) in fellow eye§				
>73 (>20/40)	59 (27)	33 (29)	46 (28)	25 (27)
73–53 (20/40–20/80)	38 (17)	23 (20)	28 (17)	17 (18)
52–34 (20/100–20/200)	26 (12)	14 (12)	15 (9)	11 (12)
<34 (<20/200)	99 (44)	44 (29)	74 (45)	39 (42)
Mean	44 (20/126−1)	48 (20/100−2)	44 (20/126−1)	46 (20/126+1)
Mean study eye contrast sensitivity (number of letters)	28	27	28	27
Micronutrient supplement use	129 (57)	73 (64)	91 (55)	59 (64)
Smoking history				
Never	86 (38)	48 (42)	63 (38)	39 (42)
Previous	105 (47)	55 (48)	76 (46)	43 (47)
Current	34 (15)	11 (10)	27 (16)	10 (11)
Lesion area composed of CNV (%)				
≥50	220 (98)	111 (97)	163 (98)	90 (98)
<50	2 (1)	3 (3)	2 (1)	2 (2)
Questionable or no CNV	3 (1)	0 (0)	1 (1)	0 (0)
CNV location				
Subfoveal	191 (85)	92 (81)	146 (88)	78 (85)
Probably subfoveal	17 (8)	11 (10)	13 (8)	7 (8)
Not subfoveal	14 (6)	10 (9)	6 (4)	6 (7)
No CNV or can't grade	3 (1)	1 (1)	1 (1)	1 (1)
Lesion area composed of classic CNV (%)				
≥50	16 (7)	3 (3)	0 (0)	0 (0)
<50 to >0	38 (17)	18 (16)	0 (0)	0 (0)
0	151 (67)	80 (70)	149 (90)	80 (87)
Questionable or can't grade	20 (9)	13 (11)	17 (10)	12 (13)
Evidence of occult CNV				
Yes	209 (93)	109 (96)	165 (99)	91 (99)
No	12 (5)	4 (4)	0 (0)	0 (0)
Questionable or can't grade	4 (2)	1 (1)	1 (1)	1 (1)

Continued on next page.

TABLE 2. Baseline Characteristics by Treatment Group* *(Continued)*

Characteristic	Entire Study Group		Occult With No Classic	
	Verteporfin (%)	Placebo (%)	Verteporfin (%)	Placebo (%)
Evidence of prior laser photocoagulation	16 (7)	5 (4)	10 (6)	1 (1)
Lesion included blood	51 (23)	31 (27)	31 (19)	25 (27)
Lesion included hypofluorescence not caused by visible blood				
Yes	33 (15)	21 (18)	19 (11)	11 (12)
No	189 (84)	93 (82)	145 (87)	81 (88)
Questionable or can't grade	3 (1)	0 (0)	2 (1)	0 (0)
Area of lesion, MPS disc areas				
≤3	79 (35)	39 (34)	49 (30)	27 (29)
>3 to 6	112 (50)	55 (48)	90 (54)	46 (50)
>6 to 9	27 (12)	17 (15)	22 (13)	16 (17)
>9	3 (1)	2 (2)	3 (2)	2 (2)
No CNV or can't grade	4 (2)	1 (1)	2 (1)	1 (1)
Greatest linear dimension, μm				
Mean	3954	4087	4122	4337

CNV = choroidal neovascularization; MPS = Macular Photocoagulation Study.

*Occult with no classic choroidal neovascularization includes identification by Photograph Reading Center graders of occult choroidal neovascularization with no classic choroidal neovascularization as well as questionable or ungradable classic choroidal neovascularization in 17 verteporfin-treated patients (10%) and 12 placebo-treated patients (13%).

†Definite hypertension was defined as systolic blood pressure of 160 mm Hg or higher or of 140 to 159 mm Hg with a history of hypertension or use of antihypertension medications or diastolic blood pressure of 95 mm Hg or higher or of 90 to 94 mm Hg with a history of hypertension or use of antihypertension medications.

‡Approximate Snellen equivalent.

§Three verteporfin-treated patients had no fellow eye visual acuity assessment.

average of 3.1 and 3.5 treatments of a possible total of 4 (including the initial treatment) were given before the month 12 examination and an average of 1.8 and 2.4 of a possible total of 4 were given in the second 12 months in the verteporfin-treated and placebo-treated patients, respectively.

• **VISION OUTCOMES:** Verteporfin-treated patients had a treatment benefit compared with placebo-treated patients noted for the primary outcome between the month 12 and 24 examinations. A small difference was evident in the primary outcome between verteporfin-treated and placebo-treated patients at the month 12 examination. At the month 12 examination, 114 of 225 verteporfin-treated patients (51%) compared with 62 of 114 placebo-treated patients (54%) lost at least 15 letters ($P = .52$). After that time point, the verteporfin-treated eyes were less likely to deteriorate so that, by the month 24 examination, 121 of 225 verteporfin-treated patients (54%) compared with 76 of 114 placebo-treated patients (67%) lost at least 15 letters ($P = .023$). Sixty-seven of the 225 verteporfin-treated patients (30%) compared with 54 of the 114 placebo-treated patients (47%) lost at least 30 letters by the month 24 examination ($P = .001$).

Because previous reports[3,8] indicated that the treatment effect varied based on the lesion composition, additional analyses are reported for the large subgroup of patients with age-related macular degeneration in the Verteporfin In Photodynamic Therapy Trial with occult with no classic choroidal neovascularization at baseline as judged primarily by the Photograph Reading Center. For the primary outcome, this subgroup had an outcome (Figure 2) similar to the total study population. This subgroup included 166 of the 225 verteporfin-treated patients (74%) and 92 of the 114 placebo-treated patients (81%). By the month 24 examination in this subgroup, 91 of the verteporfin-treated patients (55%) compared with 63 of the placebo-treated cases (68%) lost at least 15 letters ($P = .032$). For the remainder of the lesions, the Photograph Reading Center could determine if the lesion was predominantly classic or minimally classic in 54 of 59 cases assigned to verteporfin and 21 of 22 cases assigned to placebo. Based on this Photograph Reading Center evaluation at baseline, for the predominantly classic lesions, 10 of 16 verteporfin-treated patients (62%) compared with three of three placebo-treated patients (100%) lost at least 15 letters at the month 24 examination. For the minimally classic lesions, 19 of 38 verteporfin-treated patients (50%) compared with 10 of 18 placebo-treated patients (56%) lost at least 15 letters at the month 24 examination.

