Verteporfin Therapy of Subfoveal Choroidal Neovascularization in Patients With Age-Related Macular Degeneration

Additional Information Regarding Baseline Lesion Composition's Impact on Vision Outcomes—TAP Report No. 3

*Treatment of Age-Related Macular Degeneration With Photodynamic Therapy (TAP) Study Group**

Objective: To explore how baseline lesion composition influenced vision outcomes in patients with age-related macular degeneration (AMD) undergoing photodynamic therapy with verteporfin (Visudyne) for subfoveal choroidal neovascularization (CNV) in the Treatment of Age-Related Macular Degeneration With Photodynamic Therapy Investigation.

Methods: Patients with subfoveal lesions secondary to AMD with evidence of classic CNV were categorized into 2 subgroups based on baseline color photographs and fluorescein angiograms assessed by graders at the Wilmer Photograph Reading Center (The Johns Hopkins University School of Medicine) before any outcome analyses as follows: (1) predominantly classic CNV (area of classic CNV ≥50% of the area of the entire lesion) or (2) minimally classic CNV (area of classic CNV <50% but >0% of the area of the entire lesion). Additional exploratory analyses were performed in the predominantly classic subgroup to investigate the effects of visual acuity, lesion size, prior laser photocoagulation, phakic status, micronutrient use, and presence of occult CNV on vision outcomes.

Main Outcome Measures: Subgroup analyses of vision and fluorescein angiographic outcomes at 1 and 2 years after study enrollment were examined in an intent-to-treat analysis from 2 multicenter, double-masked, placebo-controlled, randomized clinical trials.

Results: Compared with patients who had minimally classic CNV, patients with predominantly classic CNV had a worse initial mean visual acuity and smaller lesions and were more likely to have lesions that included blood or blocked fluorescence. When evaluated by treatment assignment and lesion composition, 84% to 88% completed the month 24 examination. In the subgroup with predominantly classic lesions, visual acuity outcomes were consistently better in verteporfin-treated patients. Outcomes for patients with predominantly classic lesions without occult CNV tended to be better than outcomes for patients with predominantly classic lesions with occult CNV, although the former tended to have smaller lesions and lower levels of visual acuity at baseline. Contrast sensitivity and fluorescein angiographic outcomes (total lesion size, progression of classic CNV, and absence of classic CNV) were better in verteporfin-treated patients than in placebo-treated patients in the predominantly classic and the minimally classic CNV subgroups. In patients with predominantly classic CNV, no interaction of the treatment benefit by phakic status, micronutrient use, or prior laser photocoagulation therapy was noted.

Conclusions: Verteporfin therapy can safely reduce the risk of moderate and severe vision loss in patients with subfoveal lesions that are predominantly classic CNV secondary to AMD. While this benefit seemed to be even greater in the absence of occult CNV, the effect may be related to the smaller lesions and worse visual acuity associated with predominantly classic lesions without occult CNV and not solely to the lesion composition itself. These analyses support initial reports that verteporfin therapy should be used to treat patients with AMD who have predominantly classic CNV, with or without occult CNV, but suggest that further investigations should be performed to determine if lesions with a minimally classic composition might benefit when they are smaller and have lower levels of visual acuity.

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THE RESULTS from 2 multicenter, double-masked, placebo-controlled, randomized clinical trials,[1,2] the Treatment of Age-Related Macular Degeneration With Photodynamic Therapy (TAP) Investigation, demonstrated that verteporfin (Visudyne; Novartis Ophthalmics AG, Bülach, Switzerland) therapy reduces the risk of vision loss in patients with subfoveal choroidal neovascularization (CNV) secondary to age-related macular degeneration (AMD) as early as 3 months and continuing through at least 24 months. Patients enrolled in the TAP Investigation had to have some evidence of classic CNV, as determined by fluorescein angi-

**The names of the authors, as well as information on other members of the TAP Study Group, are listed at the end of the article.*

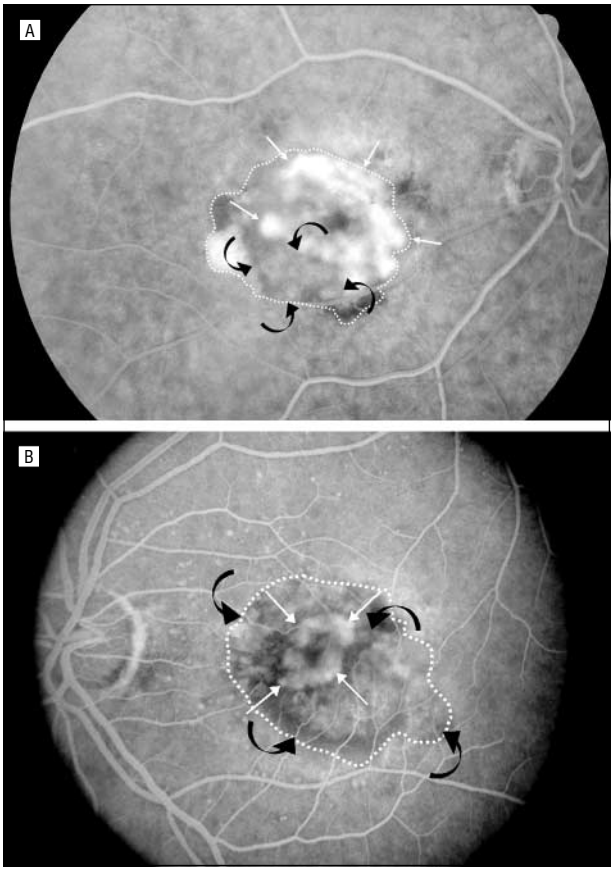

Figure 1. Early-phase fluorescein angiograms demonstrating predominantly classic choroidal neovascularization (CNV) (area of classic CNV ≥50% of the area of the entire lesion) (A) and minimally classic CNV (area of classic CNV <50% but >0% of the area of the entire lesion) (B). The broken line indicates the area of the entire lesion; straight arrows, the area of classic CNV; and curved arrows, the area of occult CNV.

ography, although the proportion of the lesion that was composed of classic CNV could range from a small area to the entire lesion.

Eyes that were judged by independent graders at the Wilmer Photograph Reading Center, The Johns Hopkins University School of Medicine, to have predominantly classic lesions (area of classic CNV ≥50% of the area of the entire lesion) at baseline (**Figure 1**A) had a greater visual acuity benefit through the month 24 examination compared with eyes with minimally classic lesions.[2] Based on this information, verteporfin therapy is recommended for the treatment of predominantly classic subfoveal lesions, with or without occult CNV, in patients with AMD. This report expands on TAP Reports 1[1] and 2[2] by comparing vision outcomes through 24 months in patients with lesions composed of predominantly classic CNV and those with lesions composed of minimally classic CNV (area of classic CNV <50% but >0% of the area of the entire lesion, as shown in Figure 1B) to provide greater detail for ophthalmologists regarding the risks and benefits of this therapy. Furthermore, the report explores what characteristics accompany these lesion compositions that might explain the different outcomes for these 2 lesion compositions reported in the TAP Investigation.

