Photodynamic Therapy of Subfoveal Choroidal Neovascularization in Pathologic Myopia with Verteporfin

1-Year Results of a Randomized Clinical Trial—VIP Report No. 1

Verteporfin in Photodynamic Therapy (VIP) Study Group

Objective: To determine if photodynamic therapy with verteporfin (Visudyne; CIBA Vision Corp, Duluth, GA) can improve the chance of stabilizing or improving vision (<8 letter loss) safely in patients with subfoveal choroidal neovascularization (CNV) caused by pathologic myopia.

Design: Multicenter, double-masked, placebo-controlled, randomized clinical trial at 28 ophthalmology practices in Europe and North America.

Participants: One hundred twenty patients with subfoveal CNV caused by pathologic myopia with a greatest linear dimension no more than 5400 μm and best-corrected visual acuity (Snellen equivalent) of approximately 20/100 or better.

Intervention: Patients were randomly assigned (2:1) to verteporfin (6 mg per square meter of body surface area; n = 81) or placebo (5% dextrose in water; n = 39) administered via intravenous infusion of 30 ml over 10 minutes. Fifteen minutes after the start of the infusion, a laser light at 689 nm was delivered at an intensity of 600 mW/cm^2 over 83 seconds to give a light dose of 50 J/cm^2 to a round spot size on the retina with a diameter of 1000 μm larger than the greatest linear dimension of the choroidal neovascular lesion. At follow-up examinations every 3 months, retreatment with either verteporfin or placebo (as assigned at baseline) was applied to areas of fluorescein leakage if present.

Main Outcome Measures: The primary outcome was the proportion of eyes at the follow-up examination 12 months after study entry with fewer than eight letters (approximately 1.5 lines) of visual acuity lost, adhering to an intent-to-treat analysis.

Results: At baseline, more than 90% of each group had evidence of classic CNV (regardless of whether occult CNV was present) and only 12 (15%) and 5 (13%) cases in the verteporfin and placebo groups, respectively, had occult CNV (regardless of whether classic CNV was present). Seventy-nine of the 81 verteporfin-treated patients (98%) compared with 36 of the 39 placebo-treated patients (92%) completed the month 12 examination. Visual acuity, contrast sensitivity, and fluorescein angiographic outcomes were better in the verteporfin-treated eyes than in the placebo-treated eyes at every follow-up examination through the month 12 examination. At the month 12 examination, 58 (72%) of the verteporfin-treated patients compared with 17 (44%) of the placebo-treated patients lost fewer than eight letters ($P < 0.01$), including 26 (32%) versus 6 (15%) improving at least five letters (≥1 line). Seventy (86%) of the verteporfin-treated patients compared with 26 (67%) of the placebo-treated patients lost fewer than 15 letters ($P = 0.01$). Few ocular or other systemic adverse events were associated with verteporfin therapy compared with placebo treatment.

Conclusions: Because photodynamic therapy with verteporfin can safely increase the chance of stabilizing or improving vision in patients with subfoveal CNV from pathologic myopia compared with a placebo, we recommend ophthalmologists consider verteporfin therapy for treatment of such patients. *Ophthalmology 2001; 108:841–852 © 2001 by the American Academy of Ophthalmology.*

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A complete list of the participants in the Verteporfin In Photodynamic Therapy Study Group, followed by financial interest statements, is available in the Appendix.

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Pathologic myopia has been reported to be a major cause of blindness in the United States.[1] Many of these cases of vision loss are the result of the development of choroidal neovascularization (CNV).[2] Laser photocoagulation may not be a useful treatment for subfoveal CNV in pathologic myopia, because the vision loss from subfoveal photocoagulation is likely to outweigh any treatment benefit. For CNV that does not extend under the center of the foveal avascular zone, case series[3] and clinical trials[4] have suggested that laser photocoagulation of these lesions may reduce the risk of vision loss by preventing the lesion from extending under the center of the macula, thereby reducing the chance of additional vision loss. This beneficial effect may be lost within 1 or 2 years after the subsequent development of recurrent CNV[4] or the progressive enlargement of atrophy of the retinal pigment epithelium surrounding the laser-treated area,[5] which can extend under the center of the foveal avascular zone and cause additional loss of central vision. Although, to our knowledge, there are no prospective studies before this investigation describing the natural history of subfoveal CNV resulting from pathologic myopia, the natural history of lesions that extend near, but not under, the center of the macula has been reported to be poor.[4]

Photodynamic therapy with verteporfin (Visudyne; CIBA Vision Corp, Duluth, GA) caused short-term (1–4 week) cessation of fluorescein leakage from CNV resulting from pathologic myopia without damage to retinal blood vessels apparent on fluorescein angiography or loss of vision in phase 1 and 2 investigations of 13 patients, even after multiple treatments.[6] Subsequently, approximately 6 months of additional experience with verteporfin therapy in which no serious safety problems were encountered became available from randomized clinical trials evaluating the role of verteporfin therapy for selected cases of subfoveal CNV resulting from age-related macular degeneration (AMD).[7] Based on these investigations, a randomized clinical trial, called the Verteporfin in Photodynamic Therapy (VIP) Trial, was initiated in Europe and North America. One part of the VIP Trial was to determine if verteporfin therapy could stabilize or improve vision in people with subfoveal CNV caused by pathologic myopia. This article describes effects of verteporfin therapy compared with placebo therapy on all study visits through the month 12 examination, which was completed for all patients with pathologic myopia participating in the VIP Trial as of October 7, 1999.