The risk of severe visual acuity loss (30 letters or more, approximately equivalent to 6 lines or more) for the

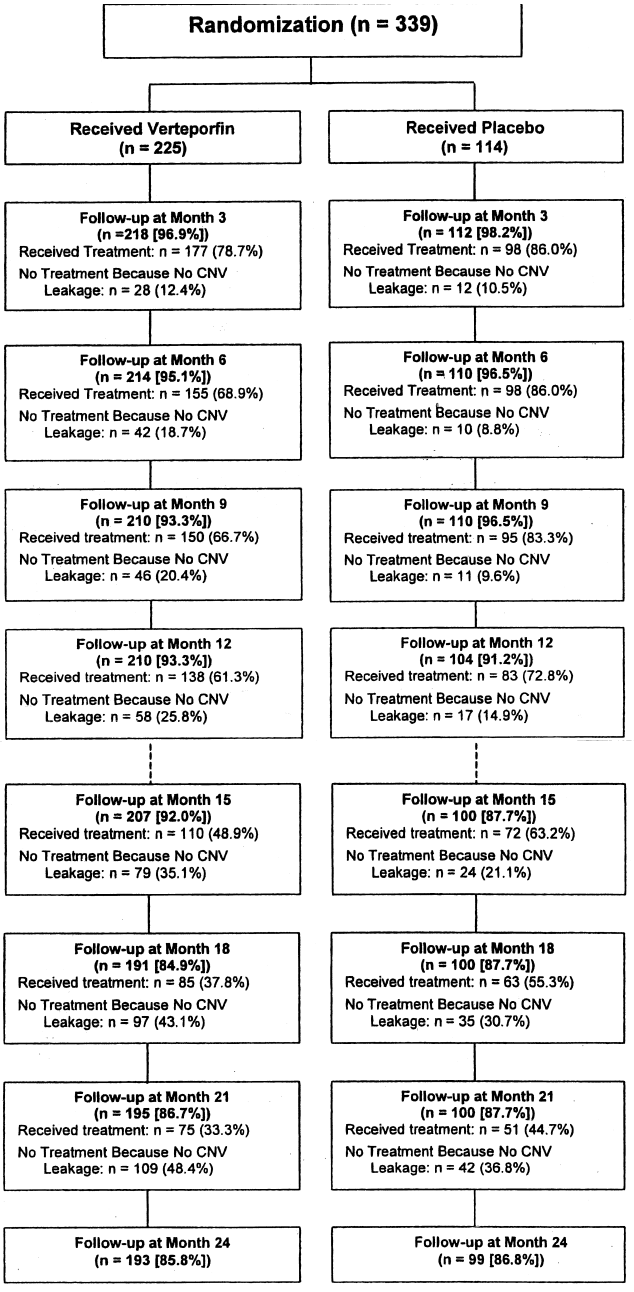


FIGURE 1. Profile of participants randomized, receiving treatment, and completing follow-up (at least a protocol visual acuity assessment) through the month 24 examination. CNV = choroidal neovascularization.

subgroup of lesions with occult with no classic choroidal neovascularization at baseline (Figure 3) favored the verteporfin-treated patients throughout the 2 years of follow-up. At the month 24 examination, 48 of the verteporfin-treated patients (29%) compared with 43 of the placebo-treated cases (47%) lost at least 30 letters ($P = .004$). The frequency distribution of changes in visual acuity from baseline at the month 12 and month 24 examinations (Table 3) favored the verteporfin-treated group at the

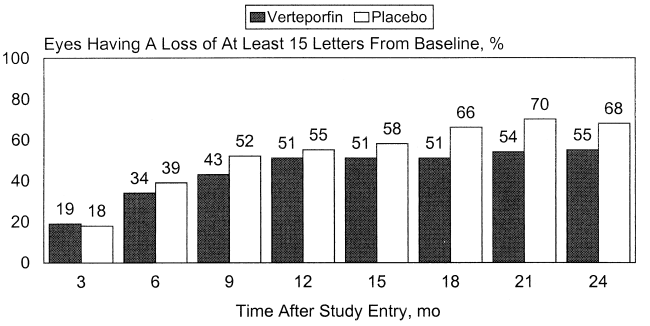


FIGURE 2. Percentage of eyes treated with verteporfin (n = 166) and eyes given placebo (n = 92) identified at baseline with occult with no classic choroidal neovascularization having at least moderate visual acuity loss (loss of at least 15 letters, equivalent to approximately 3 lines) at each 3-month study visit over time with last observation carried forward to impute for missing values.

month 12 examination. A shift in favor of the verteporfin-treated group at the month 24 examination was statistically significantly different.

The distribution of visual acuities (as approximate Snellen equivalents) at the month 12 and month 24 examinations (Table 4) for the subgroup of lesions with occult with no classic choroidal neovascularization at baseline showed a statistically significant difference at these time points. Furthermore, the percentage of cases with a visual acuity letter score less than 34 (approximate Snellen equivalent of 20/200 or worse) at the month 24 examination was significantly smaller in the verteporfin-treated group compared with the placebo-treated group for this subgroup (28% versus 45%, $P = .006$).

Mean contrast sensitivity letter score change from baseline was better in the verteporfin-treated group compared with the placebo group at the month 12 and month 24 examinations (Figure 4) for the subgroup with occult with no classic choroidal neovascularization at baseline. Thirty-

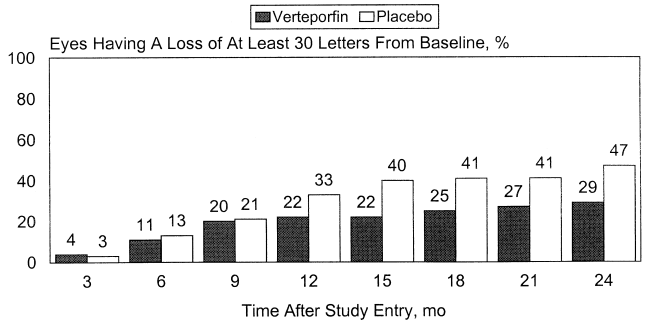


FIGURE 3. Percentage of eyes treated with verteporfin (n = 166) and eyes given placebo (n = 92) identified at baseline with occult with no classic choroidal neovascularization having severe visual acuity loss (loss of at least 30 letters, equivalent to approximately 6 lines) at each 3-month study visit over time with last observation carried forward to impute for missing values.

TABLE 3. Frequency Distribution of Changes in Visual Acuity From Baseline at the Month 12 and Month 24 Follow-up Examinations by Treatment and Visit for Subgroup of Patients Presenting With Occult With No Classic Choroidal Neovascularization

Change in Visual Acuity*	12-Month Follow-up, Number (%) of Patients		24-Month Follow-up, Number (%) of Patients	
	Verteporfin (n = 166)	Placebo (n = 92)	Verteporfin (n = 166)	Placebo (n = 92)
≥3-line to <6-line increase	5 (3)	2 (2)	8 (5)	1 (1)
≥1-line to <3-line increase	15 (9)	5 (5)	13 (8)	4 (4)
No change	36 (22)	15 (16)	25 (15)	14 (15)
≥1-line to <3-line decrease	25 (15)	19 (21)	29 (17)	10 (11)
≥3-line to <6-line decrease	48 (29)	21 (23)	43 (26)	20 (22)
≥6-line decrease	37 (22)	30 (33)	48 (29)	43 (47)
	$P = .10^{\dagger}$		$P = .006^{\dagger}$	
Mean (letters)	−15.6	−20.8	−19.0	−25.5
Median (letters)	−15.0	−22.0	−17.0	−26.0

*Using last observation carried forward to impute for missing values. Values are approximate; there are five letters per line.
†Wilcoxon rank sum test; the verteporfin-treated group had the better outcome.

