Effect of Lesion Size, Visual Acuity, and Lesion Composition on Visual Acuity Change With and Without Verteporfin Therapy for Choroidal Neovascularization Secondary to Age-related Macular Degeneration: TAP and VIP Report No. 1

TREATMENT OF AGE-RELATED MACULAR DEGENERATION WITH PHOTODYNAMIC THERAPY AND VERTEPORFIN IN PHOTODYNAMIC THERAPY STUDY GROUPS

• PURPOSE: To determine whether differences in baseline lesion size and visual acuity might explain differing results found in three different lesion compositions (predominantly classic, minimally classic, and occult with no classic) among three placebo-controlled, randomized clinical trials evaluating photodynamic therapy with verteporfin (Visudyne, Novartis AG), also termed verteporfin therapy, in patients with subfoveal choroidal neovascularization (CNV) due to age-related macular degeneration (AMD).
• METHODS: Exploratory analyses were conducted in patients with predominantly classic or minimally classic lesions at enrollment in the Treatment of AMD with Photodynamic Therapy (TAP) Investigation and in AMD patients with occult with no classic CNV in the Verteporfin In Photodynamic Therapy (VIP) Trial. Baseline characteristics of patients among these three lesion compositions were compared. In addition, multiple linear regression modeling was used to explore the effect of baseline lesion size, visual acuity, and lesion composition on mean change in visual acuity from baseline to 24 months.
• RESULTS: At baseline, the mean size of predominantly classic lesions (3.4 disk areas) was smaller than that of minimally classic (4.7 disk areas) and occult with no classic lesions (4.3 disk areas). In the multiple linear regression model of individual lesion compositions, there was a significant treatment-by-lesion-size interaction for minimally classic and occult with no classic lesions, but not for predominantly classic lesions. Interaction between treatment and baseline visual acuity was not significant for any lesion composition. Small verteporfin-treated lesions lost less vision than large verteporfin-treated lesions in each lesion composition. In the multiple linear regression model that included all lesion compositions, lesion size was a more significant predictive factor for the magnitude of treatment benefit than either lesion composition or visual acuity. Smaller (4.0 disk areas or less) minimally classic and occult with no classic lesions had similar visual acuity outcomes to those observed in predominantly classic lesions.
• CONCLUSIONS: Based on exploratory analyses, lesion size in the TAP Investigation and VIP Trial was an important predictor of the magnitude of treatment benefit with verteporfin therapy in occult with no classic and minimally classic lesion compositions. In patients with AMD, treating smaller rather than larger neovascular lesions, regardless of lesion composition, likely will result in a better level of visual acuity. (Am J Ophthalmol 2003;136:407–418. © 2003 by Elsevier Inc. All rights reserved.)

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From the Treatment of Age-related macular degeneration with Photodynamic therapy (TAP) and Verteporfin In Photodynamic therapy (VIP) study groups.

Complete lists of the participants in the TAP Investigation and VIP Study Groups are available in the *Archives of Ophthalmology* (Arch Ophthalmol 1999;117:1329–1345) and the AMERICAN JOURNAL OF OPHTHALMOLOGY (Am J Ophthalmol 2001;131:541–560).

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PHOTODYNAMIC THERAPY WITH VERTEPORFIN (VISUdyne, Novartis AG, Bulach, Switzerland), also called verteporfin therapy, can benefit selected patients with subfoveal choroidal neovascularization (CNV).[1–4] Patient selection is based in part on benefits for predominantly classic lesions (area of classic CNV at least 50% of the area of the entire lesion) as well as occult with no classic lesions and presumed disease progression but not for patients with minimally classic lesions (classic CNV less than 50% but more than 0% of the entire lesion).[5,6] It seems inconsistent that there was no benefit for minimally classic lesions, even though the risk of lesion growth was reduced in minimally classic lesions.[7] A possible explanation is that baseline factors affecting treatment benefit were different among different lesion compositions. It is also possible that factors that were not measured, such as lesion age or thickness, location of the CNV component, or epicenter of the lesion, were unbalanced between treated and control groups despite randomization, creating bias against treatment in the minimally classic lesions. This paper will evaluate more detailed analyses of inclusion criteria of the Treatment of AMD with Photodynamic therapy (TAP) Investigation and the Verteporfin In Photodynamic Therapy (VIP) Trial for possible biases of lesion size and visual acuity at baseline and compare the natural history of visual acuity loss in the different lesion compositions to determine whether these factors may help explain the lack of visual acuity benefit that was reported in minimally classic lesions.

The TAP Investigation and VIP Trial outcomes published to date have focused on losses of visual acuity score from baseline of at least 15 letters or at least 30 letters. A 15-letter loss on visual acuity charts used in the verteporfin trials represents a doubling of the visual angle and generally is considered a clinically relevant change for an individual.[8,9] A 30-letter loss on these charts represents a quadrupling of the visual angle and generally is considered a severe amount of visual acuity loss for an individual.[10] Therefore, these outcomes were also used in a variety of subgroup analyses in the TAP Investigation and VIP Trial to evaluate if different factors such as lesion composition and lesion size might influence the magnitude of the treatment benefit. For analyses in this report, most of the results use mean change from baseline in visual acuity rather than a binary (yes/no) variable as was used in outcomes of at least 15-letter (yes/no) or 30-letter (yes/no) loss to increase the power of the analysis.

METHODS

THE HIGHLIGHTS OF THE PROTOCOLS ARE DESCRIBED IN earlier reports,[1–4] and pertinent aspects are summarized below. Before patient enrollment at a center began, the study design was reviewed by a study advisory group (members of the TAP Investigation or VIP Trial Study Groups who advise the study sponsors on the scientific aspects of the investigations), the institutional review board of the participating clinical center, and a data and safety monitoring committee independent of the study sponsors and the study groups. Certification of all clinical center study personnel, as well as organization of the TAP Investigation and VIP Trial, are described in detail elsewhere.[1] Monitoring of the clinical centers (including all visual acuity examiners) and the Photograph Reading Center continued through the 2-year follow-up.

Twenty-two and 28 centers enrolled patients in the TAP Investigation and VIP Trial, respectively. Patients had to fulfill eligibility criteria determined by an ophthalmologist certified to enroll and treat study participants. Vision testing, stereoscopic color fundus photography, and fluorescein angiography to identify key features of the eligibility criteria were described previously.[1] The required visual acuity letter score using Early Treatment of Diabetic Retinopathy Study (ETDRS) charts was 73 to 34 in the TAP Investigation (Snellen equivalent approximately 20/40 to 20/200) and at least 50 in the VIP Trial (Snellen equivalent approximately 20/100 or better). Fluorescein angiographic evidence of subfoveal CNV[1] was required for both studies in which at least 50% of the lesion was CNV and in which the lesion's greatest linear dimension was no greater than 5400 μm. In the TAP Investigation the lesion had to contain some evidence of classic CNV, although the lesion could contain occult CNV or other features that could obscure the identification of classic or occult CNV on fluorescein angiography, including blood, blocked fluorescence, or serous detachment of the retinal pigment epithelium. In the VIP Trial, if the lesion had occult CNV with no evidence of classic CNV, the lesion had to have evidence of "presumed recent disease progression." This was defined as either hemorrhage associated with CNV at baseline, a loss of at least 5 letters within 3 months of the baseline vision examination using the same visual acuity assessment protocol as above, or a growth in the greatest linear dimension of the lesion of at least 10% within 3 months of the baseline examination.