METHODS

The patients and methods for the TAP Investigation have been described previously.[1] In brief, patients were enrolled from December 11, 1996, through October 8, 1997, at 22 sites in Europe and North America after reviewing and signing a written informed consent form approved by the Institutional Review Board of the participating center. Principal eligibility criteria included a best-corrected visual acuity letter score of 73 to 34 (Snellen equivalent, approximately 20/40 to 20/200) after a specific protocol refraction and visual acuity determination using Early Treatment of Diabetic Retinopathy Study charts[1] and fluorescein angiographic evidence of subfoveal CNV (classic or occult) due to AMD. Lesions were required to have CNV as the main component (ie, the area of all CNV, classic and occult, was required to be ≥50% of the area of the entire lesion). Evidence of at least some classic CNV was necessary, and the greatest linear dimension (GLD) of the lesion on the retina could be no greater than 5400 µm. The presence of occult CNV was permitted, but was not a requirement. The definitions of classic and occult CNV were based on the definitions from the Macular Photocoagulation Study (MPS) Group.[3] Some lesions with minimally classic CNV may have had a larger area of classic CNV than occult CNV if another component, such as blood, occupied a significant area (eg, a lesion in which 30% of the area was blood, 40% was classic CNV, and 30% was occult CNV).

Eligible patients were randomized to verteporfin therapy or placebo in a ratio of 2:1. All patients, treating ophthalmologists, vision examiners, and graders of fundus photographs and fluorescein angiograms were masked to the patients' treatment assignments. An assistant who was unmasked to the treatment assignment, but was not involved in any outcome assessments, prepared a 30-mL solution containing placebo (5% dextrose in water) or verteporfin (6 mg/m^2 of body surface area, calculated from the patient's height and weight on the day of treatment using a standard nomogram). The verteporfin or placebo solutions were infused intravenously for 10 minutes. Fifteen minutes after the start of the infusion, a diode laser emitting at 689 nm, equipped with a slitlamp delivery system (Coherent Inc, Palo Alto, Calif; or Zeiss Jena GmbH, Jena, Germany), delivered a light dose of 50 J/cm^2 by continuous application of laser light at an intensity of 600 mW/cm^2 for 83 seconds. The laser treatment spot size was 1000 µm larger than the lesion's GLD on the retina. Patients were instructed to avoid direct sunlight and wear sunglasses while outdoors during the next 48 hours. Follow-up visits were scheduled at 3-month intervals (±2 weeks), when a specific protocol refraction, a best-corrected visual acuity measurement, a contrast threshold measurement, an ophthalmoscopic examination, stereoscopic color fundus photography, and fluorescein angiography were performed. Retreatment was applied if there was fluorescein leakage from CNV and if no serious adverse events judged likely to be associated with prior treatment had occurred. Patients were retreated using a treatment spot size on the retina 1000 µm larger than the GLD of any leakage from classic or occult CNV (within or contiguous to an area of prior involvement by the lesion) and any contiguous serous detachment of the retinal pigment epithelium or hypofluorescence from blood. If the GLD to be retreated exceeded the maximum possible treatment spot size on the retina available at the time of the investigation (approximately 6000 µm), the treating ophthalmologist positioned the treatment spot to encompass as much of the area of leakage as possible.

The results from previously reported subgroup analyses,[1,2] planned before the database was closed and the data were un-

masked, suggested an interaction between baseline lesion composition and treatment on vision outcomes. After reporting this interaction, a subsequent analysis of covariance of the visual acuity change from baseline was conducted to evaluate this relationship and to adjust for other baseline variables that could potentially affect vision outcome. These variables, and the interaction terms, were included in this analysis of covariance. Stepwise backward elimination procedures were used to remove nonsignificant interaction terms and main effect terms from the models. The analysis of covariance in the total study population confirmed the interaction judged to be significant between treatment and lesion composition ($P=.02$).[2] The adjusted treatment differences in mean change from baseline at 12 months showed that patients with predominantly classic CNV who were treated with verteporfin lost 10.8 fewer letters of visual acuity than those given placebo ($P<.001$). Patients with minimally classic CNV treated with verteporfin lost 2.3 fewer letters of visual acuity than those given placebo ($P=.26$). Furthermore, previously reported analyses,[1,2] planned before the database was closed and the data were unmasked, demonstrated a large treatment benefit for lesions that had no occult CNV at baseline.

Taking these 2 pieces of evidence from analyses planned before the database was closed and the data were unmasked (ie, lesions composed of predominantly classic CNV and those with no occult CNV responding better to verteporfin therapy), additional exploratory analyses (to be interpreted with caution because these analyses were undertaken after knowledge of these 2 pieces of evidence) were also performed to compare outcomes for predominantly classic lesions with and without an occult component.

In addition, for patients with predominantly classic CNV, exploratory analyses were performed to investigate the percentages of patients who lost at least 15 letters and at least 30 letters of visual acuity in subgroups judged to be clinically relevant by the study group investigators. These subgroups were based on the following characteristics: (1) laser photocoagulation to CNV in the study eye, (2) micronutrient use, and (3) lens status (phakic or not phakic) in the study eye.

All analyses for this report were performed on all randomized patients using the same statistical methods reported previously, except that a Fisher exact test was used for evaluating outcomes with and without prior laser photocoagulation to CNV where the expected cell frequencies were below 5. The last observation carried forward was used for any missing efficacy values.[1] The method of last observation carried forward may not be the most advantageous way of dealing with missing values for a condition such as CNV in patients with AMD, who may have continued visual loss throughout the 2 years of follow-up. The visual acuity outcomes with last observation carried forward may tend to be better in the verteporfin- and the placebo-treated groups. However, because this method was suggested by regulatory agency personnel as the method to be used when the TAP Investigation was designed, it is the method used in this report. As noted previously,[1,2] major vision outcomes analyzed without last observation carried forward by the sponsors and the independent Data and Safety Monitoring Committee provided similar results.

RESULTS

Of the 609 patients participating in the TAP Investigation, the reading center graders determined that 242 (40%) had predominantly classic CNV, 306 (50%) had minimally classic CNV, and 61 (10%) had no classic CNV, including 4 (1%) who could not be graded for the presence or absence of classic CNV at the baseline examination. Patients identified by the graders as having no classic CNV were considered by an investigator to have lesions that contained a classic component at enrollment. Because the number of these cases (n=61) was small in the TAP Investigation, the results are not analyzed or discussed further in this report. The baseline characteristics by lesion composition for the 2 treatment groups (verteporfin and placebo) are given in **Table 1**. Within each subgroup, the baseline characteristics for these participants seemed balanced between treatment groups, with the following exceptions: for the subgroup with predominantly classic CNV, a higher percentage of women were assigned to placebo than verteporfin therapy; and for the subgroup with minimally classic CNV, a higher percentage of lesions containing blood were in the placebo group and a higher percentage of past or current smokers were assigned to verteporfin therapy than placebo.

Patients with predominantly classic CNV (combining patients receiving verteporfin and placebo therapy in each group), compared with those who had minimally classic CNV (Table 1), had a lower mean initial visual acuity (letter score, 50.1 [approximate Snellen equivalent, 20/100] vs 54.3 [approximate Snellen equivalent, $20/80^{-1}$]), smaller lesions, and a smaller GLD of the lesion; they also more frequently had lesions with a component of blood (52% vs 27%) or blocked fluorescence (62% vs 26%). Furthermore, patients with predominantly classic lesions with no occult CNV (combining patients receiving verteporfin and placebo therapy) had a lower initial visual acuity and smaller lesions compared with patients who had predominantly classic lesions with occult CNV (**Table 2**) or minimally classic lesions (Table 1). Completion of the month 24 examination for patients assigned to verteporfin and placebo therapy was 87% and 88%, respectively, with only small differences when they were examined by treatment assignment for each lesion composition subgroup (**Figure 2**).