TABLE 4. Visual Acuity Categories in Study Eyes by Treatment at the Month 12 and Month 24 Follow-up Examinations for Subgroup of Patients With Occult With No Classic Choroidal Neovascularization*

Visual Acuity, Letter Score (approximate Snellen equivalent)	Month 12 Examination, Number (%) of Patients		Month 24 Examination, Number (%) of Patients	
	Verteporfin (n = 166)	Placebo (n = 92)	Verteporfin (n = 166)	Placebo (n = 92)
>73 (>20/40)	25 (15)	6 (7)	26 (16)	6 (7)
73–53 (20/40–20/80)	51 (31)	30 (33)	42 (25)	23 (25)
52–34 (20/100–20/160)	56 (34)	26 (28)	52 (31)	22 (24)
33–22 (20/200–20/400)	24 (14)	17 (18)	21 (13)	18 (20)
<22 (<20/400)	10 (6)	13 (14)	25 (15)	23 (25)
	$P = .03^{\dagger}$		$P = .009^{\dagger}$	
Mean letter score (approximate Snellen equivalent)	50 (20/100)	44 ($20/126^{-1}$)	47 ($20/126^{+2}$)	40 (20/160)
Median letter score (approximate Snellen equivalent)	51 ($20/100^{+1}$)	44 ($20/126^{-1}$)	47 ($20/126^{+2}$)	36 ($20/200^{+1}$)

*Last observation carried forward.
†Wilcoxon rank sum test; the verteporfin-treated group had the better outcome at the month 24 examination.

two of 161 verteporfin-treated patients (20%) compared with 31 of 90 placebo-treated patients (34%) lost at least nine letters in contrast sensitivity score at the month 24 examination ($P = .01$).

When vision outcomes were analyzed without the last observation carried forward, results were similar (data not shown).

• **FLUORESCEIN ANGIOGRAPHIC OUTCOMES:** Several fluorescein angiographic outcomes demonstrated a treatment effect of verteporfin therapy for both the entire study group and the subgroup of lesions with occult with no classic choroidal neovascularization at baseline. The distribution of lesion sizes at the month 24 examination is shown in Figure 5. Placebo-treated lesions were 2.5 times more likely than verteporfin-treated lesions to be more than 9 disc areas in size at both the month 12 (data not shown) and month 24 examination (Figure 5) for the subgroup with occult with no classic choroidal neovascularization at baseline.

For the subgroup of patients who had occult with no classic choroidal neovascularization at baseline, a higher percentage of placebo-treated eyes than verteporfin-treated eyes developed evidence of classic choroidal neovascularization either within or beyond the area of the lesion identified at baseline. At the month 12 examination, 49 of the verteporfin-treated patients (30%) compared with 39 of the placebo-treated patients (42%) had developed evidence of classic choroidal neovascularization on fluorescein angiography ($P = .04$). Among these cases, 23 of the 166 verteporfin-treated patients (14%) compared with 24 of the placebo-treated patients (26%) had developed classic choroidal neovascularization that progressed beyond the boundaries of the entire lesion defined at baseline. An additional 26 of verteporfin-treated cases (16%) and 15 of placebo-treated cases (16%) had

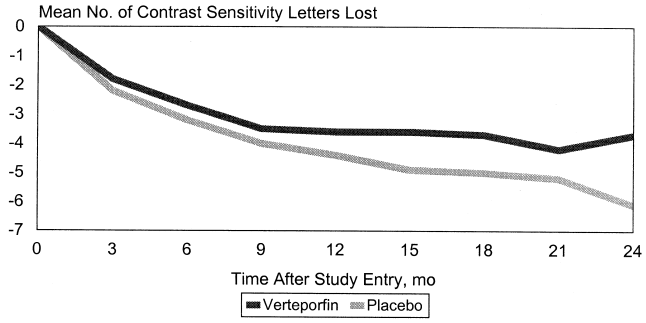


FIGURE 4. Mean number of letters of contrast sensitivity loss from baseline at each 3-month visit over time for eyes treated with verteporfin (n = 161) and eyes given placebo (n = 90) identified at baseline with occult with no classic choroidal neovascularization with last observation carried forward to impute for missing values. (Baseline contrast sensitivity was not measured at one clinical center for five cases treated with verteporfin and two cases treated with placebo.)

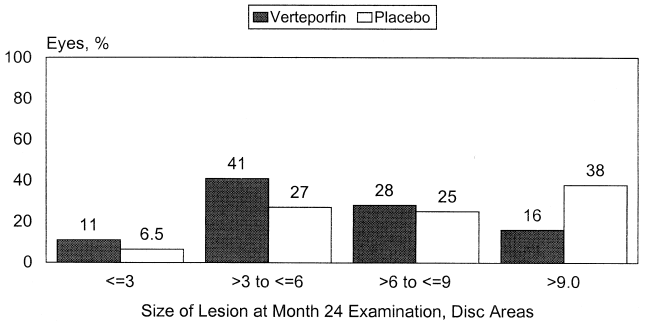


FIGURE 5. Frequency distribution of lesion sizes at the month 24 examination for 166 verteporfin-treated cases (eight could not be graded) and 92 placebo-treated cases eyes (three could not be graded) for the subgroup of cases with occult but no classic choroidal neovascularization at baseline examination using last observation carried forward to impute for missing data.

evidence of classic choroidal neovascularization at the month 12 examination within the boundaries of the lesion defined at baseline. By the month 24 examination, 45 of the verteporfin-treated patients (27%) compared with 45 of the placebo-treated patients (49%) developed evidence of classic choroidal neovascularization on fluorescein angiography (P = .001). Twenty-nine of the verteporfin-treated patients (17%) compared with 35 of the placebo-treated patients (38%) had developed classic choroidal neovascularization that progressed beyond the boundaries of the entire lesion defined at baseline.