After an informed consent process that included reviewing and signing a written informed consent form with a certified investigator (ophthalmologist), patients who were judged by a certified enrolling ophthalmologist to satisfy all eligibility criteria were assigned randomly to verteporfin or placebo infusion in a 2:1 ratio, respectively. Methodology for random assignments and masking are described elsewhere.[1]

The populations analyzed included the occult with no classic choroidal neovascular lesions at baseline from the VIP Trial (258 eyes) and classic-containing lesions at baseline from the TAP Investigation (548 eyes) as judged by the Photograph Reading Center. To maintain as homogenous a population as possible, data from the TAP Investigation patients classified as having occult with no classic choroidal neovascular lesions (61 eyes) and data

TABLE 1. Baseline Characteristics by Treatment Group and Lesion Composition

Characteristic	Predominantly Classic (TAP) (%) Verteporfin (n = 159)	Predominantly Classic (TAP) (%) Placebo (n = 83)	Predominantly Classic (TAP) (%) All (n = 242)	Minimally Classic (TAP) (%) Verteporfin (n = 202)	Minimally Classic (TAP) (%) Placebo (n = 104)	Minimally Classic (TAP) (%) All (n = 306)	Occult With No Classic (VIP AMD) (%) Verteporfin (n = 166)	Occult With No Classic (VIP AMD) (%) Placebo (n = 92)	Occult With No Classic (VIP AMD) (%) All (n = 258)
Gender, women	48.4	62.7	53.3	55.0	62.5	57.5	60.8	64.1	62.0
Age, years									
50–64	11.3	6.0	9.5	7.9	4.8	6.9	6.6	7.6	7.0
65–74	39.0	39.8	39.3	38.6	34.6	37.3	38.0	35.9	37.2
75–84	41.5	45.8	43.0	46.0	50.0	47.4	43.4	48.9	45.3
≥85	8.2	8.4	8.3	7.4	10.6	8.5	12.0	7.6	10.5
Mean	74.6	75.3	74.8	75.2	76.3	75.5	75.4	75.4	75.4
Study eye, mean visual acuity letter score									
Mean	49.9	50.6	50.1	54.6	53.7	54.3	66.0	65.2	65.7
Approximate Snellen equivalent	20/100	$20/100^{+1}$	20/100	20/80	$20/80^{-1}$	$20/80^{-1}$	$20/50^{+1}$	20/50	$20/50^{+1}$
Lesion size (MPS disk area*)†									
Category (%)	(n = 155)	(n = 83)	(n = 238)	(n = 199)	(n = 101)	(n = 300)	(n = 164)	(n = 91)	(n = 255)
≤1	6.5	6.0	6.3	3.5	4.0	3.7	3.0	1.1	2.4
≤2	21.3	14.5	18.9	9.5	5.0	8.0	9.8	5.5	8.2
≤3	21.9	26.5	23.5	11.1	15.8	12.7	17.1	23.1	19.2
≤4	15.5	16.9	16.0	14.6	14.9	14.7	18.9	13.2	16.9
≤5	16.1	15.7	16.0	17.1	20.8	18.3	18.9	18.7	18.8
≤6	10.3	10.8	10.5	20.6	21.8	21.0	17.1	18.7	17.6
≤9	8.4	8.4	8.4	20.6	16.8	19.3	13.4	17.6	14.9
≤12	0.0	1.2	0.4	1.5	1.0	1.3	1.8	2.2	2.0
≤16	0.0	0.0	0.0	1.5	0.0	1.0	0.0	0.0	0.0
Cannot grade†	2.6	0.0	1.7	1.5	3.0	2.0	1.2	1.1	1.2
Mean			3.4			4.7			4.3

AMD = age-related macular degeneration; MPS = Macular Photocoagulation Study; TAP = Treatment of Age-related macular degeneration with Photodynamic therapy Investigation; VIP = Verteporfin In Photodynamic Therapy Trial.

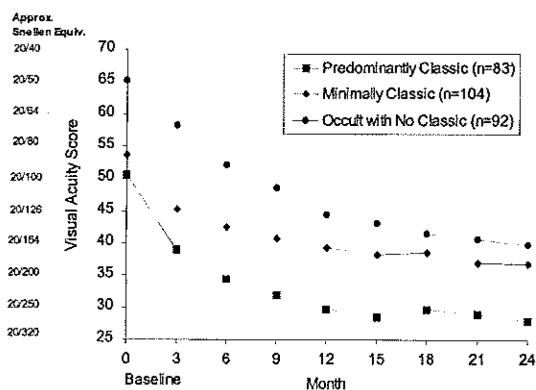
*1 MPS disk area was defined as 2.54 mm^2.

†Percentage for "cannot grade" is calculated based on all patients (N); other lesion size percentages and means are calculated based on all patients excluding "cannot grade" (n).

from those patients with classic-containing lesions from the VIP Trial (81 eyes) were not included in these exploratory analyses because they had different inclusion criteria from the main lesion composition populations. However, similar conclusions were obtained when the entire population of both the TAP Investigation and the VIP Trial were included in the multiple linear regression analyses (data available as supplementary material at http://ajo.com).

The principle of intent-to-treat analysis was followed, and all study patients were analyzed in the groups as randomized. Missing values were imputed using the method of last observation carried forward, where outcomes described at specific time points, such as at the month 24 examination, imply that the outcomes are at the month 24 examination with the last observation carried forward. When vision outcomes were analyzed without the last observation carried forward, results were similar (data available as supplementary material at http://ajo.com) using the occult with no classic choroidal neovascular lesions at baseline from the VIP Trial (258 eyes) and classic-containing lesions at baseline from the TAP Investigation (548 eyes), as judged by the Photograph Reading Center, or when using the entire population from both studies.

Demographic and baseline lesion characteristics (age, sex, visual acuity scores, lesion size) were tabulated for each treatment group to identify differences within each lesion composition. A two-sample t test was used for the comparisons of the mean visual acuity at month 24 between the treatment groups. In addition, multiple linear regression analysis of visual acuity change from baseline was performed within each lesion composition type and all three lesion composition types combined to investigate the influence of baseline lesion size, visual acuity, and the lesion composition type on the treatment effect. Apart from treatment effect, predictor variables in the model included baseline visual acuity letter score, baseline lesion size (disk areas) estimated by the Photograph Reading Center, and lesion composition (if applicable), as judged



	Month								
	0	3	6	9	12	15	18	21	24
Predominantly Classic (n=83)	50.6	38.9	34.4	31.9	29.7	28.5	29.7	28.9	28.0
Minimally Classic (n=104)	53.7	45.3	42.5	40.8	39.3	38.3	38.6	36.9	36.7
Occult With No Classic (n=92)	65.2	58.3	52.0	48.5	44.4	43.1	41.4	40.6	39.7

FIGURE 1. Mean visual acuity scores over time of the three untreated placebo groups: predominantly classic (Treatment of Age-related macular degeneration with Photodynamic therapy [TAP] Investigation), minimally classic (TAP investigation), occult with no classic (Verteporfin In Photodynamic Therapy [VIP] Trial) demonstrating the average natural history of predominantly classic lesions was worse than that of minimally classic lesions, which was worse than that of occult with no classic lesions.

by the Photograph Reading Center, as well as the interaction terms between treatment and each of the these variables. Insignificant terms (predefined as $P > .05$) were eliminated from the model one at a time through a backward elimination process, where the main-effect of any variable was not considered for elimination unless the interaction term involving the main-effect variable already had been eliminated. Model adjusted means[11] of the visual acuity change from baseline were compared between the treatment groups for each baseline lesion size category using the same final multiple linear regression model. Baseline visual acuity was adjusted to its global mean for this purpose.