Methods

The Clinical Study Protocol BPD OCR 003 (originally dated December 19, 1997) and four protocol amendments through February 10, 2000 are on file with regulatory agencies in the United States, Canada, and Europe. The key aspects of the protocol are described below. Before patient enrollment at a center, the design was reviewed by three groups functioning independently of the study sponsors. These groups included a study advisory group (members of the VIP Study Group who advise the study sponsors of the scientific aspects of the investigation organized in a manner similar to the Treatment of Age-Related Macular Degeneration with Photodynamic Therapy [TAP] Study Group[7]), the institutional review board of the participating clinical center, and a data and safety monitoring committee (identical in personnel and operations to the TAP Data and Safety Monitoring Committee[7]), which functioned independently of the study sponsors and the VIP Study Group. Certification of all clinical center study personnel was the same as procedures in the TAP Investigation, as was photographic grading, clinic monitoring, Study Advisory Group work, Operations Committee work, and biannual safety reviews by the Data and Safety Monitoring Committee occurring after initiation of enrollment.[7]

Patient Selection and Entry Evaluations

Patients were enrolled from February 1998 through September 1998, when the target sample size was attained. Vision testing, color photographs, stereoscopic fluorescein angiographs, medical histories, and ocular examinations were completed within 7 days before patients were randomly assigned to treatment in the trial.

Patient Selection. Patients had to fulfill eligibility criteria determined by an ophthalmologist certified to enroll and treat study participants. The primary criteria included a best-corrected visual acuity score (as measured in previous trials[7]) of at least 50 (Snellen equivalent approximately 20/100 or better), and are shown in Table 1. Pathologic myopia was defined as an eye requiring a distance correction of at least −6.0 diopters (D; spherical equivalent). An eye that had a spherical equivalent that was less myopic than −6.0 D was eligible if there were retinal abnormalities consistent with pathologic myopia (such as lacquer cracks) and if the axial length of the eye was at least 26.5 mm.

Fluorescein angiographic criteria, using definitions previously described,[7,8] included evidence of fluorescein leakage from CNV, presumably caused by pathologic myopia in which the CNV extended under the center of the foveal avascular zone. The lesion did not have to have evidence of classic CNV; the lesion could have classic CNV without occult CNV, classic and occult CNV, or occult CNV without classic CNV. The lesion also could include other features that obscured the identification of classic or occult CNV 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, that is, the area of any classic CNV plus any occult CNV had to occupy at least 50% of the area of the entire lesion. The greatest linear dimension of the entire lesion had to be 5400 μm or less on the retina. Patients were to be excluded if they had other potential causes of CNV (such as AMD or multifocal choroiditis) documented on color fundus photographs or fluorescein angiograms.

The Verteporfin in Photodynamic Therapy Trial Design. Study patients could be recruited from 28 clinical centers. The VIP Trial design included patients with pathologic myopia for this report, as well as a study (not part of this report but submitted for publication separately) of patients with subfoveal CNV caused by AMD with criteria that were not included in the TAP Investigation. The protocol stipulated that VIP Trial patients with pathologic myopia were to be randomized and analyzed separately from VIP Trial patients enrolled with CNV lesions from AMD.

Vision Testing, Photographs, Other Medical Aspects, and Study Entry. Vision testing, stereoscopic color fundus photographs, film-based stereoscopic fluorescein angiograms (including late-phase frames at 5 and 10 minutes after fluorescein injection), and other medical aspects were the same as procedures followed in the TAP Investigation.[7] 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 VIP-certified enrolling ophthalmologist to satisfy all

Table 1. Principal Eligibility Criteria for the Verteporfin in Photodynamic Therapy Trial of Pathologic Myopia

Inclusion criteria
Choroidal neovascularization secondary to pathologic myopia (distance correction of at least −6.0 diopters [D], spherical equivalent, or less myopic than −6.0 D with retinal abnormalities consistent with pathologic myopia, such as lacquer cracks, and an axial length at least 26.5 mm)
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 more than 5400 μm (not including any area of prior laser photocoagulation)
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 pathologic myopia (such as large drusen or multifocal choroiditis) 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
Pregnancy

eligibility criteria were assigned randomly to placebo or verteporfin infusion.

Random Assignments

Random assignments were prepared by Statprobe (Ann Arbor, MI). Statprobe also prepared sealed envelopes with random assignments and distributed them to the clinical centers. Patients were randomized in a ratio of 2:1 to verteporfin treatment or placebo (to gather more safety data on patients receiving verteporfin), with only one eye of a patient to be randomized. For cases in which an enrolling ophthalmologist believed that both eyes of a patient were eligible, the patient and ophthalmologist chose which eye would be enrolled in the study. Randomization was stratified by clinical center. Separate groups of color-coded envelopes were used to distinguish patients participating in the VIP Trial with pathologic myopia from those with AMD. A study coordinator was instructed to open the sealed envelope only after a patient was judged to meet all of the eligibility criteria and only after the enrolling ophthalmologist and the patient agreed to the patient's participation in the trial. Treatment was to begin the same day that the treatment assignment was revealed by opening the envelope.

Masking

Masking was carried out in a manner identical to procedures followed in the TAP Investigation.[7] All patients were to remain masked until all of them had completed the month 24 examination and the data collection and entry was completed.

Verteporfin Therapy, Placebo Therapy, Patient Follow-up, and Fluorescein Angiographic Assessment at Follow-up

Verteporfin therapy, placebo therapy, and patient follow-up were performed in all clinical centers according to the standard protocol followed in the TAP Investigation.[7] If the treating ophthalmologist noted any leakage from classic or occult CNV in the study eye on a fluorescein angiogram taken at a regularly scheduled follow-up visit every 3 months, retreatment with verteporfin or placebo (as assigned at the baseline examination) was recommended to the patient through 21 months of follow-up.[7] Fluorescein angiographic assessment at follow-up was graded at the Photograph Reading Center in a masked fashion as described for the TAP Investigation,[7] but was scheduled only at the month 12 and month 24 examinations. Follow-up photographs from other visits were graded at the Reading Center only if the month 12 visit was missed (in which case, the most recently obtained visit photographs were assessed) or if an adverse event was noted on visual acuity measurement or was within the posterior pole at other study visits.

Statistical Methods

Sample Size Estimation. It was estimated that 50% of the placebo-treated patients and 80% of the verteporfin-treated patients would lose fewer than eight letters by the month 12 examination. This difference was judged to be clinically relevant and achievable under this study design. To detect this difference statistically with 90% power using a chi-square test, a total sample size of 113 patients would be required for the analysis at the month 12 examination. This assumed a 2:1 randomization (75 patients to receive verteporfin and 38 patients to receive placebo) and a two-sided significance level of 0.05.