At the month 12 and month 24 examinations, respectively, 91 (55%) and 77 (46%) of 166 verteporfin-treated patients compared with 67 (73%, P = .004) and 52 (57%, P = .12) of 92 placebo-treated cases had progression of occult choroidal neovascularization. Absence of leakage from occult choroidal neovascularization was not common in either group at the month 12 examination; it was noted in 32 of the verteporfin-treated cases (19%) compared with 10 of the placebo-treated cases (11%; P = .08). Absence of leakage from occult choroidal neovascularization was more common by the month 24 examination; it was noted in 70 of the verteporfin-treated cases (42%) compared with 27 of the placebo-treated cases (29%; P = .04). No fluorescein leakage from both classic and occult choroidal neovascularization at the month 12 and 24 examinations, respectively, was noted in 23 (14%) and 58 (35%) of verteporfin-treated cases compared with 4 (4%, P = .02) and 13 (14%, P = <.001) of placebo-treated cases.

• **SUBGROUP ANALYSES IN OCCULT WITH NO CLASSIC CHOROIDAL NEOVASCULARIZATION:** To understand the treatment effects in different subpopulations within the subgroup of patients with occult with no classic choroidal neovascularization at baseline, prospectively defined additional subgroup analyses, based on losing at least 15 letters at the month 24 examination (Table 5) were undertaken. Additional exploratory analyses were done based on losing at least 30 letters. No subgroups were identified in which eyes treated with a placebo fared significantly better than eyes treated with verteporfin to suggest any harmful effect. However, these analyses (Table 5) suggested that the benefit was greater for patients presenting with either smaller lesions (4 disc areas or less), regardless of initial visual acuity, or lower levels of visual acuity (letter score less than 65, an approximate Snellen equivalent $20/50^{-1}$ or worse), regardless of initial lesion size. Multivariable logistic regression analysis confirmed this finding where significant interactions between treatment and baseline lesion size (P = .024) and between treatment and baseline visual acuity (P = .003) were observed. Of the 123 verteporfin-treated patients and 64 placebo-treated patients with either lesion size 4 disc areas or less at baseline or visual acuity score less than 65 (approximate Snellen equivalent $20/50^{-1}$ or worse), 60 (49%) and 48 (75%) lost at least 15 letters (P < .001), respectively, and 26 (21%) and 31 (48%) lost at least 30 letters (P < .001), respectively at the month 24 examination. Figure 6 shows that the treatment benefit for this subgroup of lesions was evident throughout the 2 years of follow-up with respect to losing at least 15 letters (Figure 6 top), whereas the risk of losing at least 30 letters was approximately halved (Figure 6 bottom). Other secondary outcomes were consistent with these findings (Table 6). Conversely, an exploratory analysis suggests no treatment benefit in the subgroup of patients presenting with both large lesions (greater than 4 disc areas) and good visual acuity (letter score 65 and greater, an approximate Snellen equivalent 20/50 or better) as noted in the next to last row of Table 5.

• **SAFETY:** Ten patients with age-related macular degeneration subjectively reported severe visual acuity decrease within 7 days after treatment with verteporfin and subsequently were noted to have lost at least 20 letters of visual acuity compared with pretreatment acuity (Table 7). One

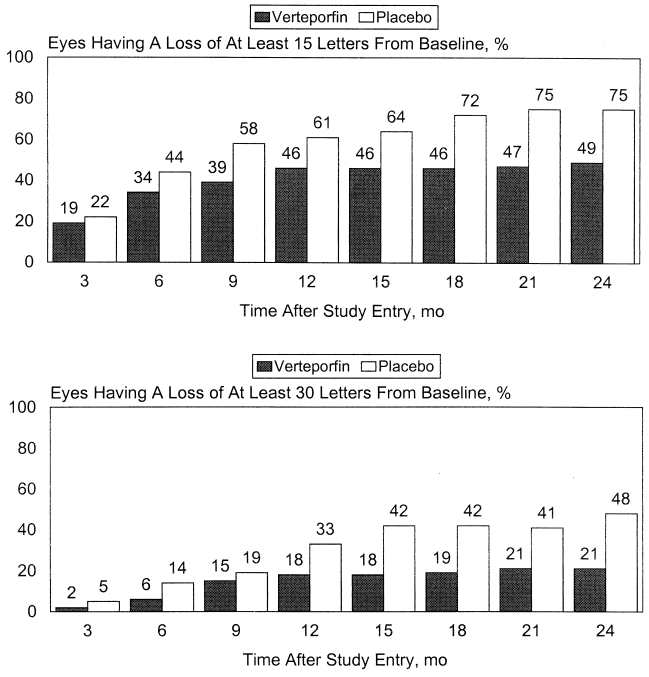


FIGURE 6. Percentage of eyes treated with verteporfin (n = 123) and eyes given placebo (n = 64) identified at baseline with occult with no classic choroidal neovascularization with either smaller lesions (4 disc areas or less) or lower levels of visual acuity (letter score less than 65, an approximate Snellen equivalent $20/50^{-1}$) having (top) a loss of at least 15 letters (3 lines or more) or (bottom) a loss of at least 30 letters (6 lines or more) at each 3-month study visit over time with last observation carried forward to impute for missing values.

case was associated with the development of extensive subretinal fluid associated with choroidal hypofluorescence (Figure 7), three cases with subretinal pigment epithelium hemorrhage on fluorescein angiography (Figure 8), and six cases with no obvious cause. At the baseline examination, eight of these 10 patients had occult with no classic choroidal neovascularization; the other two patients had evidence of classic choroidal neovascularization at the baseline evaluation. Nine of these events occurred after the initial treatment, and one occurred after a patient's second treatment. Eight of these patients received no retreatment after this adverse event. Visual acuity subsequently improved to varying degrees in some of these patients. At 3 months after the events, five of the 10 patients had recovery of vision to less than 20 letters lost compared with pretreatment letter score, including two patients who had fewer than 15 letters lost (one who had 11 letters lost and one who had three letters gained). Two of these 10 patients lost fewer than 15 letters from baseline at the month 12 examination. One of these two patients was a patient who had lost fewer than 15 letters 3 months after the event. Any subjective visual disturbance (categorized from the patient's statement as abnormal vision, decreased vision, or visual field defect), irrespective of whether the treating ophthalmologist judged that it was related to therapy or not, was reported in 94 of the verteporfin-treated cases (42%) compared with 26 of the placebo-treated cases (23%; $P < .001$). These events were usually transient and mild to moderate in intensity.

An adverse event (irrespective of relationship to treatment) was reported in 201 of the 225 patients (89%) in the verteporfin-treated group and 94 of 114 patients (83%) in the placebo-treated group. Adverse events considered by the treating ophthalmologist to be associated with treatment were reported in 96 of the verteporfin-treated cases (43%) compared with 21 of those given placebo (18%). Additional adverse events judged to be clinically relevant from experience in the Treatment of Age-related Macular Degeneration With Photodynamic Therapy Investigation[3] are listed in Table 7. Injection-site adverse events occurred in 18 of verteporfin-treated patients (8%) compared with six of placebo-treated patients (5%). There were five cases (2%) of infusion-related back pain in the verteporfin-treated patients, all of which were first experienced within the first year of follow-up, and none in placebo-treated patients. For nonocular adverse events, only one patient in each group experienced a photosensitivity reaction. Four deaths in the verteporfin-treated group and three deaths in the placebo-treated group were reported in the study. All of these deaths were judged not to be related to the study therapy and were consistent with the age and medical histories of the total study population. Treatment was discontinued because of an adverse event in nine cases, including eight who had a severe decrease in vision (at least 20 letters) within 7 days after a treatment as described above, and one that had a nonocular adverse event judged by the treating ophthalmologist to be unrelated to the therapy.