The midpoint of each baseline lesion size category was used in the mean lesion size calculation as well as in the multiple linear regression model (for example, for the categories 1 disk area or less and 2 disk areas or less, the midpoints used were 0.5 and 1.5, respectively). A P value of .05 or less was considered statistically significant. No adjustment was made for multiple comparisons.

RESULTS

THE DATA SETS INCLUDED ALL 242 PATIENTS (VERTEPORFIN, 159; placebo, 83) with predominantly classic lesions and all 306 patients (verteporfin, 202; placebo, 104) with minimally classic lesions from the TAP Investigation, and all 258 patients (verteporfin, 166; placebo, 92) who had occult with no classic lesions from the VIP Trial. Main baseline characteristics of the different lesion composition types are given in Table 1. The percentage of verteporfin-treated women with predominantly classic lesions was slightly lower than that of verteporfin-treated women with minimally classic or occult with no classic lesion compositions. No difference in mean visual acuity score was found between the verteporfin and placebo treatment groups within any lesion composition type. However, the mean visual acuity scores of 50.1 (approximate Snellen equivalent: 20/100) for all predominantly classic lesions, 54.3 (approximate Snellen equivalent: $20/80^{-1}$) for all minimally classic lesions, and 65.7 (approximate Snellen equivalent: $20/50^{+1}$) for all occult with no classic lesions were different from each other. Sample sizes for multiple linear regression analyses that included lesion size were slightly smaller because the Reading Center could not define the lesion size in 13 patients owing to inadequate photograph quality. These are identified as "cannot grade" in Table 1. There were no differences in the mean lesion size at baseline between the verteporfin and placebo treatment groups within any lesion composition type. However, the mean size of predominantly classic lesions (3.4 disk areas) was smaller than that of either minimally classic lesions (4.7 disk areas) or occult with no classic lesions (4.3 disk areas). The mean size of minimally classic lesions was slightly larger than that of occult lesions. Of 238 predominantly classic lesions that could be graded, 154 (65%) were 4 disk areas or less while only 21 (9%) were larger than 6 disk areas. Of the 300 minimally classic lesions and 255 occult with no classic lesions that could be graded, 117 (39%) and 119 (47%), respectively, were 4 disk areas or less while 65 (22%) and 43 (17%), respectively, were larger than 6 disk areas.

The natural history of visual acuity loss was assessed. Untreated patients with predominantly classic lesions had a lower mean visual acuity letter score (51, approximate Snellen equivalent: $20/100^{+1}$) than untreated patients with minimally classic lesions (54, approximate Snellen equivalent: $20/80^{-1}$) on entry into the TAP Investigation (Figure 1). Despite the lower baseline mean visual acuity, by the month 24 examination untreated patients with predominantly classic lesions lost more visual acuity (23 letters) than those with minimally classic lesions (17 letters). By the month 24 follow-up examination, the mean visual acuity letter score of untreated patients with predominantly classic lesions was 28 (approximate Snellen equivalent: $20/250^{-2}$) compared with 37 (approximate Snellen equivalent: $20/200^{+2}$) in untreated patients with

TABLE 2. Visual Acuity Categories in Untreated (Placebo) Eyes at Baseline and Month 24 Follow-up by Lesion Composition*

Visual Acuity Letter Score (Approximate Snellen Equivalent)	Predominantly Classic (n = 83) No. (%)		Minimally Classic (n = 104) No. (%)		Occult with No Classic (n = 92) No. (%)	
	Baseline	Month 24	Baseline	Month 24	Baseline	Month 24
>73 (>20/40)	0 (0)	0 (0)	0 (0)	5 (5)	14 (15)	6 (7)
73–54 (20/40–20/80)	35 (42)	10 (12)	55 (53)	13 (13)	71 (77)	23 (25)
53–34 (20/100–20/160)	48 (58)	17 (21)	49 (47)	38 (37)	7 (8)	22 (24)
≤33 (≤20/200)	0 (0)	56 (68)	0 (0)	48 (46)	0 (0)	41 (45)
Mean, letter score (approximate Snellen equivalent)	51 ($20/100^{+1}$)	28 ($20/250^{-2}$)	54 ($20/80^{-1}$)	37 ($20/200^{+2}$)	65 (20/50)	40 (20/160)

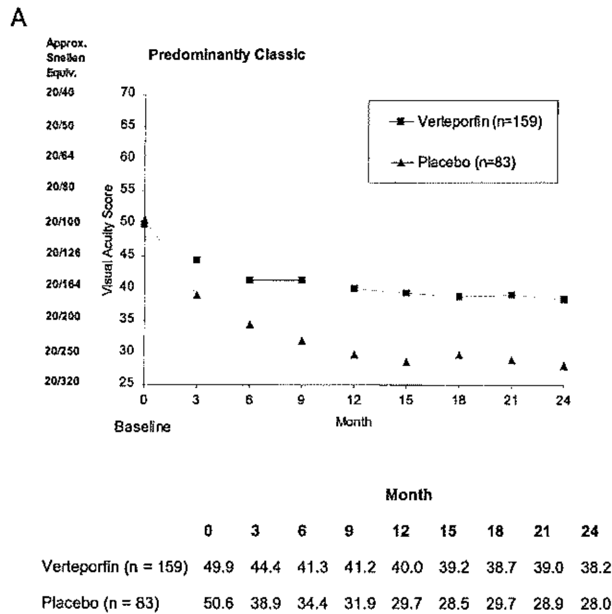
*Using the last observation carried forward for missing values.

minimally classic lesions (Table 2, Figure 1). Untreated patients who had occult with no classic lesions entered the study with a mean visual acuity letter score of 65 (approximate Snellen equivalent: 20/50), declining to 40 (approximate Snellen equivalent: 20/160) by the month 24 examination. The rate of the visual acuity decline for untreated patients was different among the three lesion compositions. In patients with predominantly classic lesions, most vision loss occurred within the first 6 months with little vision loss after the first year. Untreated patients who had occult with no classic lesions had a more constant decline in mean visual acuity during the first year with the rate of decline slowing markedly over the second year. Untreated patients with minimally classic lesions initially lost vision at a rate in between those with other lesion compositions with most vision loss occurring within the first 6 months. In untreated patients with all lesion composition types, the vision loss between the month 18 and month 24 examination after inclusion in the studies was negligible (Figure 1). A broad heterogeneity of visual acuity outcomes by the month 24 examination was found in the study eyes of the 92 untreated patients with occult with no classic lesion composition, with 6 (7%) retaining a Snellen equivalent better than 20/40 and 29 (32%) having 20/80 or better (Table 2). Untreated patients with minimally classic lesions also had a broad heterogeneity of outcomes, with 5 (5%) of 104 patients having a Snellen equivalent better than 20/40 despite no patients having this higher level of visual acuity at baseline (Table 2). Untreated patients with predominantly classic lesions had the least heterogeneity of outcomes, with 56 (68%) of 83 patients having a Snellen equivalent worse than 20/200 and only 10 (12%) retaining a Snellen equivalent of 20/40 to 20/80 (Table 2).