During the first 12 months, verteporfin-treated patients with either predominantly classic CNV or minimally classic CNV received an average of 3.4 treatments, compared with 2.0 and 2.3 treatments, respectively, during the second 12 months. Before the month 12 examination, there was little difference, based on lesion composition, in the proportion of patients assigned to verteporfin who received retreatment for leakage identified by the treating ophthalmologist. From the month 12 examination onward, progressively fewer patients were retreated in both subgroups, and the proportion receiving retreatment was lower in the predominantly classic group than in the minimally classic group at the month 12 examination (57% vs 68%; $P=.02$) and at the month 21 examination (39% vs 48%; $P=.11$). Retreatment applied at the month 24 examination was not part of the TAP Investigation because the study procedure concluded with vision, photographic, and safety assessments at that visit.

VISION OUTCOMES

The changes in visual acuity from baseline by lesion composition at the month 12 and 24 examinations are shown in **Table 3**. At the month 12 examination in the pre-

Table 1. Baseline Characteristics by Treatment Group and Lesion Composition*

Characteristic	Patients With Predominantly Classic CNV		Patients With Minimally Classic CNV	
	Verteporfin Group (n = 159)	Placebo Group (n = 83)	Verteporfin Group (n = 202)	Placebo Group (n = 104)
Gender				
Women	77 (48)	52 (63)	111 (55)	65 (62)
Men	82 (52)	31 (37)	91 (45)	39 (38)
Race				
White	158 (99)	82 (99)	199 (99)	101 (97)
Other	1 (1)	1 (1)	3 (1)	3 (3)
Age, y				
50-64	18 (11)	5 (6)	16 (8)	5 (5)
65-74	62 (39)	33 (40)	78 (39)	36 (35)
75-84	66 (42)	38 (46)	93 (46)	52 (50)
≥85	13 (8)	7 (8)	15 (7)	11 (11)
Mean	74.6	75.3	75.2	76.3
Definite hypertension†	67 (42)	32 (39)	82 (41)	37 (36)
Visual acuity letter score (approximate Snellen equivalent)				
Study eye				
73-54 (20/40-20/80)	62 (39)	35 (42)	114 (56)	55 (53)
53-34 (20/100-20/200)	97 (61)	48 (58)	88 (44)	49 (47)
Mean	49.9 (20/100)	50.6 (20/100)	54.6 (20/80)	53.7 (20/80)
Fellow eye, mean	47.1 (20/126)	52.7 (20/80)	50.5 (20/100)	51.6 (20/100)
Study eye contrast sensitivity (letters), mean	23.2	23.2	24.7	25.2
Micronutrient supplement use	80 (50)	45 (54)	120 (59)	60 (58)
Smoking history				
Never smoker	54 (34)	34 (41)	67 (33)	48 (46)
Current smoker	19 (12)	14 (17)	40 (20)	10 (10)
Previous smoker	86 (54)	35 (42)	95 (47)	46 (44)
Location of CNV				
Subfoveal	140 (88)	77 (93)	184 (91)	94 (90)
Probably subfoveal	10 (6)	6 (7)	13 (6)	3 (3)
Not subfoveal	9 (6)	0	5 (2)	7 (7)
Evidence of occult CNV	69 (43)‡	39 (47)‡	200 (99)	100 (96)
Evidence of prior laser photocoagulation	25 (16)	6 (7)	30 (15)	13 (12)
Lesion includes				
Blood	82 (52)	44 (53)	46 (23)	37 (36)
Blocked (hypo-) fluorescence not from visible blood	93 (58)	56 (67)	56 (28)	24 (23)
Serous pigment epithelial detachment	0	0	1 (<1)	0
Lesion size, MPS DA				
≤3	77 (48)	39 (47)	48 (24)	25 (24)
>3 to ≤6	65 (41)	36 (43)	104 (51)	58 (56)
>6 to ≤9	13 (8)	7 (8)	41 (20)	17 (16)
>9	0	1 (1)	6 (3)	1 (1)
Cannot grade	4 (3)	0	3 (1)	3 (3)
Greatest linear dimension, diameter of the MPS DA circle				
≤3	59 (37)	28 (34)	37 (18)	16 (15)
>3 to ≤6	65 (41)	40 (48)	71 (35)	50 (48)
>6 to ≤9	27 (17)	12 (14)	71 (35)	32 (31)
>9	5 (3)	3 (4)	20 (10)	3 (3)
Cannot grade	3 (2)	0	3 (1)	3 (3)
Eligible for laser photocoagulation per MPS guidelines§				
New subfoveal CNV	19 (12)	10 (12)	1 (<1)	3 (3)
Recurrent subfoveal CNV	11 (7)	2 (2)	1 (<1)	1 (1)
No	129 (81)	71 (86)	200 (99)	99 (95)
Cannot determine	0	0	0	1 (1)

*Data are given as number (percentage) of patients unless otherwise indicated. Percentages may not total 100 because of rounding. CNV indicates choroidal neovascularization; MPS, Macular Photocoagulation Study; and DA, disc area.

†Defined as follows: (1) a systolic blood pressure of 160 mm Hg or higher or 140 to 159 mm Hg with a history of hypertension or use of antihypertensive medications or (2) a diastolic blood pressure of ≥95 mm Hg or higher or 90 to 94 mm Hg with a history of hypertension or use of antihypertensive medications.

‡Totals include 3 verteporfin-treated patients and 1 placebo-treated patient who had questionable occult CNV.

§New subfoveal CNV was judged eligible for laser photocoagulation per MPS guidelines when lesions had well-demarcated boundaries, evidence of classic CNV, and an area of 2 MPS DAs or less. Recurrent subfoveal CNV was judged eligible for laser photocoagulation per MPS guidelines when lesions had well-demarcated boundaries, evidence of classic CNV, and an area (including the area of prior laser treatment) of 6 MPS DAs or less.

dominantly classic CNV subgroup, 33% of the eyes treated with verteporfin had lost at least 15 letters (equivalent to a loss of ≥3 lines) of visual acuity compared with 61% of the eyes given placebo ($P<.001$). At the month 24 examination in the predominantly classic CNV subgroup, 41% of the verteporfin-treated eyes had lost at least 15 letters of visual acuity compared with 69% of the eyes given placebo ($P<.001$).

Table 2. Selected Baseline Characteristics in Study Eyes by Treatment Group in Patients With Predominantly Classic Lesions*

Characteristic	Patients Without Occult CNV		Patients With Occult CNV	
	Verteporfin Group (n = 90)	Placebo Group (n = 44)	Verteporfin Group (n = 69)	Placebo Group (n = 39)
Study eye visual acuity letter score (approximate Snellen equivalent)				
73-54 (20/40-20/80)	28 (31)	17 (39)	34 (49)	18 (46)
53-34 (20/100-20/200)	62 (69)	27 (61)	35 (51)	21 (54)
Visual acuity letter score (approximate Snellen equivalent), mean	48.3 ($20/100^{-2}$)	50.0 (20/100)	51.9 ($20/100^{+2}$)	51.2 ($20/100^{+1}$)
Lesion size, MPS DA				
≤3	59 (66)	25 (57)	18 (26)	14 (36)
>3 to ≤6	28 (31)	16 (36)	37 (54)	20 (51)
>6 to ≤9	1 (1)	2 (5)	12 (17)	5 (13)
>9	0	1 (2)	0	0
Cannot grade	2 (2)	0	2 (3)	0

*Data are given as number (percentage) of patients unless otherwise indicated. CNV indicates choroidal neovascularization; MPS, Macular Photocoagulation Study; and DA, disc area.