DISCUSSION

VERTEPORFIN THERAPY SIGNIFICANTLY REDUCED THE RISK of moderate and severe visual acuity loss in patients with age-related macular degeneration included in this trial. Because previous reports[3,8] indicated that the treatment effect from verteporfin therapy was affected by the lesion composition at presentation, additional analyses were reported for the large subgroup of patients with age-related macular degeneration in the Verteporfin In Photodynamic Therapy Trial with occult with no classic choroidal neovascularization at baseline, as judged primarily by the Photograph Reading Center. This group constituted approximately 76% of the entire study group.

Although the risk of at least moderate visual acuity loss was similar for the verteporfin-treated and placebo-treated eyes presenting with occult but no classic choroidal neovascularization through the month 12 examination, a variety of other visual and angiographic outcomes suggested a treatment benefit at that time. By the month 24 examination, both the primary and secondary visual acuity

TABLE 5. Eyes With a Loss of At Least 15 Letters and At Least 30 Letters at Month 24 Examination by Treatment Group and Baseline Characteristics for Subgroup Presenting With Occult With No Classic Choroidal Neovascularization

Characteristic	Treatment Group, n	Loss ≥15 Letters, %	P^*	P_i	Loss ≥30 Letters, %	P^*	P_i
Age (years)							
<75	V, 74	53%	.81	.09	22%	.009	.33
	P, 40	55%			45%		
≥75	V, 92	56%	.007		35%	.12	
	P, 52	79%			48%		
Gender							
Men	V, 65	49%	.18	.96	29%	.19	.60
	P, 33	64%			42%		
Women	V, 101	58%	.11		29%	.01	
	P, 59	71%			49%		
Systemic hypertension							
Definite‡	V, 80	47%	.06	.61	25%	.16	.51
	P, 43	65%			37%		
Others	V, 86	62%	.25		33%	.01	
	P, 49	71%			55%		
Smoking history							
Never	V, 63	57%	.49	.42	30%	.03	.64
	P, 39	64%			51%		
Past	V, 76	51%	.09		30%	.20	
	P, 43	67%			42%		
Current	V, 27	59%	.08		22%	.10	
	P, 10	90%			50%		
Evidence of prior laser photocoagulation							
Yes	V, 10	50%	.19	.98	20%	.03	.97
	P, 2	100%			100%		
No	V, 156	55%	.05		29%	.01	
	P, 90	68%			46%		
Lesion included blood							
Yes	V, 31	58%	.88	.15	29%	.25	.81
	P, 25	56%			44%		
No	V, 135	54%	.009		29%	.008	
	P, 67	73%			48%		
Subretinal/intraretinal hemorrhage							
Yes	V, 106	58%	.18	.53	32%	.09	.22
	P, 67	69%			45%		
No	V, 60	48%	.10		23%	.01	
	P, 25	68%			52%		
Initial number of letters read (visual acuity‖) in study eye							
≥65 (≥20/50)	V, 87	67%	.64	.004	42%	.34	.048
	P, 51	63%			51%		
<65 (≤20/50^{-1})	V, 79	42%	<.001		14%	<.001	
	P, 41	76%			41%		
Lesion size, MPS disc areas							
≤4 disc areas	V, 80	45%	.006	.04	21%	.005	.16
	P, 39	72%			46%		
>4 disc areas	V, 84	65%	.99		37%	.29	
	P, 52	65%			46%		

Continued on next page.

outcomes were significantly better in the verteporfin-treated group. To achieve this benefit, patients were examined every 3 months and were to be retreated if fluorescein leakage from choroidal neovascularization was evident. The visual acuity outcomes were complemented by beneficial outcomes for contrast-sensitivity, in which

TABLE 5. Eyes With a Loss of At Least 15 Letters and At Least 30 Letters at Month 24 Examination by Treatment Group and Baseline Characteristics for Subgroup Presenting With Occult With No Classic Choroidal Neovascularization *(Continued)*

Characteristic	Treatment Group, n	Loss ≥15 Letters, %	P^*	P_i	Loss ≥30 Letters, %	P^*	P_i
Initial number of letters read (visual acuity[§]) in study eye and lesion size, MPS disc areas							
≥65 (≥20/50) and >4 disc areas	V, 43	72%	.09[¶]	.001	51%	.40[¶]	.005
	P, 27	52%			41%		
<65 (≤20/50^{-1}) or ≤4 disc areas	V, 123	49%	<.001		21%	<.001	
	P, 64	75%			48%		

CNV = choroidal neovascularization; MPS = Macular Photocoagulation Study; NA = not applicable; P = placebo-treated group; V = verteporfin-treated group.

*Test for treatment effect within subgroups.

†Test of interaction between subgroups using a simple logistic regression model that includes treatment.

‡Definite hypertension was defined as systolic blood pressure of 160 mm Hg or higher or of 140 to 159 mm Hg with a history of hypertension or use of antihypertension medications or diastolic blood pressure of 95 mm Hg or higher or of 90 to 94 mm Hg with a history of hypertension or use of antihypertension medications.

§Includes one case graded as questionable evidence of prior laser.

‖Approximate Snellen equivalent.

¶The placebo-treated group had the better outcome.

TABLE 6. Secondary Efficacy Outcomes in Patients Who Had Occult With No Classic Choroidal Neovascularization With Either Lesion Size ≤4 Disc Areas or Visual Acuity Letter Score Less Than 65 (Approximate Snellen Equivalent 20/50 or Worse) at Baseline*

Outcome	Verteporfin, Number (%) or Letters (Lines) (n = 123)	Placebo, Number (%) or Letters (Lines) (n = 64)	$P^†$
<34 letter score (≤20/200) at month 12	23 (19)	22 (34)	.017
<34 letter score (≤20/200) at month 24	30 (24)	32 (50)	<.001
Mean change in visual acuity letter score from baseline at month 12	−13.1 (−2.6)	−20.8 (−4.2)	.006
Mean change in visual acuity letter score from baseline at month 24	−15.2 (−3.0)	−26 (−5.2)	<.001
Developed classic CNV at month 12	36 (29)	26 (41)	.118
Developed classic CNV at month 24	31 (25)	33 (52)	.001
Absence of occult CNV at month 12	23 (19)	6 (9)	.017
Absence of occult CNV at month 24	52 (42)	15 (23)	.013
Lesion size ≤6 disc areas at month 12	81 (66)	29 (45)	.001
Lesion size ≤6 disc areas at month 24	74 (60)	25 (39)	.001