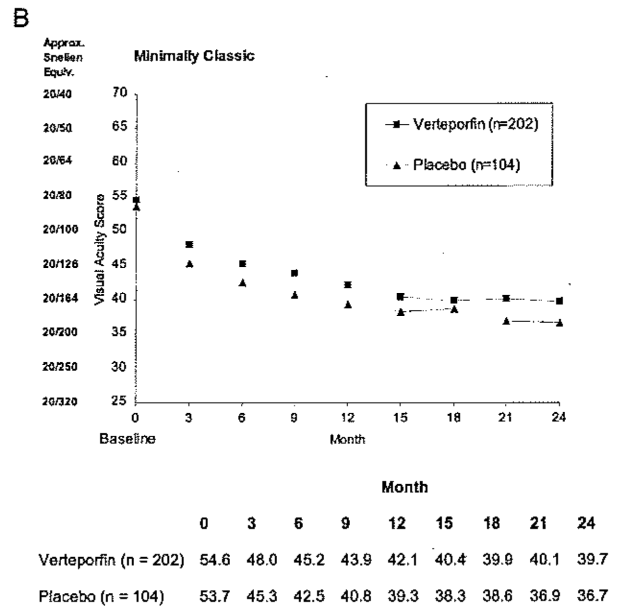
The impact of verteporfin therapy on visual acuity decline was evaluated. Verteporfin-treated groups had less mean visual acuity decline in all lesion compositions (Figure 2), although the magnitude of treatment benefit was greatest in predominantly classic lesions (Figure 2A) and least in minimally classic lesions (Figure 2B).

Multiple linear regression analysis of the visual acuity change from baseline to the month 24 examination for each lesion composition, including baseline visual acuity, baseline lesion size, as well as interaction terms between treatment and each of these two variables in the model, showed a significant interaction between treatment and lesion size for occult with no classic lesions ($P = .03$) and minimally classic lesions ($P = .03$) indicating a better treatment effect in smaller rather than larger lesions but not for predominantly classic lesions ($P = .19$). No significant interaction was found between treatment and baseline visual acuity for any of the three lesion types (predominantly classic lesions $P = .34$, minimally classic lesions $P = .48$, and occult with no classic lesions $P = .49$).

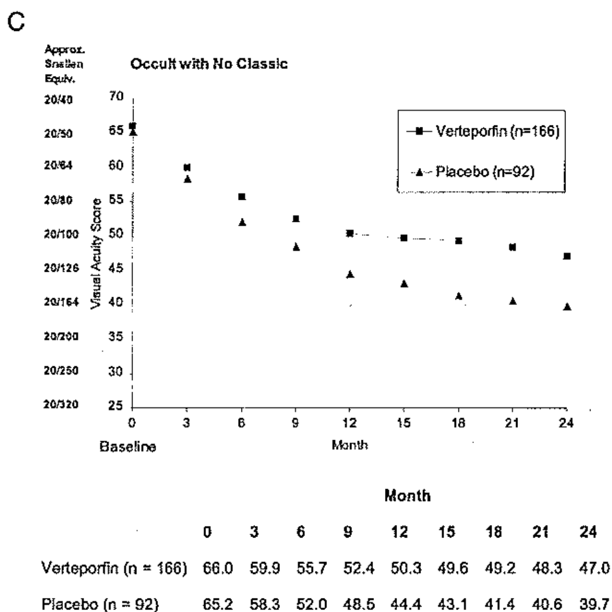
Multiple linear regression analysis of the visual acuity change from baseline to the month 24 examination for all three lesion compositions combined, including lesion composition, baseline visual acuity, baseline lesion size, as well as interaction terms between treatment and each of these three variables in the model, showed a better treatment effect in smaller than larger lesions ($P = .01$) but no significant interaction between either treatment and the lesion composition type ($P = .18$) or treatment and baseline visual acuity ($P = .53$). This analysis showed that of the three baseline factors included in the model lesion size had a more significant impact on verteporfin treatment benefit than either lesion composition or visual acuity at baseline. When the same analysis was conducted using the observed dataset (without the last observation carried forward) at the month 24 examination, the conclusion was the same, with only the treatment by lesion size interaction being significant ($P = .006$). When the same analysis was conducted using the entire population of all patients enrolled in the TAP Investigation (n = 609) and the VIP Trial (n = 339), with or without the last observation carried forward at the month 24 examination, the conclusion was the same, with the treatment by lesion size interaction being significant ($P = .032$ with last observation carried forward and $P = .043$ without last observation carried forward).



	Month								
	0	3	6	9	12	15	18	21	24
Verteporfin (n = 159)	49.9	44.4	41.3	41.2	40.0	39.2	38.7	39.0	38.2
Placebo (n = 83)	50.6	38.9	34.4	31.9	29.7	28.5	29.7	28.9	28.0



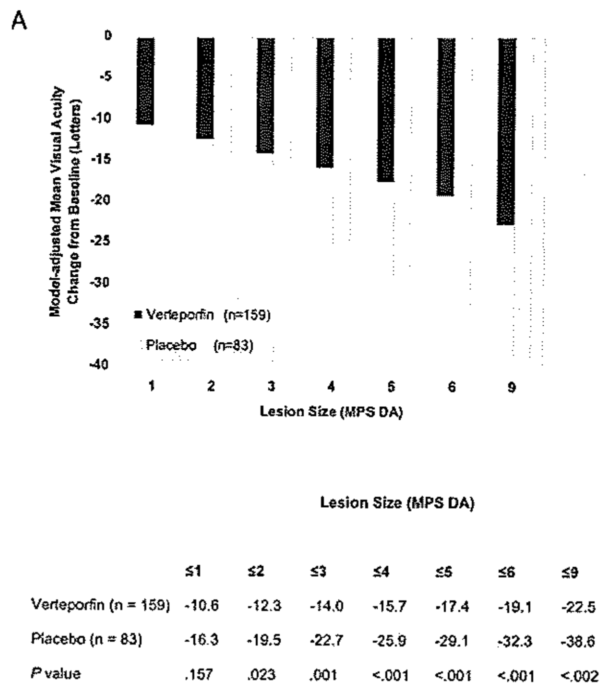
	Month								
	0	3	6	9	12	15	18	21	24
Verteporfin (n = 202)	54.6	48.0	45.2	43.9	42.1	40.4	39.9	40.1	39.7
Placebo (n = 104)	53.7	45.3	42.5	40.8	39.3	38.3	38.6	36.9	36.7



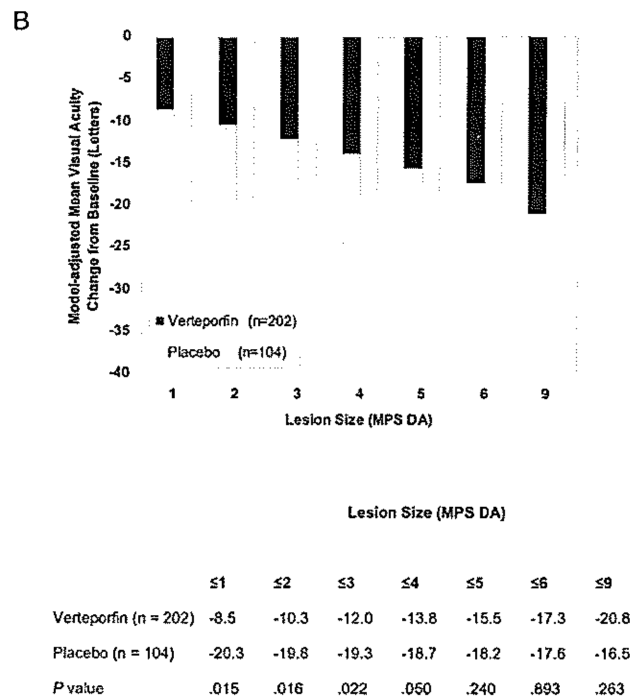
	Month								
	0	3	6	9	12	15	18	21	24
Verteporfin (n = 166)	66.0	59.9	55.7	52.4	50.3	49.6	49.2	48.3	47.0
Placebo (n = 92)	65.2	58.3	52.0	48.5	44.4	43.1	41.4	40.6	39.7

FIGURE 2. Mean visual acuity scores over time (verteporfin therapy vs placebo) in (A) patients with predominantly classic choroidal neovascularization (CNV), (B) patients with minimally classic CNV, and (C) patients with occult with no classic CNV at baseline.