Outcome Measurements. The primary efficacy outcome was the proportion of eyes that had fewer than eight letters lost (approximately <1.5 lines of visual acuity loss, corresponding to less than a 1.5-times increase of the visual angle) at 1 year after study entry compared with the baseline examination. This outcome specifically was different from the primary outcome in the TAP Investigation (<15 letters or <3 lines of visual acuity loss[7]) because it was expected that eyes with subfoveal CNV from pathologic myopia were likely to lose less vision than eyes with subfoveal CNV from AMD. Secondary efficacy outcomes included the proportion of eyes that had fewer than 15 or 30 letters lost (approximately <3 or <6 lines of visual acuity loss) at the month 12 examination compared with the baseline examination, mean changes in visual acuity, proportion of eyes with a letter score less than 34 (≤20/200 Snellen equivalent) at the month 12 examination, mean changes in contrast threshold, and angio-

graphic outcomes (progression of classic CNV and size of lesion) at the month 12 examination. *P* values for secondary outcomes were not adjusted for multiple comparisons.

Statistical Analysis. 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 120 randomized patients were included in the primary efficacy analyses. Demographic and baseline characteristics were summarized and tested for treatment group comparability using a Fisher's exact test for categorical variables[9] and a Wilcoxon rank-sum test for continuous variables.[10] The proportions of eyes that lost fewer than 8 or 15 letters from baseline to 1 year were analyzed using a Pearson chi-square test.[9] The distributions of changes in visual acuity from baseline, visual acuity categories, and changes in contrast sensitivity from baseline were compared between groups using a Wilcoxon rank-sum test. Assessments of fluorescein leakage were compared between groups using a Pearson chi-square test. The intent-to-treat analysis included all patients who were randomized; missing values were imputed using the method of last observation carried forward.

To confirm the results of the analyses of the primary and main secondary efficacy variables (specifically, the proportion of responders or eyes losing fewer than 8 letters and fewer than 15 letters of visual acuity from baseline) at the month 12 examination, logistic regression methods were used.[11] A set of explanatory variables were evaluated in logistic models to examine their possible effect on the proportion of responders, as well as to adjust for possible imbalance of baseline characteristics between treatment groups. Variables included in the models consisted of the following: treatment group; baseline visual acuity letter score (treatment group [$\geq$60, $<$60]); patient age; greatest linear dimension (μm); location of lesion (definitely subfoveal, not definitely subfoveal); presence of blood (yes, no); gender; and the interactions between treatment and each of these variables.

A forward selection procedure was used to include terms sequentially in the model and eliminate them if nonsignificant (defined as $P > 0.10$). Variables and their interactions with treatment were entered into the model in the order listed above. Sequentially, a main effect entered the model and was evaluated for statistical significance. The main effect then remained in the model in the next step, and its interaction with treatment was included. Main effects then were removed if nonsignificant and if the interaction term for that effect also was nonsignificant. Odds ratios and their 95% confidence intervals (CI) were also calculated for the treatment effect as well as for any significant effects in the final logistic model.

Data Monitoring and Reporting

Data monitoring was performed by the same Data and Safety Monitoring Committee as in the TAP Investigation.[7] No prospectively defined stopping rules were used. The only major protocol deviation was one patient who had dyspnea and flushing during the initial infusion; the infusion was stopped and light treatment was not applied. The randomization code was not broken for any patient through the month 12 examination. No safety concerns were voiced by the committee at its reviews of the VIP Trial for pathologic myopia patients on January 28, 1999 and August 9, 1999. On March 22, 2000, 12-month data analyzed by the sponsors were reviewed 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 via a news release from the sponsors on March 27, 2000. The data on which this public announcement were based were reviewed by the VIP Study Advisory Group and the VIP Study Group on April 15, 2000 and are presented in this report.

Results

One hundred twenty eyes in 120 patients were assigned randomly to verteporfin therapy (81 eyes) or placebo treatment (39 eyes) at 26 of the 28 clinical centers (two centers did not enroll any patients with pathologic myopia into the VIP Trial). The baseline characteristics for these participants were balanced (Table 2) with the following exceptions: more women were assigned to verteporfin therapy, more patients assigned to placebo had blood as a lesion component in the study eye, and the median age of patients assigned to verteporfin was older. Sixty-nine of the 81 eyes (85%) in the verteporfin-treated group and 31 of the 39 eyes (79%) in the placebo-treated group had a predominantly classic lesion with evidence of classic CNV that was at least 50% of the entire lesion. Only 12 eyes (15%) of the verteporfin-treated group and 5 eyes (13%) of the placebo-treated group had evidence of any occult CNV at the baseline examination. Only four CNV lesions (5%) in the verteporfin-treated group and 4 (10%) in the placebo group were more than three disc areas in size at baseline. The median greatest linear dimension of the lesion was 1900 μm in the verteporfin-treated group and 1840 μm in the placebo-treated group ($P = 0.65$).

Seventy-nine of the 81 patients (98%) in the verteporfin-treated group compared with 36 of the 39 patients (92%) in the placebo-treated group completed the month 12 examination (Fig 1). At the month 12 examination, 46 (57%) and 20 (51%) of the verteporfin- and placebo-treated groups, respectively, received retreatment (Fig 1); 2 (2%) of the verteporfin patients and 3 (8%) of the placebo patients who did not return for follow-up examination at that visit were counted as not receiving retreatment. Of a maximum of four possible treatments, an average of 3.4 treatments compared with 3.2 treatments were given to the patients treated with verteporfin or placebo, respectively, by the month 12 examination (including treatment at baseline but not including any treatment given at the month 12 examination).