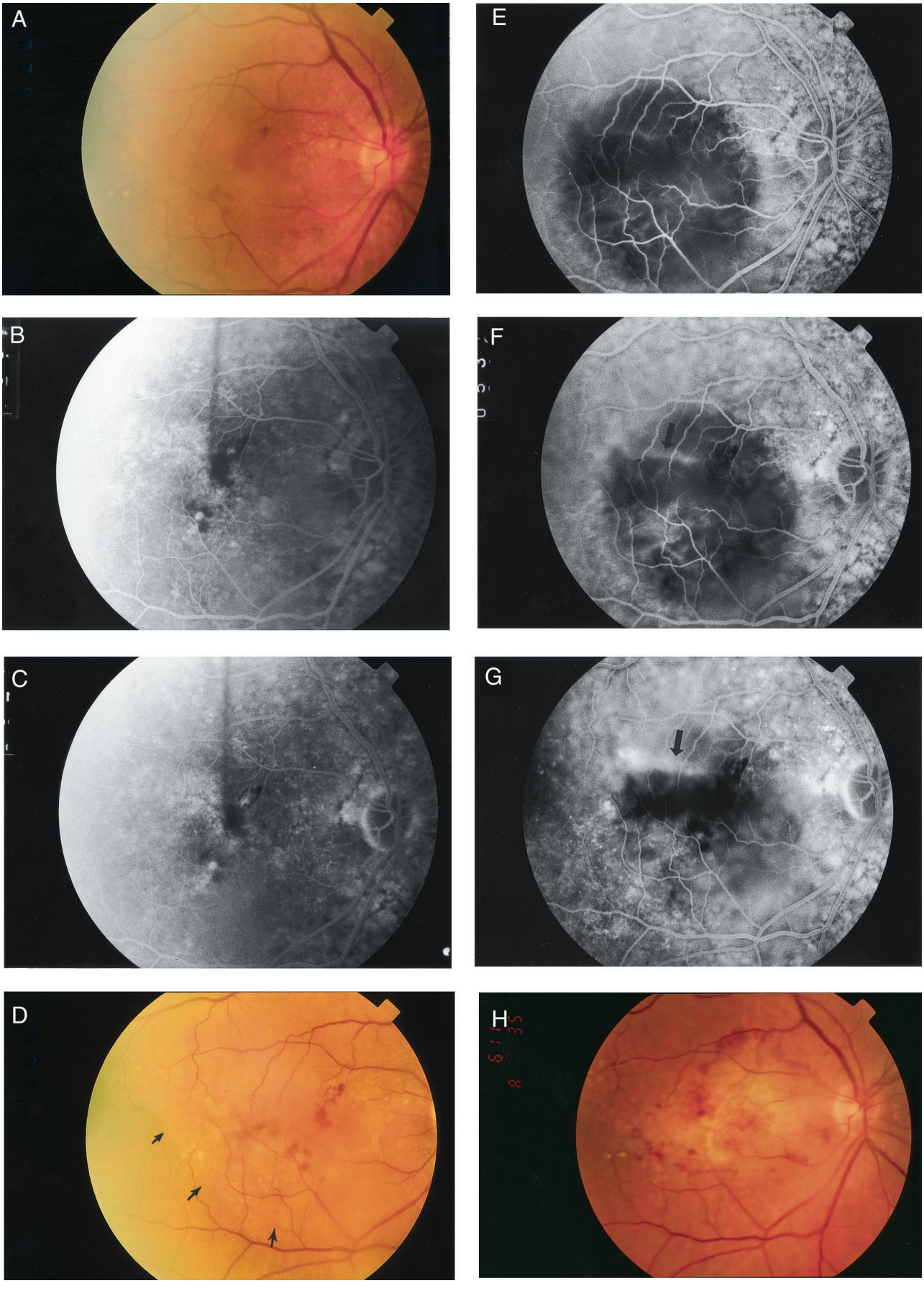
CNV = choroidal neovascularization; VA = visual acuity.

*With last observation carried forward.

†For letter score less than 34, a chi-squared test was used. For mean change in visual acuity, a two-sample *t* test was used. For absence of leakage from occult choroidal neovascularization and lesion size, a Cochran-Mantel-Haenszel chi squared test was used to test significance between treatment groups for the overall distribution of categories.

the risk of losing at least nine letters (approximately 0.45 log units, a value shown to be associated with a significant impact on visual function tasks[9]) was less in the verteporfin group. Fluorescein angiographic assessments at follow-up examinations suggested that verteporfin treatment reduced the chance of lesion growth, increased the chance of cessation of leakage from choroidal neovascularization, and decreased the chance of developing classic choroidal neovascularization beyond the area of the lesion identified at baseline. The Verteporfin In Photodynamic Therapy Trial is the first large-scale randomized clinical trial to show a significant treatment benefit in patients with age-related macular degeneration presenting with occult with no classic choroidal neovascularization.

The treatment benefit is highly unlikely to be the result of chance because of consistent results across multiple sites (data not shown), consistent results across two vision outcome assessments (visual acuity and contrast sensitivi-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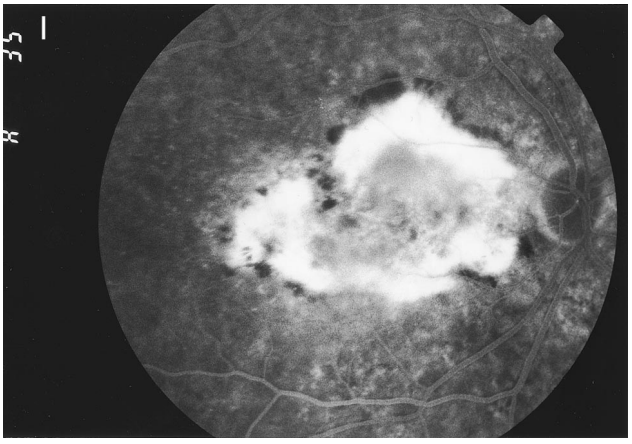


FIGURE 7. Example of a patient developing severe decrease of at least 20 letters within 7 days after verteporfin treatment associated with extensive subretinal fluid accompanied by extensive choroidal hypoperfusion. (A) Color fundus photograph at baseline shows subretinal hemorrhage just superonasal to subretinal fluid extending through center of macula. (B) Early-phase and (C) late-phase fluorescein angiogram at baseline shows hypofluorescence corresponding to hemorrhage and stippled areas of hyperfluorescence corresponding to occult choroidal neovascularization. (D) Color fundus photograph 7 days after initial treatment shows extensive subretinal fluid (arrows), accompanied by hypofluorescence corresponding to treatment spot in (E) early-phase and (F) mid-phase fluorescein angiogram as well as hyperfluorescence (arrow) of intermediate-sized choroidal vessels. (G) Late-phase fluorescein angiogram shows leakage (arrow) from larger choroidal vessel and persistent hypofluorescence within center of treated area. (H) Color fundus photograph 12 months after initial verteporfin treatment (with no retreatment given) shows fibrosis and subretinal hemorrhage with fluorescein leakage (I) on angiography.