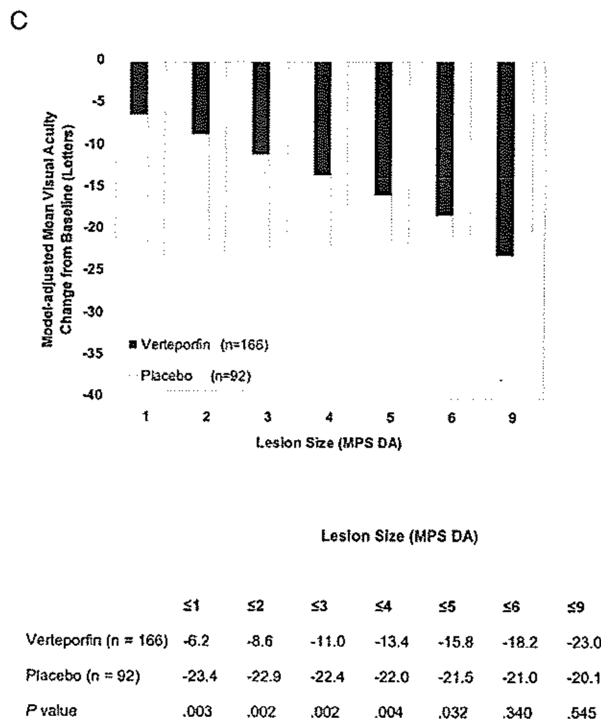
Model-adjusted means of visual acuity change from baseline from the multiple linear regression analyses of individual lesion compositions and of the combination of the 3 lesion compositions show the lesion size effect (Figure 3). Placebo-treated minimally classic and occult with no classic lesions lost similar amounts of visual acuity (mean loss 17 to 23 letters), independent of the lesion size, by the month 24 examination. Conversely, in placebo-treated predominantly classic lesions, the magnitude of mean visual acuity loss increased with increasing baseline lesion size; the mean visual acuity loss in the largest lesions allowed in the study was more than twice that in the smallest lesions. When the same analysis was conducted using the observed dataset (without last observation car-



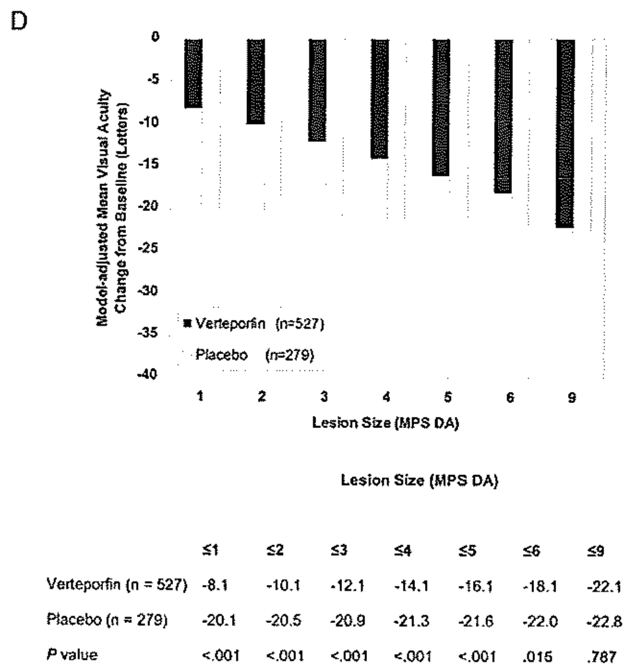
	≤1	≤2	≤3	≤4	≤5	≤6	≤9
Verteporfin (n = 159)	-10.6	-12.3	-14.0	-15.7	-17.4	-19.1	-22.5
Placebo (n = 83)	-16.3	-19.5	-22.7	-25.9	-29.1	-32.3	-38.6
P value	.157	.023	.001	<.001	<.001	<.001	<.002



	≤1	≤2	≤3	≤4	≤5	≤6	≤9
Verteporfin (n = 202)	-8.5	-10.3	-12.0	-13.8	-15.5	-17.3	-20.8
Placebo (n = 104)	-20.3	-19.8	-19.3	-18.7	-18.2	-17.6	-16.5
P value	.015	.016	.022	.050	.240	.893	.263



	≤1	≤2	≤3	≤4	≤5	≤6	≤9
Verteporfin (n = 166)	-6.2	-8.6	-11.0	-13.4	-15.8	-18.2	-23.0
Placebo (n = 92)	-23.4	-22.9	-22.4	-22.0	-21.5	-21.0	-20.1
P value	.003	.002	.002	.004	.032	.340	.545

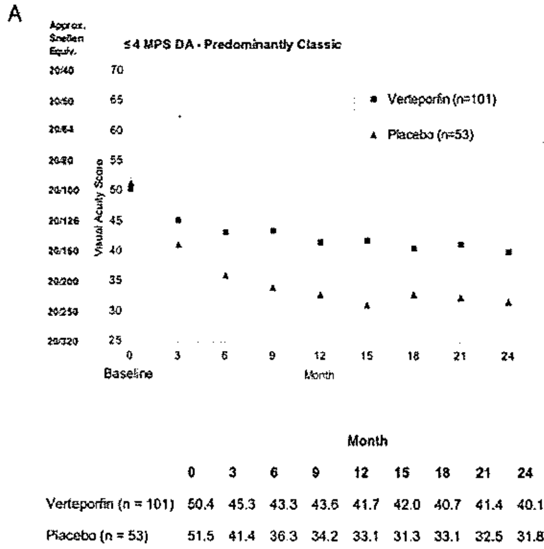


	≤1	≤2	≤3	≤4	≤5	≤6	≤9
Verteporfin (n = 527)	-8.1	-10.1	-12.1	-14.1	-16.1	-18.1	-22.1
Placebo (n = 279)	-20.1	-20.5	-20.9	-21.3	-21.6	-22.0	-22.8
P value	<.001	<.001	<.001	<.001	<.001	.015	.767

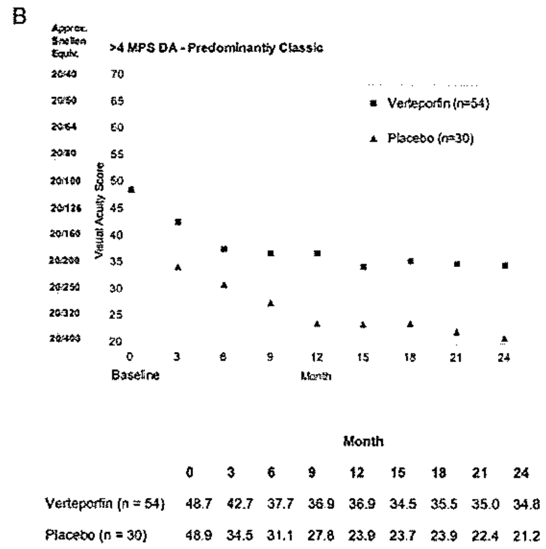
FIGURE 3. Model-adjusted means of visual acuity change between baseline and month 24 examination for treated and untreated lesions by baseline lesion size based on multiple linear regression analysis in (A) patients with predominantly classic choroidal neovascularization (CNV), (B) patients with minimally classic CNV, (C) patients with occult with no classic CNV, and (D) all patients regardless of lesion composition at baseline. MPS DA = Macular Photocoagulation Study disk area.

ried forward) at the month 24 examination, the conclusion was the same (data available as supplementary material at http://ajo.com).