Vision Outcomes

For the primary outcome, beginning with the month 3 examination through the month 12 examination, the visual acuity of the verteporfin-treated group had a greater chance of remaining stable (losing $<$8 letters) compared with the placebo-treated group (Fig 2). At the month 3 examination, 62 eyes (77%) of the verteporfin-treated group compared with 22 eyes (56%) of the placebo-treated group ($P = 0.02$) lost fewer than eight letters, a 21% absolute difference. By the month 12 examination, this difference increased to 28% when 58 eyes (72%) of the verteporfin-treated group compared with 17 eyes (44%) of the placebo-treated group lost fewer than eight letters ($P < 0.01$). The change in visual acuity from baseline at the month 3 and month 12 examinations is shown in Table 3. Beneficial effects of verteporfin therapy compared with placebo treatment with respect to the distribution of changes in visual acuity were noted starting with the month 3 examination ($P = 0.01$) and persisting at the month 12 examination ($P < 0.01$). The eyes in the verteporfin-treated group also were less likely to have at least moderate visual acuity loss ($\geq$15 letters or $\geq$3 lines; Fig 3); at the month 12 examination, this event occurred only in 11 eyes (14%) of the verteporfin-treated group compared with 13 eyes (33%) of the placebo-treated group ($P = 0.01$). Severe visual acuity loss ($\geq$30 letters or $\geq$6 lines) occurred in six

Table 2. Baseline Characteristics by Treatment Group*

Characteristic	Verteporfin, No. (%)	Placebo, No. (%)	P†
Patients	81 (100)	39 (100)	—
Gender			
Women	57 (70)	23 (59)	0.22
Men	24 (30)	16 (41)	
Race			
White	74 (91)	36 (92)	1.00
Asian	3 (4)	2 (5)	
Hispanic	4 (5)	1 (3)	
Age (yrs)			
<30	4 (5)	1 (3)	
30–49	32 (40)	22 (56)	
50–64	33 (41)	12 (31)	
≥65	12 (15)	4 (10)	
Median	51	46	0.06
Definite hypertension‡	14 (17)	9 (23)	0.47
Letter score (approximate visual acuity Snellen equivalent§) in study eye			
≥70 (≥20/40)	13 (16)	6 (15)	
69–50 (20/40–20/100)	68 (84)	31 (80)	
<50 (<20/100)	0 (0)	2 (5)	
Median	62 (20/64+2)	58 (20/64−2)	0.07
Letter score (approximate visual acuity Snellen equivalent§) in fellow eye			
≥70 (≥20/40)	41 (51)	21 (54)	
69–50 (20/40–20/100)	15 (19)	2 (5)	
<50 (<20/100)	25 (31)	16 (41)	
Median	70 (20/40)	75 (20/32)	0.86
Median study eye contrast sensitivity			
No. of letters¶	28	30	0.05
Micronutrient supplement use	30 (37)	16 (41)	0.69
Smoking history			
Never	43 (53)	26 (67)	0.39
Previous	23 (28)	7 (18)	
Current	15 (19)	6 (15)	
Lesion area composed of CNV (%)			
≥50	77 (95)	35 (90)	0.47
<50	2 (2)	2 (5)	
No CNV or can't grade	2 (2)	2 (5)	
CNV location			
Subfoveal	50 (62)	27 (69)	0.81
Probably subfoveal	15 (19)	7 (18)	
Not subfoveal	11 (14)	3 (8)	
No CNV or cannot grade‖	5 (6)	2 (5)	
Lesion area composed of classic CNV (%)			
≥50	69 (85)	31 (79)	0.58
<50–>0	9 (11)	5 (13)	
0	1 (1)	2 (5)	
Cannot grade	2 (2)	1 (3)	
Evidence of occult CNV			
Yes	12 (15)	5 (13)	1.000
No	67 (83)	33 (85)	
Cannot grade	2 (2)	1 (3)	
Evidence of prior laser photocoagulation	7 (9)	4 (10)	0.75
Lesion included blood			
Yes	37 (46)	28 (72)	0.01
No	42 (52)	11 (28)	
Cannot grade	2 (2)	0 (0)	
Lesion included hypofluorescence not caused by visible blood			
Yes	48 (59)	20 (51)	0.74
No	31 (38)	18 (46)	
Cannot grade	2 (2)	1 (3)	
Area of lesion (MPS disc areas)			
No CNV lesion‖	1 (1)	0 (0)	0.29
≤1	51 (63)	22 (56)	
>1–≤2	14 (17)	9 (23)	
>2–≤3	9 (11)	3 (8)	
>3	4 (5)	4 (10)	
Cannot grade or no lesion	2 (2.5)	1 (3)	

(*continues*)

Table 2. (*continued*)

Characteristic	Verteporfin, No. (%)	Placebo, No. (%)	P†
Greatest linear dimension of lesion (μm)			
Median	1900	1840	0.65
Range	480–4120	348–4680	
Cannot grade or no lesion	4 (5)	2 (5)	

CNV = choroidal neovascularization; MPS = Macular Photocoagulation Study.

*Percentages may not always add up to 100 because of rounding.

†Fisher exact test for categoric variables. Wilcoxon rank sum test for continuous variables.

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

§Approximate Snellen equivalent.

¶Contrast sensitivity testing was not performed in eight patients assigned to verteporfin and in three patients assigned to placebo.

‖No CNV indicates fluorescein staining of fibrovascular lesion from CNV but no fluorescein leakage.

verteporfin-treated patients (7%) compared with three placebo-treated patients (8%) at the month 12 examination.

Although the visual acuity of most patients did not improve, verteporfin therapy did increase a person's chance of improved visual acuity compared with placebo. Specifically, at the month 12 examination, the verteporfin-treated group was approximately twice as likely to have improvement of at least five letters (one line) in visual acuity with 26 eyes (32%) of this group compared with 6 eyes (15%) of the placebo-treated group. Large improvements of visual acuity (at least 15 letters or 3 lines) were rare, with 5 cases (6%) in the verteporfin-treated group compared with 1 case (3%) in the placebo-treated group. The median change in visual acuity differed by 10 letters (Snellen equivalent of approximately two lines) at the month 12 examination when the verteporfin-treated group gained 1 letter (0.2 lines) compared with the placebo group, which lost 9 letters (−1.8 lines).