TABLE 7. Clinically Relevant Adverse Events Irrespective of Relationship to Treatment

Event	Verteporfin (n = 225), n (%)	Placebo (n = 114), n (%)
Severe vision decrease within 7 days*	10 (4.4)	0 (0)
Visual disturbance†	94 (42)	26 (23)
Injection site adverse events‡	18 (8)	6 (5)
Infusion-related back pain	5 (2.2)	0 (0)
Allergic reactions	3 (1)	3 (3)
Photosensitivity reactions	1 (<1)	1 (1)

*Reports of severe vision decrease within 7 days after treatment and subsequently noted to have lost at least 20 letters of visual acuity compared with pretreatment acuity.

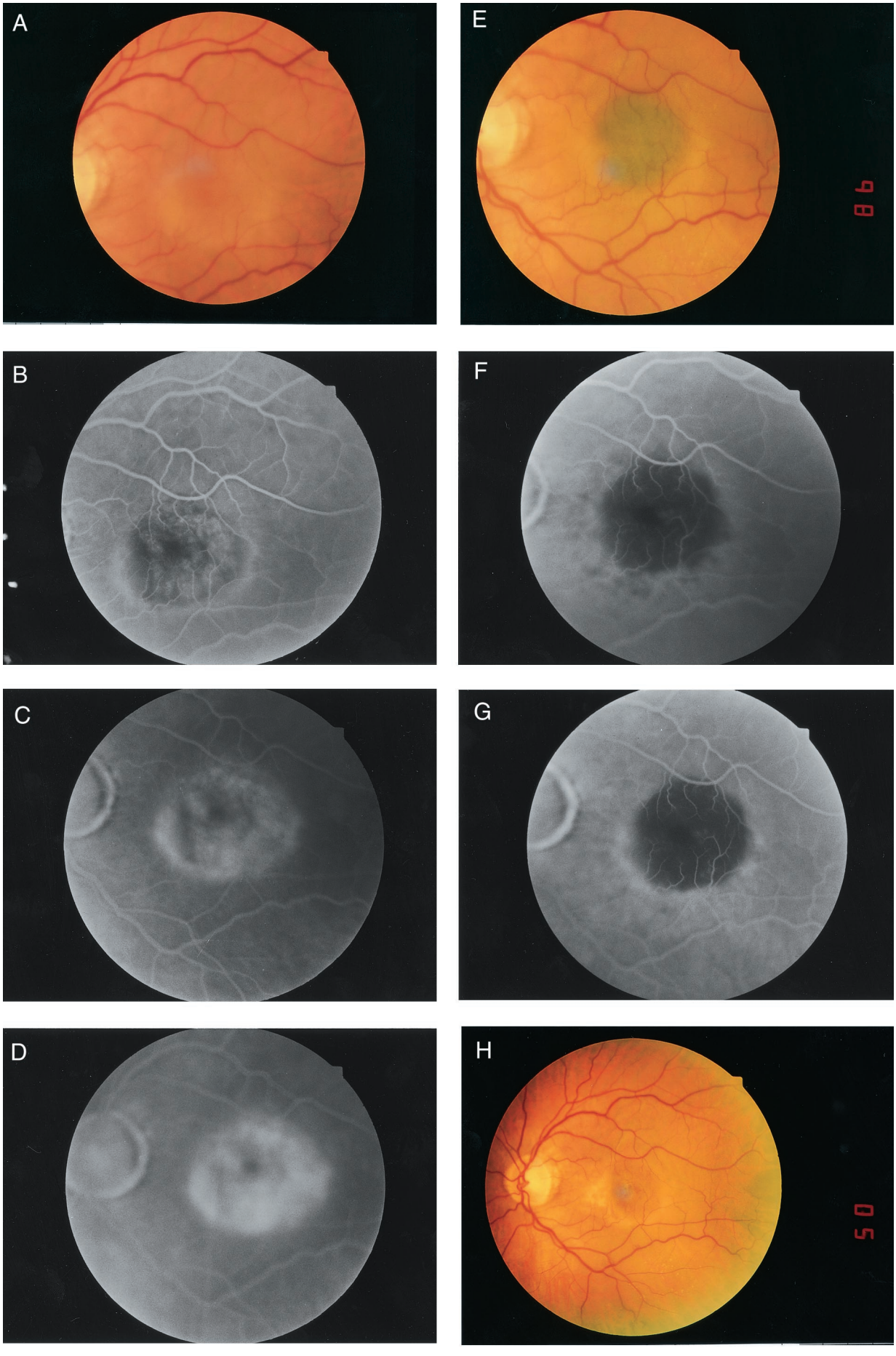
†Includes reports in verteporfin-treated and placebo-treated eyes, respectively, of abnormal vision in 39 (17.3%) and 11 (9.6%) cases, decreased vision in 62 (27.6%) and 13 (11.4%), and visual field defect in 32 (14.2%) and six (5.3%) cases at month 12 examination and abnormal vision in 46 (20%) and 14 (12%) cases, decreased vision in 67 (30%) and 15 (13%), and visual field defect in 34 (15%) and eight (7%) cases at month 24 examination.

‡Includes reports in verteporfin-treated and placebo-treated patients, respectively, of discoloration in two (0.9%) and zero cases, edema in six (2.7%) and zero cases, extravasation in seven (3.1%) and four (3.5%) cases, hemorrhage in one (0.4%) and zero cases, hypersensitivity in one (0.4%) and zero cases, and inflammation in three (1.3%) and one (0.9%) cases, and pain in nine (4%) and one (0.9%) cases at month 12 examination and discoloration in two (1%) and zero cases, edema in seven (3%) and zero cases, extravasation in 12 (5%) and four (4%) cases, hemorrhage in one (1%) and zero cases, hypersensitivity in two (1%) and one (1%) cases, and inflammation in five (2%) and one (1%) cases, and pain in 10 (4%) and one (1%) cases.

ty), and confirmatory information on fluorescein angiography. In addition, the results are qualitatively consistent with the Treatment of Age-related Macular Degeneration With Photodynamic Therapy Investigation results of the subgroup that had no evidence of classic choroidal neovascularization at baseline.[3,8]

Bias is unlikely given the masking of the patients, treating ophthalmologists, vision examiners, and photograph graders. Baseline characteristics appeared balanced in the two treatment groups. The use of the last observation carried forward method to account for missing data had little impact on the overall results, because the loss to follow-up was relatively small, and analyses without the last observation carried forward produced similar results (data not shown).