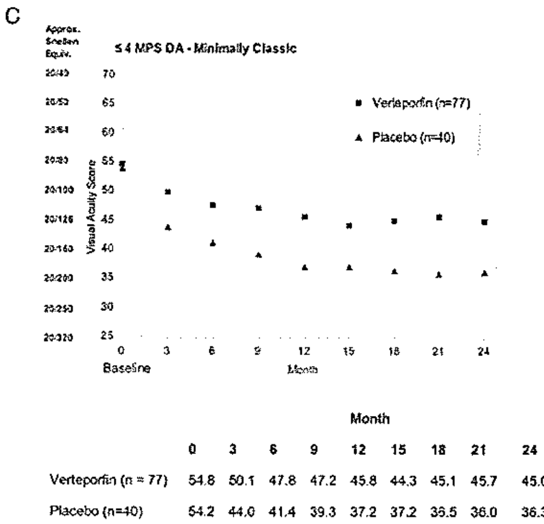
For all verteporfin-treated lesions, irrespective of lesion composition, the amount of mean visual acuity loss appeared to be related to lesion size (Figure 3). In occult with



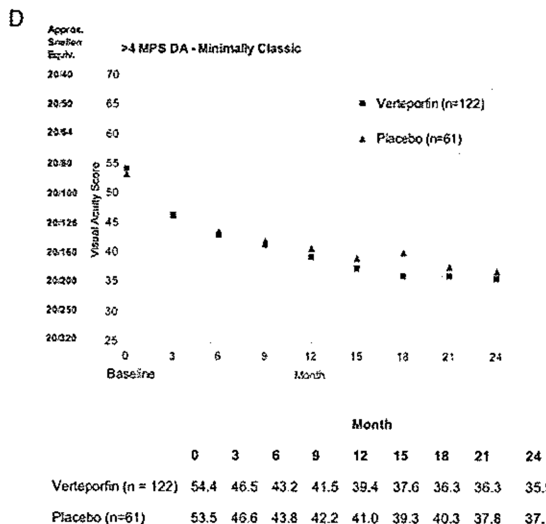
	0	3	6	9	12	15	18	21	24
Verteporfin (n = 101)	50.4	45.3	43.3	43.6	41.7	42.0	40.7	41.4	40.1
Placebo (n = 53)	51.5	41.4	36.3	34.2	33.1	31.3	33.1	32.5	31.8



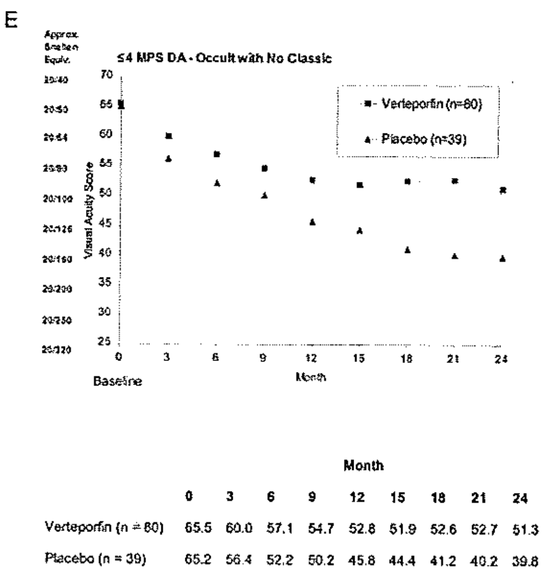
	0	3	6	9	12	15	18	21	24
Verteporfin (n = 54)	48.7	42.7	37.7	36.9	36.9	34.5	35.5	35.0	34.8
Placebo (n = 30)	48.9	34.5	31.1	27.8	23.9	23.7	23.9	22.4	21.2



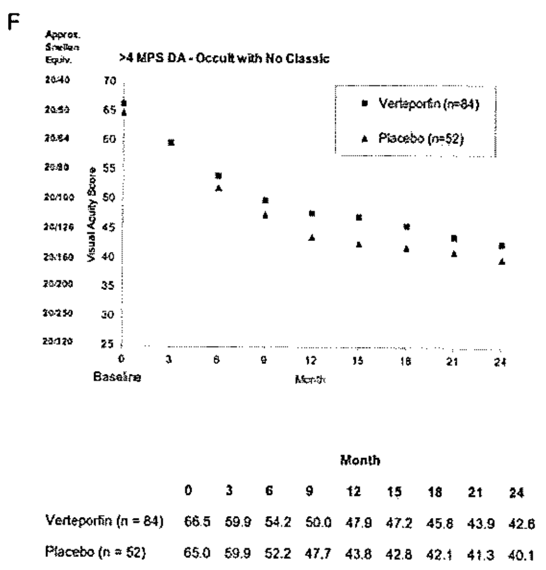
	0	3	6	9	12	15	18	21	24
Verteporfin (n = 77)	54.8	50.1	47.8	47.2	45.8	44.3	45.1	45.7	45.0
Placebo (n=40)	54.2	44.0	41.4	39.3	37.2	37.2	36.5	36.0	36.3



	0	3	6	9	12	15	18	21	24
Verteporfin (n = 122)	54.4	46.5	43.2	41.5	39.4	37.6	36.3	36.3	35.9
Placebo (n=61)	53.5	46.6	43.8	42.2	41.0	39.3	40.3	37.8	37.1



	0	3	6	9	12	15	18	21	24
Verteporfin (n = 80)	65.5	60.0	57.1	54.7	52.8	51.9	52.6	52.7	51.3
Placebo (n = 39)	65.2	56.4	52.2	50.2	45.8	44.4	41.2	40.2	39.8



	0	3	6	9	12	15	18	21	24
Verteporfin (n = 84)	66.5	59.9	54.2	50.0	47.9	47.2	45.8	43.9	42.6
Placebo (n = 52)	65.0	59.9	52.2	47.7	43.8	42.8	42.1	41.3	40.1

FIGURE 4. Mean visual acuity scores over time for smaller (≤4 MPS disk areas) or larger (>4 MPS disk areas) lesions (verteporfin therapy vs placebo) in (A, B) patients with predominantly classic choroidal neovascularization (CNV), (C, D) patients with minimally classic CNV, and (E, F) patients with occult with no classic CNV at baseline. MPS = Mean Photocoagulation Study.

no classic lesions, the mean visual acuity loss for the smallest lesions was nearly four times less than the largest lesions (Figure 3C). In verteporfin-treated lesions with a predominantly classic or minimally classic composition, the mean visual acuity loss in the smallest lesions was about half of that in the largest lesions. Subtracting the mean visual acuity loss of the treated lesions from that of the untreated lesions provided the estimation of the treatment effect with the multiple linear regression model. The treatment effect was analyzed statistically within each lesion size category, and a P value of less than .05 was found for occult with no classic lesions up to 5 disk areas, for minimally classic lesions up to 4 disk areas, and for predominantly classic lesions in all size categories except 1 disk area or less. For occult with no classic and minimally classic lesions larger than 6 disk areas, there was no benefit. Predominantly classic lesions appeared to behave differently from occult with no classic and minimally classic lesions, in that there appeared to be a treatment benefit in larger sizes ($P < .05$). However, only 21 (9%) of the 238 predominantly classic lesions were larger than 6 disk areas.

Since the multiple linear regression models indicated a treatment benefit for smaller occult with no classic lesions and minimally classic lesions, visual acuity curves of observed raw data are presented for comparison among the different lesion compositions. All lesion compositions (predominantly classic, minimally classic, and occult with no classic) with a baseline size no greater than 4 disk areas showed a similar approximately 10-letter difference ($P = .010$, $P = .031$, and $P = .004$, respectively) in visual acuity change from baseline by the month 24 examination (Figure 4).