The level of visual acuity at the month 3 and month 12 examinations is shown in Table 4. Although both groups had a similar median visual acuity at baseline (approximate Snellen equivalent of 20/64+2 for the verteporfin-treated group compared with 20/64−2 for the placebo-treated group), the median visual acuity did not change from baseline for the verteporfin-treated group, but decreased to 20/80−2 for the placebo-treated group at the month 12 examination. The number of eyes with a letter score <34 (≤20/200 Snellen equivalent) at the month 12 examination was 5 (6%) versus 7 (18%) for verteporfin-treated and placebo-treated patients, respectively ($P = 0.04$).

The mean contrast sensitivity scores were relatively unchanged in each group (Fig 4), although the verteporfin-treated group were better at each 3-month examination over time. Specifically, the mean change in number of contrast sensitivity letters read at the month 12 examination was −0.1 letters versus −2 letters for cases assigned to verteporfin or placebo, respectively. Furthermore, the verteporfin-treated group had a greater chance of improving at least three letters (at least one segment) at the month 12 examination, when 21 (29%) of the verteporfin-treated group compared with 3 (9%) of the placebo-treated group showed this amount of improvement (Table 5).

The results of the logistic regression analysis confirmed the

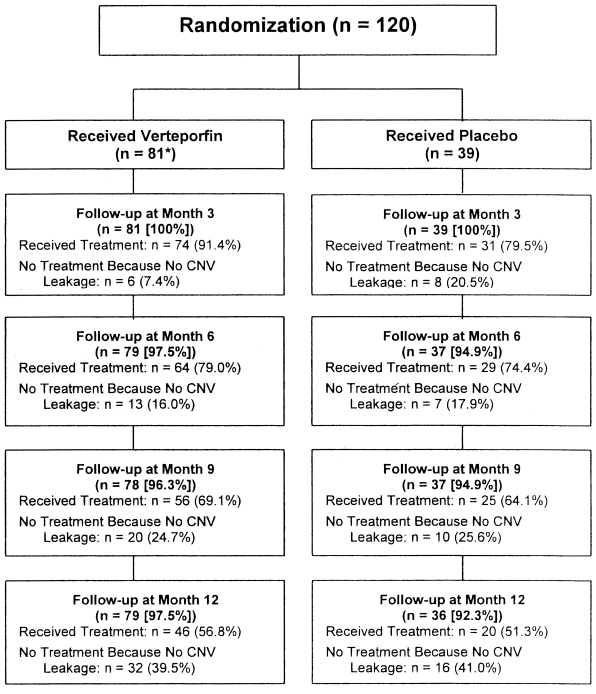

Figure 1. Profile of participants randomized, receiving treatment, and completing follow-up (at least a protocol visual acuity assessment) through the month 12 examination. One patient given verteporfin at the first visit was not given the light application because of an allergic reaction judged to be possibly related to the drug (although attributed to a concomitant medication, not verteporfin, at subsequent follow-up examinations).

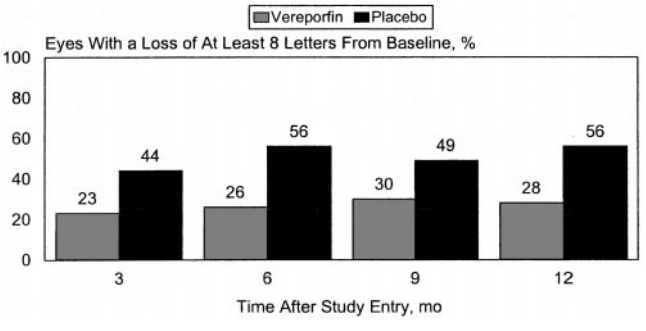

Figure 2. Percent of eyes treated with verteporfin or given placebo with at least an eight-letter (approximately 1.5-line) loss at each 3-month visit over time.

Table 3. Frequency Distribution of Changes in Visual Acuity from Baseline by Treatment and Visit

	No. (%) of Patients			
	3-month Follow-up		*12-month Follow-up*	
Change in Visual Acuity*	*Verteporfin (n = 81)*	*Placebo (n = 39)*	*Verteporfin (n = 81)*	*Placebo (n = 39)*
≥6-line increase	0 (0)	0 (0)	0 (0)	0 (0)
≥3-line to <6-line increase	2 (2)	0 (0)	5 (6)	1 (3)
≥1-line to <3-line increase	19 (23)	8 (21)	21 (26)	5 (13)
No change	33 (41)	10 (26)	24 (30)	11 (28)
≥1-line to <3-line decrease	22 (27)	13 (33)	20 (25)	9 (23)
≥3-line to <6-line decrease	5 (6)	7 (18)	5 (6)	10 (26)
≥6-line decrease	0 (0)	1 (3)	6 (7)	3 (8)
	$P = 0.01^{\dagger}$		$P < 0.01^{\dagger}$	
Median (lines)	0.0	−1.0	+0.2	−1.8

*Values are approximate; there are five letters per line.

†Wilcoxon rank sum test; the verteporfin-treated group had the better outcome.

results observed for the analysis of the primary and main secondary efficacy variables at the month 12 examination. Using a forward selection procedure, all interaction terms with treatment were found not to be significant. The final logistic regression model for both the fewer than 8-letter loss and fewer than 15-letter loss included only treatment ($P < 0.01$ for both) and age ($P = 0.03$ and 0.05, respectively). The treatment odds ratios for the fewer than 8-letter loss and fewer than 15 letter loss were 4.00 (95% CI, 1.71–9.35) and 3.88 (95% CI, 1.47–10.28), respectively. In addition, the odds ratio for a 10-year increase in the variable age (e.g., 50–60 or 60–70 years) was 0.67 (95% CI. 0.50–0.97) for a fewer than eight-letter loss and 0.69 (95% CI, 0.47–1.01) for a fewer than 15-letter loss.