Most patients in both subgroups had some degree of vision loss in their study eyes at the month 12 and 24 examinations (Table 3). However, among patients with predominantly classic CNV, the mean visual acuity loss in the verteporfin group was 2.2 lines less than in the placebo group at the month 12 and 24 examinations. Even at the month 3 examination in the predominantly classic CNV subgroup, the verteporfin-treated patients lost a mean of 1.1 lines, compared with a mean loss of 2.3 lines in the placebo group ($P=.004$) (**Figure 3**). For patients with predominantly classic CNV, the cumulative percentage of eyes with a loss of at least 15 letters, or a loss of at least 30 letters (equivalent to a loss of ≥6 lines), of visual acuity was lower with verteporfin than with placebo at every follow-up examination through 24 months (**Figure 4**). Furthermore, at least moderate improvement of vision (≥3-line increase) was noted in 9 (6%) of 159 verteporfin-treated patients at the month 12 examination and in 14 (9%) at the month 24 examination compared with 2 (2%) at the month 12 examination and 3 (4%) at the month 24 examination for the 83 patients who received placebo.

There were no statistically significant differences in visual acuity effects in the minimally classic CNV subgroup. For patients with minimally classic CNV at baseline, 44% of the verteporfin-treated eyes and 45% of the eyes that received placebo had lost at least 15 letters of visual acuity at the month 12 examination ($P=.85$), compared with 53% and 56%, respectively, at the month 24 examination ($P=.58$). For minimally classic CNV, no statistically significant difference was noted between the 2 groups for the cumulative percentage of patients losing at least 15 or at least 30 letters of visual acuity at either time point (**Figure 5**). Among patients with minimally classic CNV, the difference between the mean change in visual acuity in verteporfin- and placebo-treated patients was small and not statistically significant, with an average difference in the mean visual acuity of 0.4 lines in favor of the verteporfin-treated group at the month 12 and 24 examinations (Table 3). However, at least moderate improvement of vision (equal to a 3-line increase) was observed in 13 (6%) of 202 verteporfin-treated patients at the month 12 examination and in 17 (8%) at the month 24 examination compared with 2 (2%) at the month 12 examination and 5 (5%) at the month 24 examination for the 104 patients who received placebo.

The mean change in visual acuity over time showed a treatment benefit for verteporfin-treated patients through the month 24 examination for predominantly classic lesions only (Figure 3). The distribution of approximate Snellen visual acuity based on the letter score at the month 24 examination is shown in **Table 4**. By month 24, the mean visual acuity in eyes with predominantly classic CNV treated with verteporfin was $20/160^{-2}$, compared with $20/250^{-2}$ in eyes given placebo. The overall distribution of the visual acuity for predominantly classic CNV favored the verteporfin-treated eyes, which were more likely to have a visual acuity better than 20/200 at the month 24 examination than eyes that received placebo (55% vs 32%; $P<.001$). For minimally classic CNV, the difference in the overall visual acuity distribution in this group was not statistically significant ($P=.18$).

The mean change from baseline in contrast sensitivity score by lesion composition and treatment assignment at each follow-up examination is given in **Figure 6**. The predominantly classic and minimally classic subgroups fared better with verteporfin therapy than with placebo, although the differences were greater in the predominantly classic subgroup. In this subgroup, the mean number of contrast sensitivity letters lost by the month 24 examination was 0.2 in verteporfin-treated eyes compared with 6.4 in eyes given placebo ($P<.001$). In the subgroup with minimally classic CNV, there was a mean loss of 2.0 letters with verteporfin therapy compared with 4.4 letters for the placebo group by the month 24 examination ($P=.02$).

ADDITIONAL VISUAL ACUITY OUTCOMES FROM SUBGROUP ANALYSES OF PREDOMINANTLY CLASSIC LESIONS

Patients were divided into subgroups based on prior laser photocoagulation (lesions that had or had not been treated with laser photocoagulation before enrollment),

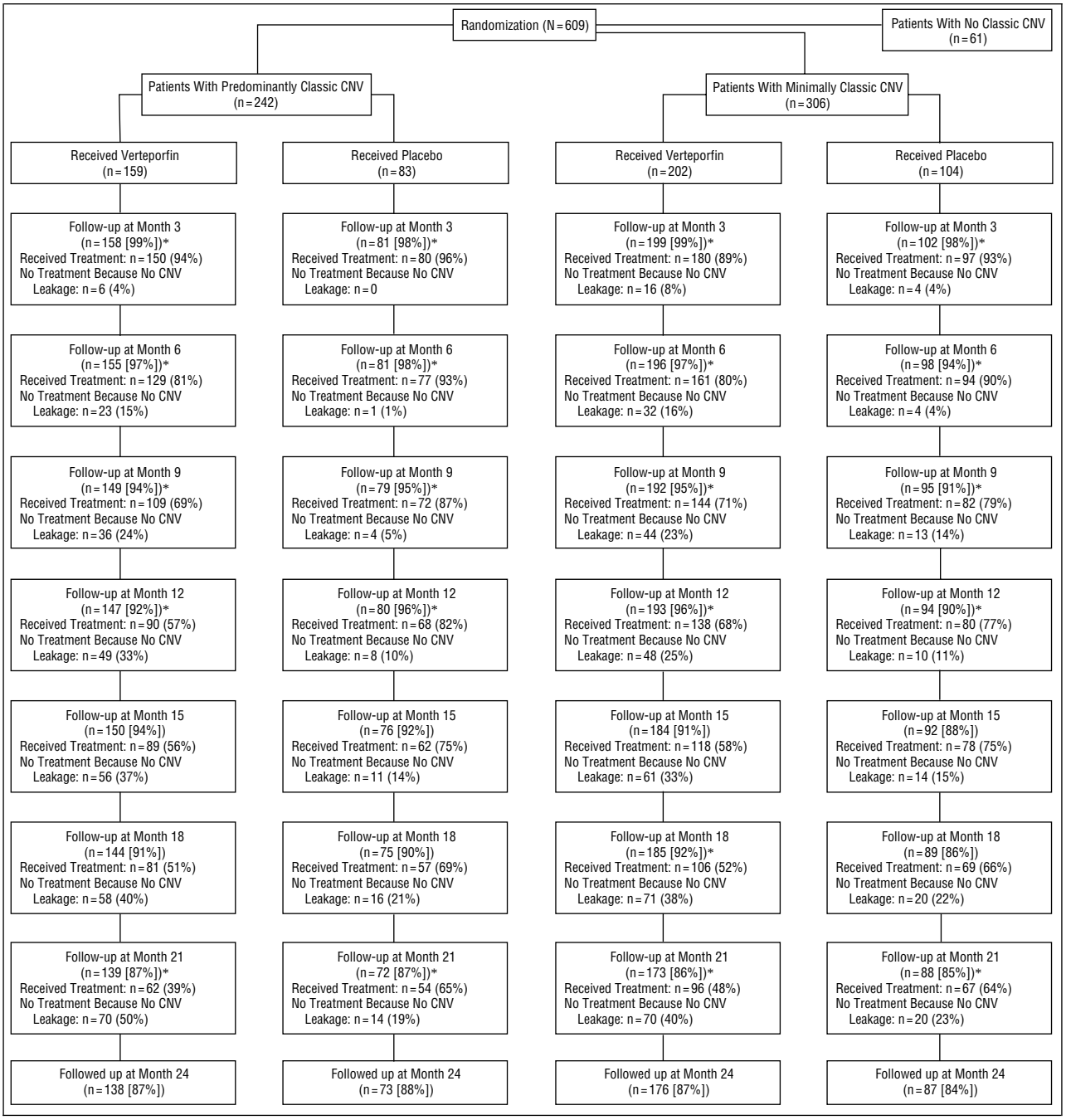

Figure 2. Profile of randomized patients receiving treatment and subsequently completing follow-up through 24 months stratified by lesion composition at baseline. The percentage of patients receiving retreatment is expressed as a percentage of the total number of patients randomized to each arm of the study. The percentage of patients who did not receive treatment because there was no choroidal neovascularization (CNV) is expressed as a percentage of the number of patients followed up. The "patients with no classic CNV" group includes 4 patients who could not be graded for the presence or absence of classic CNV. The asterisk indicates that values are the number (percentage) of patients who had a visual acuity assessment at that visit.