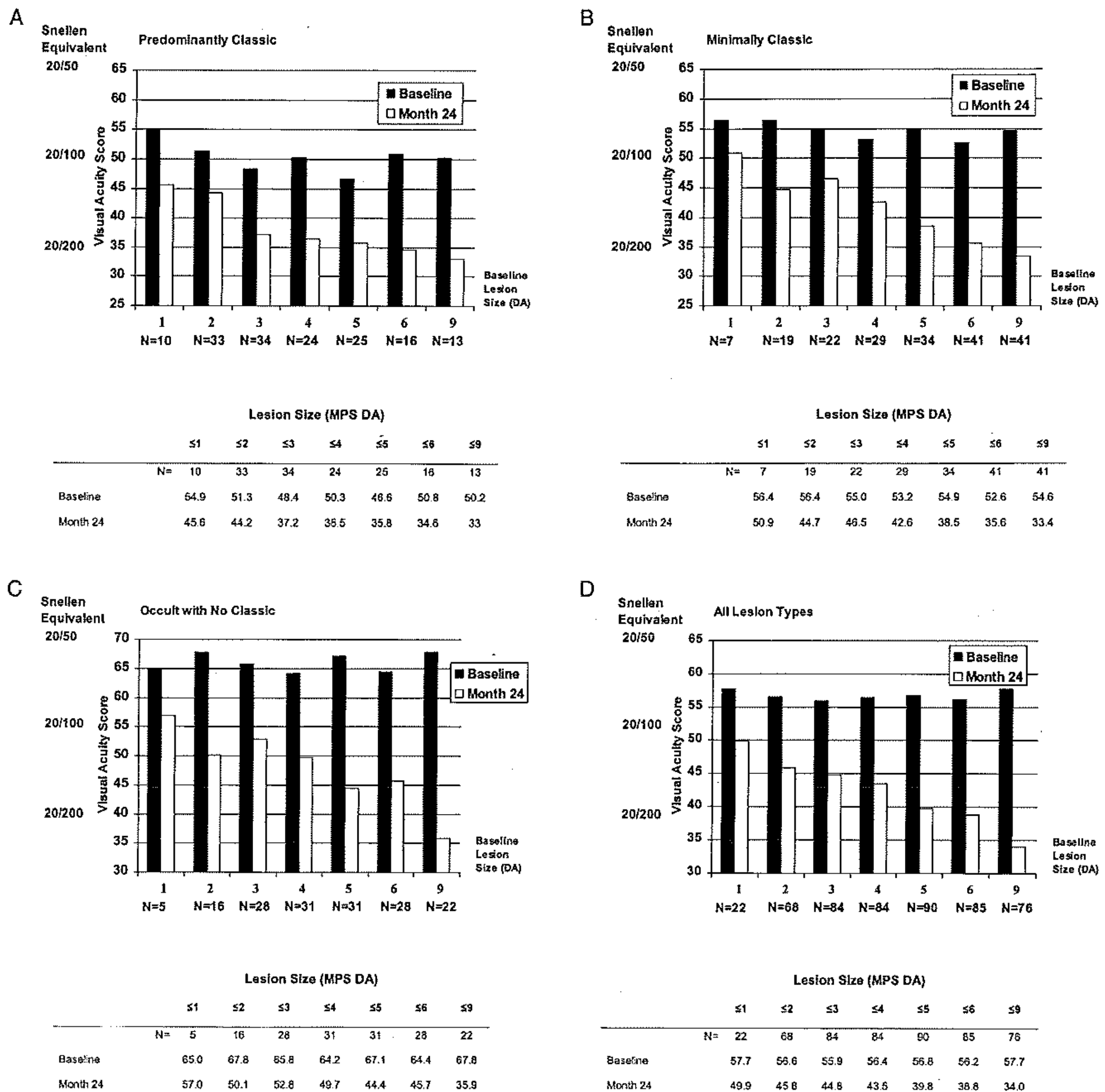
Mean visual acuity within verteporfin-treated lesions was relatively similar at baseline for each lesion size category. However, by 24 months smaller treated lesions retained greater visual acuity than larger lesions independent of lesion composition (Figure 5).

When visual acuity outcomes were analyzed using the incidence of a 15 or more letter loss from baseline to month 24 there was a significant interaction between treatment and baseline lesion size ($P = .03$) and treatment and baseline visual acuity ($P = .03$) when using the method of last observation carried forward for missing data at the month 24 examination. Using observed data (without last observation carried forward) at the month 24 examination, only the treatment by lesion size interaction was significant ($P = .009$) for the 15 or more letter loss outcome.

DISCUSSION

THESE EXPLORATORY ANALYSES WERE INITIATED BECAUSE prospectively planned subgroup analyses in AMD patients presenting with occult with no classic lesions included in the VIP Trial indicated that both baseline lesion size and baseline visual acuity score significantly affected the magnitude of treatment benefit.[4] Patients with smaller lesions had more benefit than those with larger lesions, while patients with worse visual acuity had more benefit than those with better visual acuity. This finding prompted a review of the classic-containing lesions included in the TAP Investigation to determine whether similar interactions might exist, and perhaps provide a biological rationale as to why verteporfin therapy provided visual acuity benefit in predominantly classic and occult with no classic lesions but not in minimally classic lesions.

Review of the baseline characteristics in the TAP Investigation and the VIP Trial demonstrates that there were differences in the lesion size and baseline visual acuity among the different lesion compositions. In the TAP Investigation, predominantly classic lesions were, on average, smaller than minimally classic lesions (Table 1). This difference was not noted in TAP Report 1[1] because the lesion size for the total population was reported independent of lesion composition. In a more recent publication[7] that examined the baseline characteristics and outcomes of predominantly classic vs minimally classic lesions, this lesion size difference between these two lesion composition types was less apparent because the lesion size categories were grouped into ranges as defined in the TAP Investigation analysis plan (3 or less, more than 3 to 6 or less, more than 6 to 9 or less, and more than 9 disk areas) while in the current analyses lesion size was evaluated as a numerical variable and included all lesion size categories. The occult with no classic lesions included in the VIP Trial were larger than the predominantly classic lesions and slightly smaller than the minimally classic lesions included in the TAP Investigation. The occult with no classic lesions had a better mean baseline visual acuity than classic-containing lesions from the TAP Investigation, likely due to the different range of visual acuities permitted within the inclusion criteria in the VIP Trial. The VIP Trial allowed a visual acuity of 20/100 or better, while the TAP Investigation allowed a visual acuity of 20/40 to 20/200. Although the inclusion criteria of both studies allowed lesion sizes up to 9 disk areas, the better range of visual acuity required for eligibility coupled with the requirement for presumed recent disease progression in the VIP Trial may have selected smaller occult with no classic lesions than if the TAP Investigation criteria (lower



A — Lesion Size (MPS DA)

	≤1	≤2	≤3	≤4	≤5	≤6	≤9
N=	10	33	34	24	25	16	13
Baseline	54.9	51.3	48.4	50.3	46.6	50.8	50.2
Month 24	45.6	44.2	37.2	36.5	35.8	34.6	33

B — Lesion Size (MPS DA)

	≤1	≤2	≤3	≤4	≤5	≤6	≤9
N=	7	19	22	29	34	41	41
Baseline	56.4	56.4	55.0	53.2	54.9	52.6	54.6
Month 24	50.9	44.7	46.5	42.6	38.5	35.6	33.4

C — Lesion Size (MPS DA)

	≤1	≤2	≤3	≤4	≤5	≤6	≤9
N=	5	16	28	31	31	28	22
Baseline	65.0	67.8	65.8	64.2	67.1	64.4	67.8
Month 24	57.0	50.1	52.8	49.7	44.4	45.7	35.9

D — Lesion Size (MPS DA)

	≤1	≤2	≤3	≤4	≤5	≤6	≤9
N=	22	68	84	84	90	85	76
Baseline	57.7	56.6	55.9	56.4	56.8	56.2	57.7
Month 24	49.9	45.8	44.8	43.6	39.8	38.8	34.0

FIGURE 5. Mean visual acuity among verteporfin-treated lesions at baseline and the month 24 examination for each lesion size category in (A) predominantly classic lesions, (B) minimally classic lesions, and (C) occult with no classic lesions at baseline. MPS DA = Mean Photocoagulation Study disk area.

levels of visual acuity and no evidence of presumed recent disease progression) had been used to select these lesions.