Fluorescein Angiographic Outcomes

Progression of classic CNV beyond the area of the lesion identified at baseline at the month 12 examination occurred in 29 of 81 patients (36%) in the verteporfin-treated group compared with 21 of 39 patients (54%) in the placebo-treated group. Fluorescein leakage was absent from classic CNV in 27 of the 78 verteporfin-treated patients (35%) compared with 10 of the 36 placebo-treated patients (28%) by the month 12 examination for those who had classic CNV at the baseline examination (for example, as in Fig 5). The lesion size at the month 12 examination, as shown in Fig 6, indicated that verteporfin-treated cases were approximately twice as likely to be no more than one disc area in size than placebo-treated cases (58% for verteporfin-treated cases vs. 28% for placebo-treated cases), whereas the placebo-treated cases were 5.5 times more likely to be more than three disc areas in size (28% for placebo-treated cases vs. 5% for verteporfin-treated cases). Although the mean greatest linear dimension of gradable lesions in the verteporfin- and placebo-treated groups was similar at baseline (2012 μm vs. 1995 μm), at the month 12 examination the mean of the greatest linear dimension of CNV leakage decreased to 1865 μm in the verteporfin-treated group compared with an increase to 3085 μm in the placebo-treated group ($P < 0.01$). There were too few cases with occult CNV to evaluate the impact of verteporfin therapy on this component of the lesion or on patients whose lesions included this component.

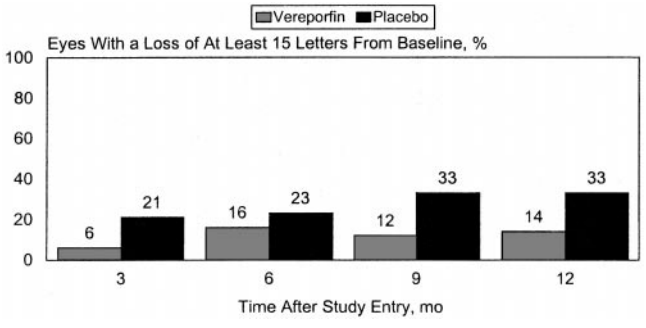

Figure 3. Percent of eyes treated with verteporfin or given placebo with at least a 15-letter (approximately three-line) loss at each 3-month visit over time.

Safety

An adverse event (regardless of relationship to treatment) was reported in 50 of the patients in the verteporfin-treated group (62%) and 24 of the patients in the placebo-treated group (62%). Adverse events judged to be clinically relevant from experience with the TAP Investigation[7] are listed in Table 6. Visual disturbances were reported in 17 of the verteporfin-treated patients (21%) compared with 8 of the placebo-treated patients (21%). There were no retinal vascular occlusive events. Photosensitivity reactions were reported in 3 of 81 verteporfin-treated patients (4%) compared with 1 of 39 placebo-treated patients (3%). Six of 81 verteporfin-treated patients (7%) and 2 of 39 placebo-treated patients (5%) had an injection-site event. Unlike in the TAP Investigation,[7] there were no instances of any patients reporting severe vision decrease within a few days after a treatment, no infusion-related back pain events, and no deaths in either group. Treatment was stopped because of an adverse event that the treating ophthalmologist judged could have been related to study treatment in only 1 of the 81 verteporfin-treated patients (1%). Two minutes into the infusion, the patient reported dyspnea and became flushed without itching. The infusion was stopped, and intravenous corticosteroid and antihistamine were administered. The dyspnea resolved within minutes; the flushing resolved later that day. With respect to potential ocular adverse events evaluated on follow-up photographs, an increase in subretinal or intraretinal hemorrhage at the month 12 examination was less common in cases assigned to the verteporfin group compared with placebo-treated cases (15% vs. 26%).

Table 4. Visual Acuity Categories in Study Eyes by Treatment and Visit

Visual Acuity, Letter Score (Approximate Snellen Equivalent)	No. (%) of Patients			
	3-month Follow-up		*12-month Follow-up*	
	Verteporfin (n = 81)	*Placebo (n = 39)*	*Verteporfin (n = 81)*	*Placebo (n = 39)*
≥70 (≥20/40)	15 (19)	5 (13)	21 (26)	6 (15)
69–50 (<20/40–20/100)	56 (69)	17 (44)	40 (49)	14 (36)
49–40 (<20/100–20/160)	8 (10)	11 (28)	14 (17)	9 (23)
39–20 (<20/160–20/400)	2 (2)	6 (15)	3 (4)	9 (23)
<20 (<20/400)	0 (0.0)	0 (0.0)	3 (4)	1 (3)
	$P < 0.01$*		$P = 0.01$*	
Median	64 (20/50−1)	53 (20/80−2)	62 (20/64+2)	53 (20/80−2)

*Wilcoxon rank sum test; the verteporfin-treated group had the better outcome.

Discussion

This randomized clinical trial shows that verteporfin therapy can increase the chance of stabilizing or improving vision (<8-letter or <1.5-line loss) safely compared with placebo therapy for at least 1 year in patients with subfoveal CNV caused by pathologic myopia. With a median baseline visual acuity (Snellen equivalent) of approximately 20/64, few patients assigned to verteporfin or placebo had large improvements in visual acuity (≥15 letters or 3 lines). However, small improvements in visual acuity were more likely in verteporfin-treated cases (26 of 81; 32%) compared with patients given placebo (6 of 39; 15%), justifying the conclusion that verteporfin therapy not only increased the chance of maintaining baseline visual acuity for at least 1 year, but also increased the chance of improving vision. Few patients had severe visual acuity loss in either group at the month 12 examination. The visual acuity results were further supported by contrast sensitivity outcomes. In addition, fluorescein angiographic outcomes provided objective, anatomic support of the visual acuity results. These outcomes included findings that the verteporfin-treated patients compared with the placebo-treated patients were less likely to have progression of classic CNV, less likely to have any leakage from classic CNV, and more likely to have lesions of fewer than three disc areas at the month 12 examination. Verteporfin therapy was well tolerated, with few adverse events. The relatively stable vision outcomes at 1 year in the verteporfin-treated group suggest that photodynamic therapy with verteporfin causes little harm to visual function of the macula. The therapy appears to affect the CNV selectively.