prior use of micronutrients (patients who were or were not taking micronutrients before enrollment), and phakic status (patients who were or were not phakic at enrollment). Based on these analyses, verteporfin-treated patients were less likely to have moderate (≥15 letters) or severe (≥30 letters) visual acuity loss at 24 months, regardless of prior laser photocoagulation, micronutrient use, or phakic status (**Table 5**). The number of patients who had undergone prior laser photocoagulation was small, so the analysis of this subgroup should be considered with caution, but the subgroups for micronutrient use and phakic status did show clinical benefit vs placebo.

An exploratory analysis not planned at the start of the TAP Investigation evaluated outcomes for predominantly classic lesions divided into those without evidence of occult CNV and those with evidence of occult CNV (**Table 6**). While the benefits of verteporfin therapy seemed greater in the predominantly classic lesions without occult CNV, almost all outcomes for predominantly

Table 3. Frequency Distribution of Changes in Visual Acuity From Baseline by Treatment Group and Lesion Composition*

	Patients With Predominantly Classic CNV				Patients With Minimally Classic CNV			
	Month 12 Follow-up		Month 24 Follow-up		Month 12 Follow-up		Month 24 Follow-up	
Change in Visual Acuity†	Verteporfin Group (n = 159)	Placebo Group (n = 83)	Verteporfin Group (n = 159)	Placebo Group (n = 83)	Verteporfin Group (n = 202)	Placebo Group (n = 104)	Verteporfin Group (n = 202)	Placebo Group (n = 104)
Increase, No. of lines								
≥6	2 (1)	0	2 (1)	0	2 (1)	0	1 (<1)	0
≥3 to <6	7 (4)	2 (2)	12 (8)	3 (4)	11 (5)	2 (2)	16 (8)	5 (5)
≥1 to <3	13 (8)	4 (5)	7 (4)	3 (4)	23 (11)	6 (6)	16 (8)	9 (9)
No change	40 (25)	11 (13)	30 (19)	9 (11)	37 (18)	20 (19)	24 (12)	14 (13)
Decrease, No. of lines								
≥1 to <3	45 (28)	16 (19)	43 (27)	11 (13)	40 (20)	29 (28)	39 (19)	18 (17)
≥3 to <6	33 (21)	22 (27)	41 (26)	27 (33)	55 (27)	30 (29)	66 (33)	30 (29)
≥6	19 (12)	28 (34)	24 (15)	30 (36)	34 (17)	17 (16)	40 (20)	28 (27)
P value‡	<.001		<.001		.62		.24	
Mean, No. of lines	−2.0	−4.2	−2.3	−4.5	−2.5	−2.9	−3.0	−3.4

*Data are given as number (percentage) of patients unless otherwise indicated. Percentages may not total 100 because of rounding. Last observation carried forward was used for missing values. CNV indicates choroidal neovascularization.

†Values are approximate; there are 5 letters per line.

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

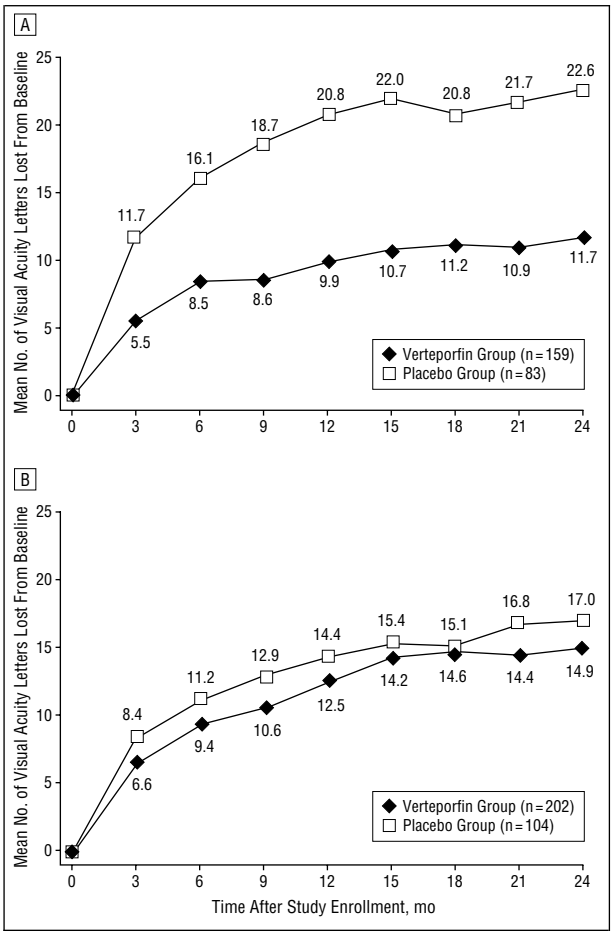

Figure 3. Mean number of letters of visual acuity lost from baseline at each 3-month study visit over time in lesions with predominantly classic choroidal neovascularization (CNV) at baseline (A) and in lesions with minimally classic CNV at baseline (B) assigned to verteporfin therapy or placebo, with last observation carried forward used for missing values.

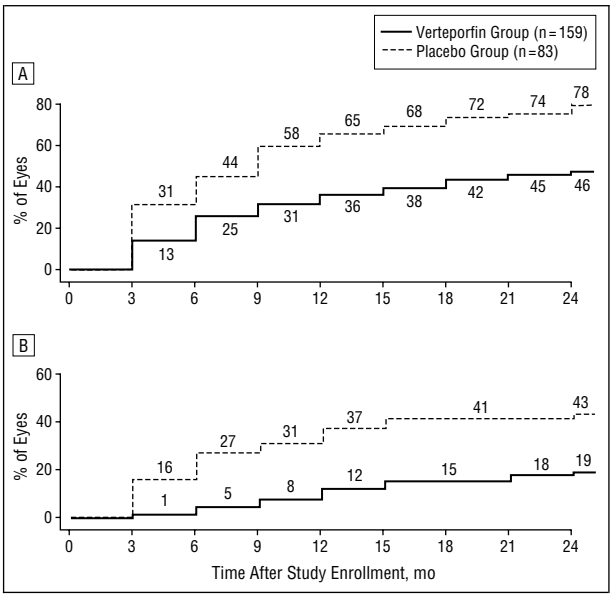

Figure 4. Kaplan-Meier estimates of the cumulative proportion of eyes at each 3-month study visit over time in patients with predominantly classic choroidal neovascularization at baseline assigned to verteporfin therapy or placebo, with at least moderate visual acuity loss (≥15 letters or approximately ≥3 lines) (A) and with severe visual acuity loss (≥30 letters or approximately ≥6 lines) (B) from baseline.

classic lesions with occult CNV favored the verteporfin-treated group, although this analysis resulted in small subgroups.