It is unknown why this difference exists. Experience suggests that predominantly classic lesions almost always cause visual symptoms promptly, perhaps allowing identification at smaller lesion sizes and before relatively large areas of occult CNV have developed, whereas minimally classic or occult with no classic lesions may or may not cause visual symptoms promptly, allowing some lesions to grow to a larger size before the patient visits an ophthalmologist.

Lesion size was a significant factor affecting the magnitude of treatment benefit in occult with no classic and minimally classic lesions but not in predominantly classic lesions. The TAP Investigation was unable to detect any treatment by lesion size interaction because the prospectively planned lesion size subgroup analyses combined the predominantly classic and minimally classic lesions, and

the predominantly classic lesions had no significant lesion size interaction with treatment benefit. However, once the individual lesion compositions were analyzed using a numerical lesion size in the multiple linear regression model, both minimally classic lesions and occult with no classic lesions demonstrated a similar lesion-size-by-treatment interaction. The importance of the lesion size effect is emphasized by the fact that there was a treatment-by-lesion-size interaction even when all lesion types were included in the multiple linear regression model.

These results do not appear to be dependent on the use of last observation carried forward for the intent-to-treat analysis since similar results were obtained when observed data (without last observation carried forward) were used. Similarly, the results do not appear to be due to the exclusion of data from the TAP Investigation patients classified as having occult with no classic choroidal neovascular lesions (61 eyes) and data from those patients with classic-containing lesions from the VIP Trial (81 eyes) that were not included in these exploratory analyses because they had different inclusion criteria from the main lesion composition populations. Similar conclusions were obtained when the entire population of both the TAP Investigation and the VIP Trial were included in the multiple linear regression analyses. Also, the conclusions were similar if visual acuity was treated as a binary outcome, that is, loss of at least 15 letters from baseline that was the primary visual acuity criterion in the TAP Investigation and VIP Trial, rather than as a mean change from baseline.

Two thirds of the predominantly classic lesions were relatively small (4 disk areas or less) compared with just over one third of minimally classic lesions and nearly one half of the occult with no classic lesions (Table 1). When the mean visual acuity change over time is compared for these smaller lesion sizes, a similar treatment benefit can be found in all lesion types (Figure 4). Lesion size is clearly not the only factor affecting verteporfin treatment benefit, since all lesion sizes appeared to benefit for predominantly classic lesions. However, when treatment was applied, smaller lesions lost less vision, on average, than larger lesions in all three lesion compositions (Figure 5). This suggests that verteporfin therapy is more likely to preserve a greater amount of visual acuity, regardless of lesion composition, when lesions are small (Figure 5). Untreated predominantly classic lesions that were large on presentation underwent rapid and significant vision loss without treatment (Figure 3). Outcomes with verteporfin therapy in this situation appear to be associated with a decreased risk of vision loss. However, in minimally classic and occult with no classic lesions, there appears to be far greater heterogeneity within the natural history that might depend on factors other than lesion composition and size.

The heterogeneity of the natural history of different lesion compositions is important to recognize when counseling patients regarding prognosis. Many minimally classic lesions and occult with no classic lesions included in the TAP Investigation and the VIP Trial had a relatively good natural history. Specifically, they presented as large lesions and maintained relatively good visual acuity throughout 24 months of follow-up. In the TAP Investigation, 28 eyes (27%) of untreated minimally classic lesions remained stable or improved (less than 5-letter loss) at the month 24 examination.[7] In untreated predominantly classic lesions, only 15 eyes (18%) remained stable or improved despite having a lower mean visual acuity at baseline (approximate Snellen equivalent of 20/100) and therefore less visual acuity to lose than minimally classic lesions (approximate Snellen equivalent 20/80 at baseline).[7] In the VIP Trial, the occult with no classic lesions presented with a better visual acuity (approximate Snellen equivalent: $20/50^{+1}$ at baseline), so large vision losses should be expected. However, of the untreated lesions with these baseline characteristics, 19 eyes (20%) still had stable or improved vision (less than 5-letter loss) at the month 24 examination.[4] The VIP Trial suggests that verteporfin treatment is not beneficial in occult with no classic lesions that were both large and had better levels of visual acuity,[4] perhaps because of the relatively benign natural history of many of these lesions. Model-adjusted means of visual acuity change from baseline from the multiple linear regression model also suggest that occult with no classic lesions and minimally classic lesions greater than 6 disk areas did not benefit in either study (Figure 4). This may be due to the presence of a significant number of "survivor" lesions in which some larger lesions presenting with relatively good levels of visual acuity represent choroidal neovascular lesion growth with minimal visual acuity loss. Alternatively, in the setting of relatively good visual acuity associated with CNV it may be easier to detect a harmful effect of treating a large area of the macula with the current verteporfin regimen in lesions with a less aggressive natural history. In most large lesions presenting with good visual acuity, therefore, it may be prudent to withhold verteporfin therapy unless a recent history of vision loss can be established.

In conclusion, within the TAP Investigation and the VIP Trial, lesion size at baseline affected the magnitude of the treatment benefit in occult with no classic lesions and minimally classic lesions. Lesion size was not shown to be a significant factor affecting treatment benefit in predominantly classic lesions, but most of these lesions were small (4 disk areas or less) at presentation. When all lesion composition types were included in the multiple linear regression model, lesion size was a more significant factor affecting treatment benefit than either lesion composition or visual acuity at baseline. This finding does not suggest that lesion composition or visual acuity on presentation are not important factors affecting treatment benefit, since these factors can reflect the expected natural history of vision loss. Using the treatment regimen tested in both studies, it appears that the benefits of verteporfin therapy

are dependent on both the lesion size and the natural history of the lesion composition on initial presentation. In patients with AMD, treating smaller rather than larger neovascular lesions, regardless of lesion composition, likely will result in a better level of visual acuity. Choroidal neovascular lesions secondary to AMD with the poorest natural history, such as predominantly classic lesions, would be expected to benefit most from verteporfin therapy, with maintenance of better levels of visual acuity at 24 months after presentation, especially when the lesion is small on presentation. These exploratory analyses support the treatment recommendations for predominantly classic lesions from results of the TAP Investigation and for occult with no classic lesions from results of the VIP Trial. The analyses also provide a potential explanation for the lack of visual acuity benefit in the total population of minimally classic lesions included in the TAP Investigation, specifically, many minimally classic lesions had a large size at baseline and, in untreated patients, a broad heterogeneity of visual outcomes (including relatively good outcomes). Furthermore, these exploratory analyses suggest that verteporfin therapy of smaller occult with no classic lesions and minimally classic lesions have a similar treatment benefit as that of smaller predominantly classic lesions.

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Complete lists of the participants in the TAP and VIP Study Groups are available in the *Archives of Ophthalmology* (1999;117:1329–1345) and the AMERICAN JOURNAL OF OPHTHALMOLOGY (2001;131:541–560), respectively.

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