Subgroup analyses within the group of patients with occult with no classic choroidal neovascularization at baseline were planned prospectively for the month 24 examination. These univariate analyses showed that within this group of patients, baseline factors of either lesion size or visual acuity affected the magnitude of the treatment benefit. Multivariable logistic regression analysis confirmed this finding where significant interactions between treatment and baseline lesion size ($P = .024$) and between treatment and baseline visual acuity ($P = .003$) were observed. These results prompted additional exploratory analyses in the group of patients with occult but no classic choroidal neovascularization who presented with either smaller lesions (4 disc areas or less) or lower levels of visual acuity (letter score less than 65, an approximate Snellen equivalent $20/50^{-1}$ or worse) and the opposite group of patients, those who presented with both larger lesions (greater than 4 disc areas) and higher levels of visual acuity (letter score 65 or greater, an approximate Snellen equivalent 20/50 or better). These analyses showed that patients with either smaller lesions or lower levels of visual acuity appeared to benefit most from verteporfin therapy, supported by other secondary outcomes (Table 6). Although those with larger lesions and higher levels of visual acuity may not benefit from treatment, this latter analysis should be interpreted with caution because of the small number of patients with both of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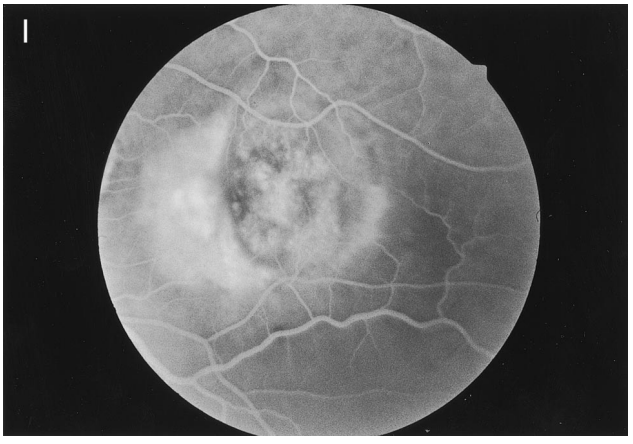

FIGURE 8. Example of a patient developing severe vision decrease of at least 20 letters within 7 days after verteporfin treatment resulting from subretinal pigment epithelium hemorrhage. (A) Color fundus photograph shows subretinal fluid extending through center of macula. (B) Early-phase and (C) mid-phase shows stippled hyperfluorescence corresponding to occult choroidal neovascularization (CNV). (D) Late-phase fluorescein angiogram shows prominent fluorescent staining and leakage of lesion. (E) Color fundus photograph 1 week after initial treatment shows dark greenish mound from subretinal hemorrhage, corresponding to hypofluorescence on (F), early-phase, and (G) late-phase fluorescein angiogram. (H) Color fundus photograph 3 months after initial treatment shows hypopigmentation at nasal aspect of lesion. (I) Early-phase fluorescein angiogram 3 months after initial treatment shows bright, uniform hyperfluorescence along nasal aspect of lesion corresponding to tear or rip of the retinal pigment epithelium with stippled fluorescence corresponding to occult choroidal neovascularization.

these characteristics at baseline and the exploratory nature of this evaluation.

Although the therapy was well tolerated in most patients, 10 patients had a severe decrease in visual acuity within 7 days of a treatment. Visual acuity subsequently improved to varying degrees in some of these patients. These events were judged to be the result of the development of extensive subretinal fluid associated with choroidal hypofluorescence (Figure 7) or subretinal pigment epithelium hemorrhage (Figure 8) or no obvious cause on fluorescein angiography. All but one case occurred after the initial treatment. The other case occurred after a patient's second treatment. These events occurred slightly more frequently in the 225 treated patients with age-related macular degeneration in the Verteporfin In Photodynamic Therapy Trial compared with the Treatment of Age-related Macular Degeneration With Photodynamic Therapy Investigation in which such an event occurred in only three of 402 treated patients (less than 1%).

With respect to other safety concerns, photosensitivity reactions occurred in less than 1% of patients, which was lower than the 3% incidence reported in the Treatment of Age-related Macular Degeneration With Photodynamic Therapy Investigation,[3] despite the shorter photosensitivity protection period of 24 hours recommended in the Verteporfin In Photodynamic Therapy Trial compared with the 48 hours in the Treatment of Age-related Macular Degeneration With Photodynamic Therapy Investigation. The Verteporfin In Photodynamic Therapy Trial confirms the low potential for unwanted photosensitivity reactions and suggests that a photosensitivity protection period of 24 to 48 hours was adequate in both the Treatment of Age-related Macular Degeneration With Photodynamic Therapy Investigation and the Verteporfin In Photodynamic Therapy Trial to avoid adverse photosensitivity events, although some regulatory authorities have recommended a protection period of 5 days. Injection site adverse events also were numerically lower in the Verteporfin In Photodynamic Therapy Trial (8% in verteporfin-treated patients and 5% in placebo-treated patients) compared with the Treatment of Age-related Macular Degeneration With Photodynamic Therapy Investigation (13% in verteporfin-treated patients and 3% in placebo-treated patients[3]). This lower rate suggests that some of these events may have been avoided by increased attention to strict infusion procedures in the Verteporfin In Photodynamic Therapy Trial based on knowledge of adverse events that occurred in the Treatment of Age-related Macular Degeneration With Photodynamic Therapy Investigation, including use of antecubital veins and avoidance of hand veins whenever possible.

CONCLUSIONS

BASED ON THESE RESULTS, THE VERTEPORFIN IN PHOTODYnamic Therapy Study Group currently recommends that verteporfin therapy should be considered in the management of patients with age-related macular degeneration with subfoveal lesions composed of occult with no classic choroidal neovascularization who are presumed to have had recent disease progression as defined in the Verteporfin In Photodynamic Therapy Trial. Ophthalmologists should consider the following: 1) verteporfin therapy will significantly reduce a patient's risk of moderate or severe visual acuity loss by the month 24 examination; 2) although a treatment benefit was established for the entire group of lesions enrolled with occult with no classic choroidal neovascularization, patients presenting with *either* smaller lesions (4 disc areas or less), regardless of initial visual acuity, *or* lower levels of visual acuity (letter score less than 65, an approximate Snellen equivalent of $20/50^{-1}$ or worse), regardless of initial lesion size, appeared to have a greater benefit; 3) additional exploratory subgroup analyses of patients with occult with no classic choroidal neovascularization on presentation, which must be interpreted with caution, suggested that verteporfin therapy, as applied in this trial, may not be beneficial for patients presenting with *both* larger lesions (greater than 4 disc areas) *and* higher levels of visual acuity (letter score 65 or greater, an

approximate Snellen equivalent of 20/50 or better); and 4) initial treatment was associated with a small (4%) risk of acute, severe vision decrease with partial recovery in some patients.

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