FLUORESCEIN ANGIOGRAPHIC OUTCOMES

Fluorescein angiographic outcomes, as judged by the reading center graders, were better with verteporfin therapy in those with predominantly classic and minimally clas-

sic lesions. These outcomes included lesion size at the month 24 examination (**Figure 7**), the proportion of eyes with progression of leakage from classic CNV over time (**Figure 8**), and the proportion of eyes with absence of leakage from classic CNV over time (**Figure 9**).

OCULAR SAFETY

There was little difference in the incidence of potentially clinically relevant adverse events in the study eye between predominantly classic CNV and minimally classic CNV (**Table 7**). Among the eyes with predominantly classic CNV at baseline, visual disturbances were reported for 20% of the verteporfin-treated eyes compared with 14% of the placebo group. Visual disturbances were reported for a higher percentage of verteporfin-treated patients with minimally classic lesions (25%) compared with verteporfin-treated patients with predominantly classic lesions (20%), while the percentage of visual disturbances in both placebo groups were similar (14% for patients with predominantly classic lesions and 15% for patients with minimally classic lesions). Abnormal vision was more likely to be reported in the verteporfin-treated group with minimally classic lesions (18%) than in the verteporfin-treated group with predominantly classic lesions (11%).

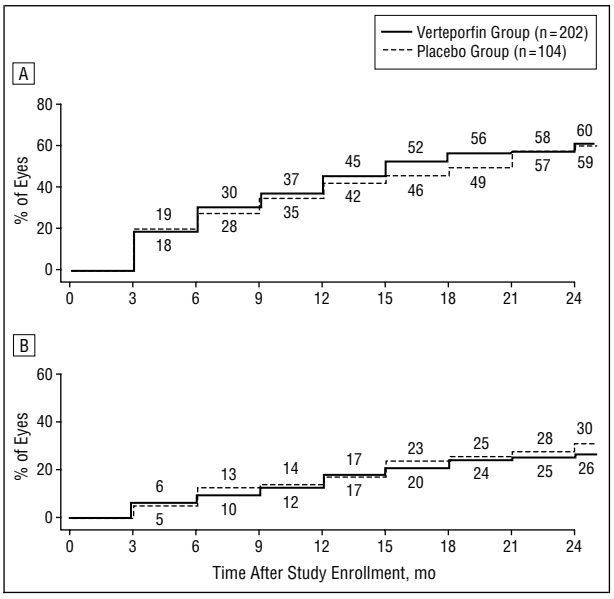

Figure 5. Kaplan-Meier estimates of the cumulative proportion of eyes at each 3-month study visit over time in patients with minimally classic choroidal neovascularization at baseline assigned to verteporfin therapy or placebo, with at least moderate visual acuity loss (≥15 letters or approximately ≥3 lines) (A) and with severe visual acuity loss (≥30 letters or approximately ≥6 lines) (B) from baseline.

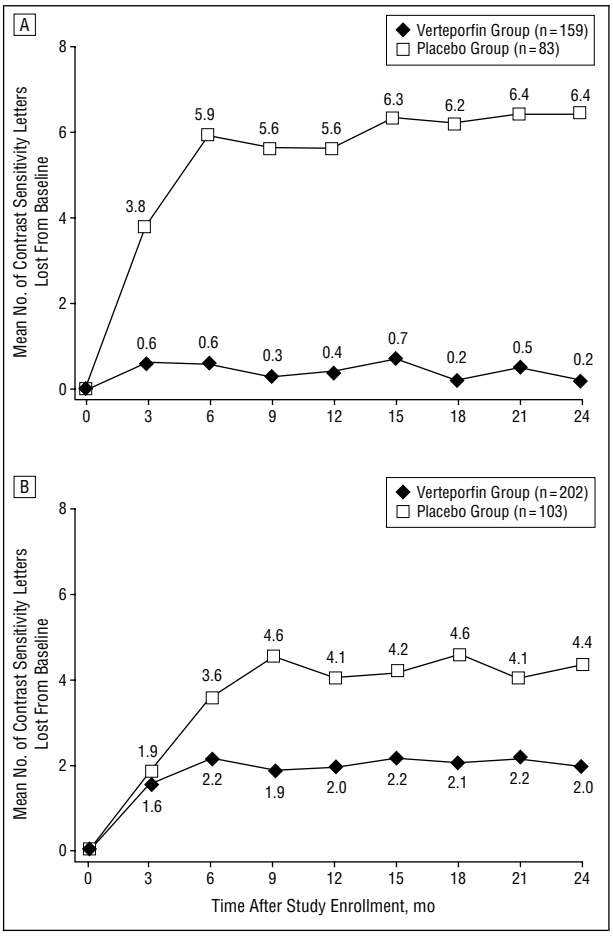

Figure 6. Mean number of letters of contrast sensitivity lost from baseline at each 3-month study visit over time for lesions with predominantly classic choroidal neovascularization (CNV) at baseline (A) and for lesions with minimally classic CNV at baseline (B) assigned to verteporfin therapy or placebo, with last observation carried forward used for missing values.

Table 4. Visual Acuity Categories in Study Eyes at the Month 24 Follow-up by Treatment Group and Lesion Composition*

	Patients With Predominantly Classic CNV		Patients With Minimally Classic CNV	
Visual Acuity Letter Score (Approximate Snellen Equivalent)	Verteporfin Group (n = 159)	Placebo Group (n = 83)	Verteporfin Group (n = 202)	Placebo Group (n = 104)
>73 (>20/40)	7 (4)	0	12 (6)	5 (5)
73-54 (20/40-20/80)	21 (13)	10 (12)	38 (19)	13 (12)
53-34 (20/100-20/160)	61 (38)	17 (20)	71 (35)	38 (37)
≤33 (≤20/200)	70 (44)	56 (67)	81 (40)	48 (46)
P value†	.001		.18	
Mean	38 (20/160^{-2})	28 (20/250^{-2})	40 (20/160)	37 (20/200^{+2})

*Data are given as number (percentage) of patients unless otherwise indicated. Percentages may not total 100 because of rounding. Last observation carried forward was used for missing values. CNV indicates choroidal neovascularization.

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

Table 5. Eyes With Moderate and Severe Vision Loss at Month 24 for Patients With Predominantly Classic Lesions

Characteristic	Loss of ≥15 Letters of Visual Acuity*	*P* Value 1†	*P* Value 2‡	Loss of ≥30 Letters of Visual Acuity*	*P* Value 1†	*P* Value 2‡
Evidence of prior laser photocoagulation						
Yes						
Verteporfin goup (n = 25)	10 (40)	.21		2 (8)	.06	
Placebo group (n = 7)	5 (71)		.85	3 (43)		.31
No						
Verteporfin group (n = 134)	55 (41)	<.001		21 (16)	.002	
Placebo group (n = 76)	52 (68)			27 (36)		
Phakic at enrollment						
Yes						
Verteporfin group (n = 124)	51 (41)	.001		19 (15)	<.001	
Placebo group (n = 62)	41 (66)		.44	23 (37)		.91
No						
Verteporfin group (n = 35)	14 (40)	.009		5 (14)	.09	
Placebo group (n = 21)	16 (76)			7 (33)		
Micronutrient use						
Yes						
Verteporfin group (n = 80)	33 (41)	<.001		11 (14)	<.001	
Placebo group (n = 45)	33 (73)		.44	18 (40)		.37
No						
Verteporfin group (n = 79)	32 (41)	.02		13 (16)	.06	
Placebo group (n = 38)	24 (63)			12 (32)		

*Data are given as number (percentage) of patients.
†Test for treatment effect within subgroups; the Fisher exact test was used for lesions that underwent prior laser photocoagulation.
‡Test of interaction between subgroups using a simple logistic regression model that includes treatment.