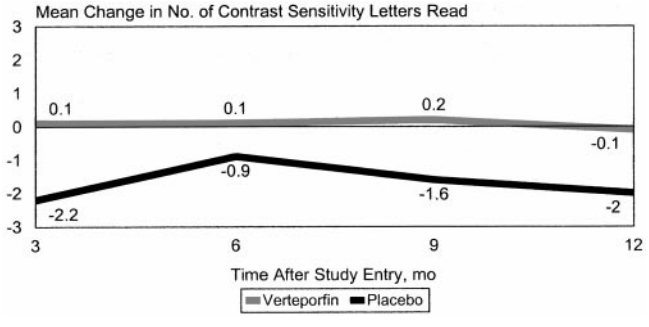

Figure 4. Mean number of letters of contrast sensitivity lost at each 3-month visit over time for eyes assigned to verteporfin therapy or placebo.

The treatment benefit is highly unlikely to be the result of chance because of the consistent results across two vision outcomes (visual acuity and contrast sensitivity), the statistically significant results, as well as confirmatory information on fluorescein angiography. Bias is highly unlikely given the masking of the patients, treating ophthalmologists, vision examiners, and photograph graders. Differences in the baseline characteristics of the treatment groups do not seem to weaken the confidence in the study results, as suggested by the final logistic regression analysis that adjusted for possible imbalance of baseline characteristics between treatment groups and found that only treatment was significant in the models. The odds ratio in the final logistic model was significant for a fewer than 8-letter loss ($P < 0.01$) and a fewer than 15-letter loss ($P = 0.01$). The treatment odds ratio for the fewer than 8-letter and fewer than 15-letter loss indicated that verteporfin patients were more likely to have these outcomes than placebo patients.

The use of the last observation carried forward method to

Table 5. Frequency Distribution of Changes in Contrast Sensitivity from Baseline by Treatment at the Month 12 Examination

Change in Contrast Sensitivity Score†	No. (%) of Patients*	
	Verteporfin (n = 73)	*Placebo (n = 34)*
≥3-segment increase	1 (1)	0 (0)
≥1-segment increase to <3-segment increase	20 (27)	3 (9)
No change	37 (51)	17 (50)
≥1-segment to <3-segment decrease	12 (16)	12 (35)
≥3-segment decrease	3 (4)	2 (6)
	$P = 0.02$‡	
Median	0.0	−1.5

*Contrast sensitivity was not performed in eight patients assigned to the verteporfin group and in five patients assigned to the placebo group.

†Values are approximate; there are three letters per segment.

‡Wilcoxon rank sum test; the verteporfin-treated group had the better outcome.