COMMENT

Based on subgroup analyses of data from 2 randomized clinical trials,[1,2] the TAP Study Group recommended verteporfin therapy for patients with AMD who are seen with predominantly classic lesions in which the CNV extends under the center of the foveal avascular zone (subfoveal CNV). Since completion of the month 24 examination for patients assigned to verteporfin therapy or to placebo was 87% and 86%, respectively, with only small differences when they were examined by treatment assignment and lesion composition, the use of last observation carried forward likely gives similar results compared with analyses that would not include last observation carried forward. This report also provides additional information to substantiate the original recommendation of the TAP Study Group, provides greater detail to ophthalmologists about the risks and benefits of verteporfin therapy for predominantly classic lesions in patients with AMD who have subfoveal CNV, and suggests additional hypotheses that treatment benefits may depend not only on the lesion composition when patients are first seen but also on an interaction among lesion composition, lesion size, and visual acuity when patients are first seen.

A report[4] on verteporfin therapy for lesions with occult CNV but no classic CNV in the Verteporfin in Photodynamic Therapy Trial suggested that the therapy was beneficial for either smaller lesions, regardless of initial visual acuity, or larger lesions when associated with a lower level of visual acuity. This finding may help to explain why a treatment benefit in the TAP Investigation seemed greater for predominantly classic lesions compared with minimally classic lesions and why a treatment benefit seemed greater for predominantly classic lesions without occult CNV compared with predominantly classic lesions with occult CNV. Specifically, eyes with predominantly classic CNV had a lower mean visual acuity and a smaller lesion size than eyes with minimally classic CNV. Perhaps the lack of a treatment benefit with respect to visual acuity outcomes for minimally classic lesions in the TAP Investigation is related to the fact that most of the minimally classic lesions were larger and had a higher (better) level of visual acuity, characteristics that did not favor verteporfin therapy in the Verteporfin in Photodynamic Therapy Trial of lesions composed of occult CNV with no classic CNV. Further support for this concept was an exploratory analysis[5] that showed that patients in the TAP Investigation with a minimally classic lesion composition with smaller lesions (≤4 MPS disc areas) and lower (worse) levels of visual acuity seemed to benefit from therapy. A randomized placebo-controlled study of patients with smaller minimally classic lesions, the Verteporfin in Minimally Classic CNV Trial, has been initiated to determine if this exploratory finding can be confirmed.

In a similar manner, the predominantly classic lesions without occult CNV seemed to be smaller and to have a lower level of visual acuity than predominantly classic lesions with occult CNV. These different lesion size and visual acuity characteristics associated with different lesion compositions were consistent with similar findings from a clinical trial reported by the MPS Group.[6] Specifically, in the MPS trial of patients with AMD who had subfoveal CNV, patients with classic CNV with no occult CNV had a lower initial mean visual acuity and a smaller lesion size than those patients with classic and occult CNV at study enrollment.

The larger lesion size and higher level of visual acuity for predominantly classic lesions with occult CNV com-

Table 6. Vision Outcomes in Study Eyes by Treatment Group in Patients With Predominantly Classic Lesions

Outcome	Patients Without Occult CNV		Patients With Occult CNV	
	Verteporfin Group (n = 90)	Placebo Group (n = 44)	Verteporfin Group (n = 69)	Placebo Group (n = 39)
≥15-Letter loss				
Month 12	21 (23)	32 (73)	31 (45)	18 (46)
Month 24	27 (30)	33 (75)	38 (55)	24 (62)
≥30-Letter loss				
Month 12	9 (10)	18 (41)	10 (14)	10 (26)
Month 24	12 (13)	16 (36)	12 (17)	14 (36)
Mean change in VA letter score				
Month 12	−8.2	−24.7	−12.1	−16.4
Month 24	−9.4	−25.0	−14.7	−19.9
Mean change in CS				
Month 12	−0.7	−6.8	0.03	−4.3
Month 24	−0.1	−6.9	−0.3	−5.9
Lesion ≤6 MPS DAs				
Month 12	57 (63)	8 (18)	28 (41)	11 (28)
Month 24	59 (66)	10 (23)	28 (41)	11 (28)

*Data are given as number (percentage) of patients unless otherwise indicated. The last observation carried forward was used for missing values. CNV indicates choroidal neovascularization; VA, visual acuity; CS, contrast sensitivity; MPS, Macular Photocoagulation Study; and DA, disc area.

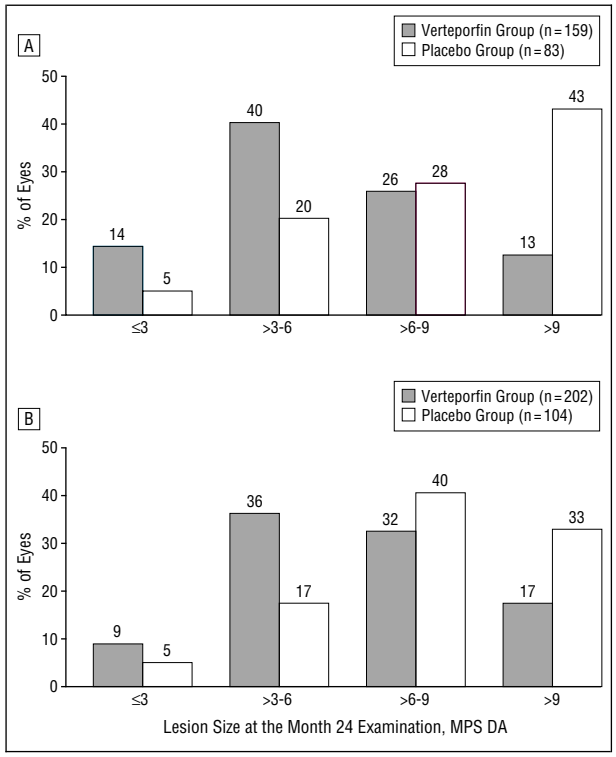

Figure 7. Distribution of lesion sizes at the month 24 examination for patients with predominantly classic choroidal neovascularization (CNV) (A) and for patients with minimally classic CNV (B) treated with verteporfin therapy or placebo, with last observation carried forward used for missing values. MPS indicates Macular Photocoagulation Study; DA, disc area.

pared with those without occult CNV perhaps explain why the benefits of verteporfin therapy seemed greater for predominantly classic lesions without occult CNV compared with predominantly classic lesions with occult CNV. Caution is indicated when evaluating the exploratory analyses that remove lesions with classic CNV but no occult CNV from the subgroup of predominantly classic lesions (with and without occult CNV) because these analyses were not planned before data unmasking and result in small numbers (eg, only 39 placebo-treated patients). Therefore, these results should not be viewed as confidently as the results for the entire subgroup of predominantly classic lesions, and formal statistical analyses of such subgroups should be avoided.

In verteporfin-treated eyes, the mean visual acuity deterioration seen in patients with minimally classic CNV was not necessarily greater than that seen in patients with predominantly classic CNV (−3.0 vs −2.3 lines lost at the month 24 examination; $P=.10$). If this difference is real, it could be related to the approximately 1-line better mean baseline visual acuity in the patients with minimally classic lesions, the larger mean lesion size requiring treatment (at least at the initial visit, if not thereafter) in lesions with minimally classic CNV compared with those with predominantly classic CNV, or both reasons. Alternatively, or in addition, lesions with minimally classic CNV given placebo were more likely to have evidence of blood as a lesion component than those treated with verteporfin. This difference may have had an effect on the natural course of these lesions, resulting in an increased chance of spontaneous improvement, which, in turn, could reduce the likelihood of a beneficial effect of verteporfin therapy in this subgroup. However, the eligibility criteria were designed to reduce this possibility. The lesions included had to have CNV, and not blood, as the main component and as the component that extended under the center of the foveal avascular zone. Several factors at baseline, then, may have diminished the chance of patients with minimally classic CNV having a visual acuity benefit with verteporfin therapy, compared with placebo. These factors included larger lesions and better visual acuity on average in the verteporfin group (with larger lesions associated with poorer vision outcomes), more blood in the placebo group (with more chance of spontaneous resolution), and other unknown imbalances at baseline.

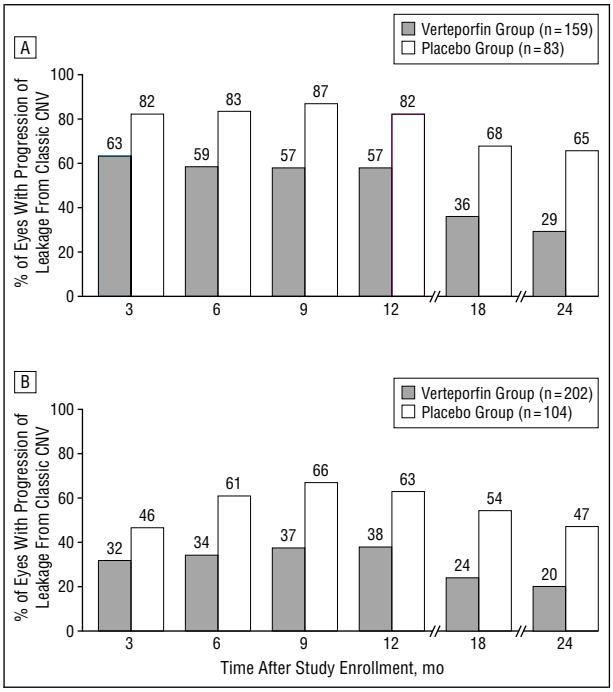

Figure 8. Percentage of eyes with progression of leakage from classic choroidal neovascularization (CNV) beyond the area of the lesion at baseline over time for patients with predominantly classic CNV (A) and for patients with minimally classic CNV (B) treated with verteporfin therapy or placebo, with last observation carried forward used for missing values.

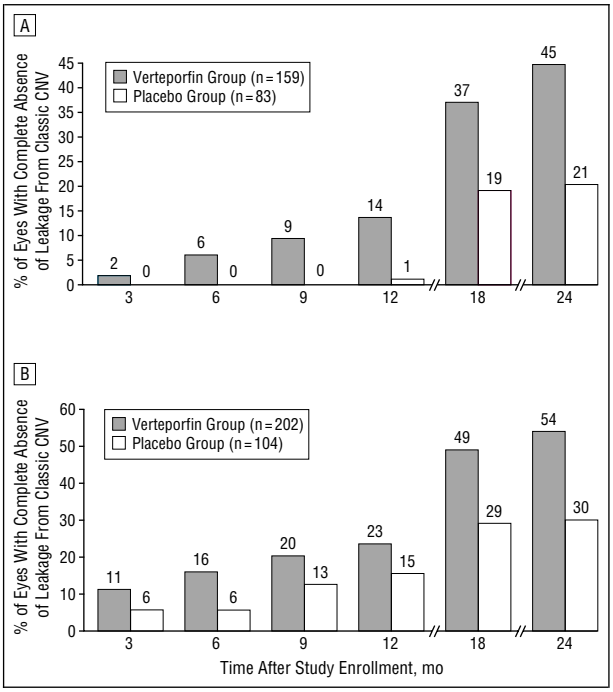

Figure 9. Percentage of eyes with complete absence of leakage from classic choroidal neovascularization (CNV) over time for patients with predominantly classic CNV (A) and for patients with minimally classic CNV (B) treated with verteporfin therapy or placebo, with last observation carried forward used for missing values.

Table 7. Incidence of Potentially Clinically Relevant Study Eye Adverse Events Reported by the End of 24 Months of Follow-up for the Entire Study Group by Lesion Composition at Baseline*

	Patients With Predominantly Classic CNV		Patients With Minimally Classic CNV	
Ocular Adverse Event	Verteporfin Group (n = 159)	Placebo Group (n = 83)	Verteporfin Group (n = 202)	Placebo Group (n = 104)
Cataract	22 (14)	8 (10)	27 (13)	15 (14)
Conjunctivitis	11 (7)	6 (7)	13 (6)	5 (5)
Photophobia	2 (1)	2 (2)	3 (1)	2 (2)
Retinal capillary nonperfusion	0	1 (1)	1 (<1)	1 (1)
Visual disturbance†	32 (20)	12 (14)	51 (25)	16 (15)
Vision abnormal	17 (11)	11 (13)	37 (18)	9 (9)
Vision decreased	15 (9)	3 (4)	23 (11)	8 (8)
Visual field defect	12 (8)	3 (4)	11 (5)	4 (4)
Vitreous hemorrhage	1 (1)	2 (2)	5 (2)	0

*Data are given as number (percentage) of patients. Individual adverse events are listed if they occurred in at least 1% of the patients in any group. CNV indicates choroidal neovascularizaion.

†Visual disturbance is a summary term; individual terms are listed below it.

CONCLUSIONS

These findings support previously published conclusions that verteporfin therapy can reduce the risk of moderate and severe vision loss through 24 months of follow-up after the initiation of therapy, compared with placebo, in patients with AMD who have predominantly classic subfoveal lesions. The finding that this benefit seemed to be even greater in the absence of occult CNV may not be because of occult CNV per se, but instead may be related to the smaller lesion size and worse initial visual acuity associated with predominantly classic lesions in the absence of occult CNV. In patients with minimally classic CNV, verteporfin therapy was associated with better contrast sensitivity and fluorescein angiographic outcomes, but not with better visual acuity outcomes. Verteporfin therapy should be considered for lesions with predominantly classic CNV, with or without occult CNV, extending under the center of the foveal avascular zone. Predominantly classic lesions tend to have a smaller initial lesion size and a worse initial visual acuity than minimally classic lesions. This detailed report, coupled with results from a randomized clinical trial of patients with AMD who have subfoveal lesions composed of occult CNV with no classic CNV, suggests that treatment benefits may depend not only on the lesion composition when patients are first seen, but also on an

interaction among lesion composition, lesion size, and visual acuity when patients are first seen. For minimally classic lesions, these findings suggest that further investigation might be warranted to determine if these lesions might benefit from verteporfin therapy compared with no treatment when they are smaller and have lower levels of visual acuity.

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