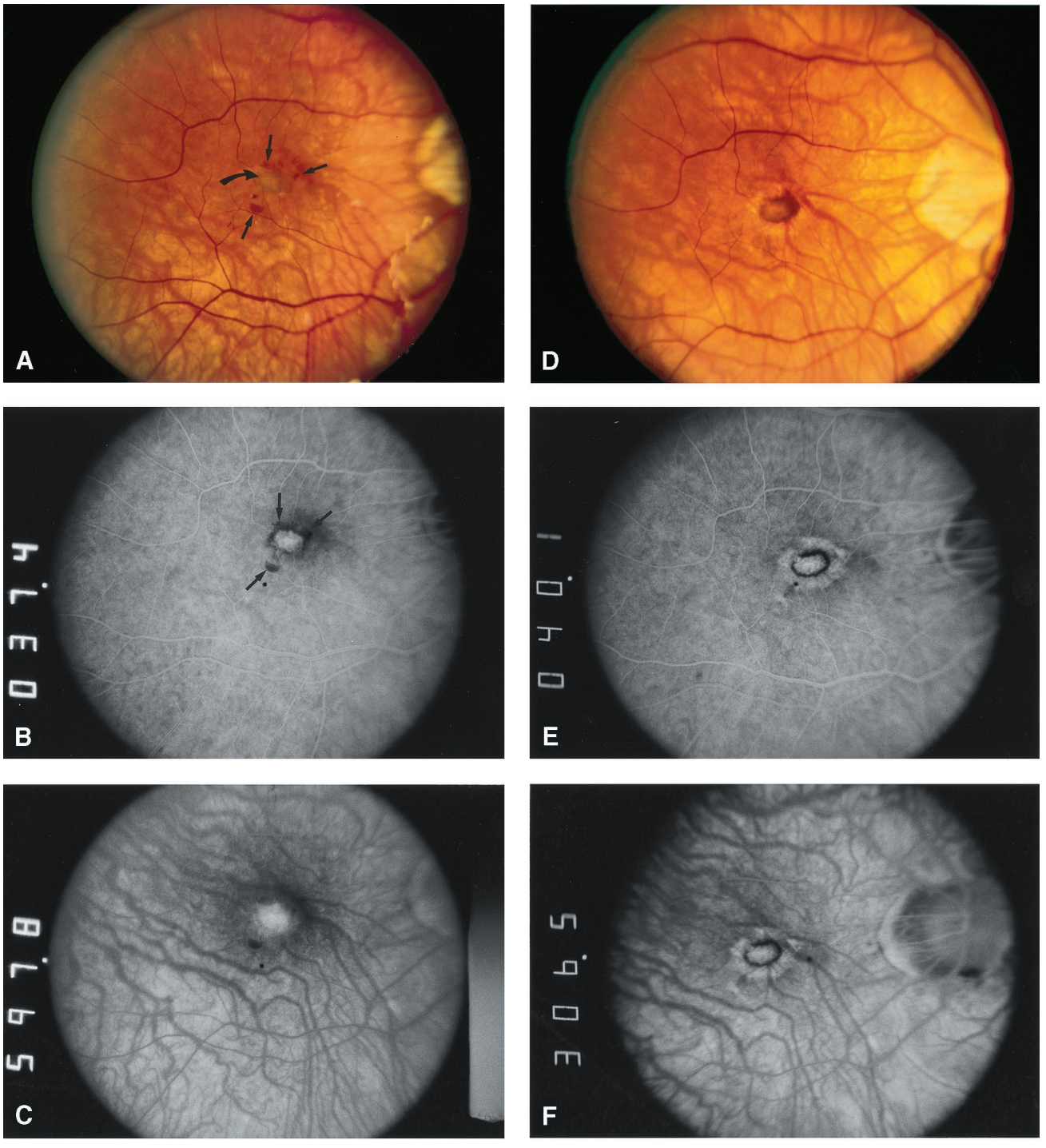

Figure 5. Example of verteporfin treatment of subfoveal choroidal neovascularization (CNV) resulting from pathologic myopia in which absence of classic CNV leakage with no progression beyond the area of the lesion identified at baseline was noted by the month 12 examination. The black dot in the center of each photograph is an artifact of a dot on the main delivery lens of the fundus camera, designed to remove reflections on the cornea, but appearing in focus when imaging highly myopic fundi. **A,** Color fundus photograph at baseline shows a right eye with pathologic myopia and subretinal hemorrhage (straight arrows) along the superior edge of a grayish-green lesion (curved arrow) with additional hemorrhage (straight arrow) inferior to this lesion. Baseline visual acuity letter score was 66 (Snellen equivalent, 20/50+1). **B,** Early-phase fluorescein angiogram shows a bright area of fluorescence extending under the center of the foveal avascular zone surrounded by hypofluorescence (straight arrows) corresponding to the hemorrhage seen on the color fundus photograph. **C,** Late-phase fluorescein angiogram at baseline shows leakage at the boundaries of hyperfluorescence noted in the early phase, representing classic CNV. The entire area of the lesion is less than one disc area. **D,** Color fundus photograph 12 months after initial treatment shows depigmentation of the retinal pigment epithelium (RPE) surrounding the lesion with a pigmented boundary and fibrous center. The visual acuity letter score changed from baseline to +1, 0, +12, and +9 for a Snellen equivalent of 20/32 at the month 12 examination; the contrast sensitivity score decreased by one letter at this visit; retreatment had been applied at the month 3 and 6 examinations but not at the month 9 or 12 examination. **E,** Early-phase fluorescein angiogram shows hyperfluorescence corresponding to depigmentation of the RPE on a color fundus photograph, surrounding the area of hypofluorescence corresponding to the pigmented boundary on the color fundus photograph, which in turn surrounds an area of hyperfluorescence. **F,** Late-phase fluorescein angiogram shows staining of hyperfluorescent areas identified in the early-phase frame with no leakage from classic CNV either within the area of the lesion identified at baseline or beyond the boundaries of the lesion identified at baseline. The entire area of the lesion was still less than one disc area.

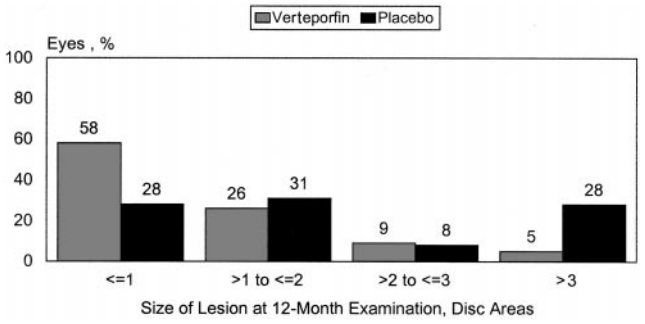

Figure 6. Distribution of lesion sizes at the month 12 examination for 81 eyes assigned to verteporfin treatment and 39 eyes assigned to placebo. One eye in each group had no lesion to grade at the month 12 examination.

account for missing data had little impact on the overall results, because the loss to follow-up was minimal in each group at the month 12 examination. When all of the main analyses were performed without the last observation carried forward, the same conclusions could be made (data not shown).

With the results reported here, verteporfin therapy has now been shown to have a significant treatment benefit for subfoveal CNV caused by pathologic myopia as well as for subfoveal CNV that is predominantly classic in AMD.[7] Of note, patients did not have to have classic CNV or a predominantly classic lesion to be eligible for the VIP Trial of pathologic myopia; nevertheless, most patients in this trial with pathologic myopia had a predominantly classic lesion. Although it is not known at this time whether the beneficial outcomes noted in this report will change with a longer follow-up period, the VIP Trial has been designed to obtain follow-up within the group to which the patient was assigned for up to 2 years. The VIP Study Group anticipates reporting the results of further analyses, including the second year of follow-up examinations, in subsequent reports. Maintaining these benefits in patients who develop subfoveal CNV resulting from pathologic myopia develops could have a significant impact on the quality of life of these patients for many years.

Conclusions

The significantly increased incidence of stable or improved visual acuity noted with verteporfin therapy in this investigation, coupled with the absence of any clinically significant risk of ocular or nonocular harm through 1 year of follow-up, leads us to recommend verteporfin therapy in the treatment of patients with subfoveal CNV caused by pathologic myopia.

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Verteporfin in Photodynamic (VIP) Therapy Study Group

Participating Clinics, Investigators (Principal Investigators are listed first), Clinic Coordinators, Vision Examiners, Photographers, Central Resource Groups, and Committees in the VIP Study Group as of April 15, 2000.

Table 6. Clinically Relevant Adverse Events Regardless of Relationship to Treatment

Event	Verteporfin (n = 81), No. (%)	Placebo (n = 39), No. (%)
Visual disturbance*	17 (21)	8 (21)
Injection site adverse events†	6 (7)	2 (5)
Infusion-related back pain	0 (0)	0 (0)
Allergic reactions	3 (4)	1 (3)
Photosensitivity reactions	3 (4)	1 (3)

*Includes reports in verteporfin-treated and placebo-treated eyes, respectively, of abnormal vision in seven cases (9%) and one case (3%), decreased vision in 11 cases (14%) and seven cases (18%), and visual field defect regardless of judgment of relationship to study treatment in three cases (4%) and two cases (5%).

†Includes edema (two patients treated with verteporfin [2%]), extravasation (one patient treated with verteporfin [1%], and one patient given placebo [3%]), hemorrhage (one patient treated with verteporfin [1%]), discoloration (one patient treated with verteporfin [1%]), inflammation (two patients treated with verteporfin [2%]), and injection-site pain (four patients treated with verteporfin [5%] and one patient given placebo [3%]).

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