Objective: To determine whether data from patients with age-related macular degeneration (AMD) assigned to the placebo group in the Verteporfin in Photodynamic Therapy (VIP) Trial provide a rationale for continuation or cessation of follow-up of individuals with subfoveal occult choroidal neovascularization (CNV) with no classic lesions, presumed recent disease progression, larger lesion size (>4 disc areas), and a higher level of visual acuity (approximate Snellen equivalent, ≥20/50 in the affected eye) in whom no treatment is given at initial examination.

Methods: In a prospective, noncomparative case series, angiograms of participants assigned to a placebo group who had occult with no classic lesion composition at baseline were reviewed to identify conversion to minimally classic (area of classic CNV ≥0% but <50% of the entire lesion area) or predominantly classic (area of classic CNV ≥50% of the entire lesion area) composition.

Results: Of the 114 patients with AMD assigned to the placebo group, 89 were judged to have occult with no classic lesion composition at baseline in the study eye when fluorescein angiograms were reviewed in late 2001 for this report. By 24 months, 7 (8%) of the 89 patients had lesions that converted to predominantly classic composition, and 41 (46%) had minimally classic composition. Among the 24 patients with a baseline visual acuity better than 20/50⁻¹ and lesion size greater than 4 disc areas whose lesions did not convert to predominantly classic composition, the visual acuity of 18 (75%) dropped below 20/50. Six of these 18 continued to have occult with no classic CNV with a visual acuity of 20/100 or better and had a lesion size no greater than 9 disc areas at the time that visual acuity dropped below 20/50.

Conclusions: Continued monitoring, rather than cessation of follow-up, is recommended for patients with occult with no classic lesions, similar to those patients enrolled in the VIP Trial who did not initially receive treatment when they had relatively large lesions with good visual acuity. In these cases, if visual acuity decreases or predominantly classic features develop, photodynamic therapy with verteporfin or pegaptanib sodium injections may be considered.

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predominantly classic lesions in AMD, pathologic myopia, and ocular histoplasmosis syndrome.

In this setting, investigators participating in the VIP Trial questioned whether the data from patients with AMD assigned to the placebo group could provide a rationale for continuation or cessation of follow-up for those who were seen at randomization with subfoveal occult with no classic lesions, presumed recent disease progression, larger lesion size (>4 MPS disc areas), and a higher level of visual acuity (approximate Snellen equivalent, ≥20/50). Furthermore, the investigators wanted to determine in how many patients in the VIP Trial untreated occult with no classic lesions converted to predominantly classic lesions (area of classic CNV ≥50% of the entire lesion area).

**METHODS**

The methods of the VIP Trial have been reported previously. In brief, study participants were enrolled in a double-masked randomized clinical trial between February 1998 and September 1998 at any 1 of 28 clinical centers throughout North America and Europe after an informed consent process and form were approved by the respective center’s institutional review board or ethics committee. Principal eligibility criteria included the presence of subfoveal CNV due to AMD in which the lesion on fluorescein angiography had a greatest linear dimension on the retina no greater than 5400 µm and in which at least 50% of the lesion components were CNV following specific definitions of these criteria. If no classic CNV was present, presumed recent disease progression was to have been documented, which required at least 1 of the following: (1) blood associated with CNV; (2) best-corrected visual acuity deterioration of at least 5 letters within the past 12 weeks in which both measurements followed the protocol used in the Treatment of Age-Related Macular Degeneration with Photodynamic Therapy (TAP) Investigation; or (3) an increase in the greatest linear dimension of the lesion of at least 10% within the past 12 weeks. At study entry, patients had a study eye assigned randomly to verteporfin therapy or infusion of a placebo with a sham treatment in a double-masked fashion. The fellow eye could not be enrolled in the study at baseline or during follow-up. Patients were to be followed every 3 months for at least 2 years, with baseline and follow-up examinations that included best-corrected visual acuity following a standardized protocol refraction and stereoscopic color fundus photographs and fluorescein angiograms. The original VIP Trial protocol included evaluation of follow-up angiograms at the 12- and 24-month examinations by the photograph reading center for the presence of classic CNV; however, no attempt was made to determine the proportion of the lesion that was classic.

Beginning in late 2001 for this report, follow-up angiograms in which classic CNV was identified were reanalyzed to determine how many occult with no classic lesions converted to predominantly classic (Figure 1) or minimally classic (Figure 2) composition at a follow-up examination. Because follow-up angiograms were reanalyzed, baseline angiograms were also reanalyzed to minimize temporal variability in the grading process, described previously. This reanalysis of baseline angiograms resulted in changes in the total number of placebo-treated lesions originally reported as occult with no classic lesions (n=92) from the VIP Trial. The group of 92 patients originally included 13 lesions in which the presence of either classic or occult CNV was questionable. Of these 13 lesions, all were included in the occult with no classic CNV group based on the enrolling ophthalmologist’s assessment that the lesions were of occult with no classic composition. Of the 13 lesions originally graded as questionable, 11 were judged to be occult with no classic CNV and 2 were subsequently judged to contain classic CNV in the late 2001 re-review; these latter 2 lesions were not analyzed further for this report. Of the 79 lesions originally graded as occult with no classic CNV, 1 was subsequently judged to contain classic CNV and also was not analyzed further for this report. Thus, 89 occult with no classic lesions assigned to placebo were analyzed for this report. The late 2001 reevaluation of angiograms to determine lesion composition for this report was performed according to the same procedures as for initial evaluations (ie, 2 independent graders, open adjudication, and review by a reading center ophthalmologist). For lesions that converted to pre-
entire lesion area) lesions by the 12-month or 24-month follow-up examination. Of the 114 patients with AMD assigned to placebo in the VIP Trial, 89 were judged to have an occult with no classic lesion (>4 disc areas) at baseline (A) with a visual acuity (approximate Snellen equivalent) of 20/50 or higher. Database information at the 6-month examination indicates evidence of classic choroidal neovascularization (CNV). Subsequent grading of lesion composition of the fluorescein angiogram at the 6-month examination (B) indicates a minimally classic lesion (very bright area of fluorescence in the superotemporal portion of the lesion within a larger area of occult CNV) in which the area of classic CNV is less than 50% of the entire lesion (>4 disc areas), with a visual acuity of 20/63².

At each of the 3-month follow-up intervals, VIP Trial data from study participants who received placebo and who started the study with an occult with no classic lesion with both a larger lesion size (>4 MPS disc areas) and a higher level of visual acuity (approximate Snellen equivalent, ≥20/50) were also reviewed to determine how many experienced deterioration to a lower level of visual acuity (approximate Snellen equivalent, ≥20/50). The status of these eyes by the 24-month examination is summarized in Figure 4. By the 24-month examination, 3 (11%) of these 27 eyes converted to a predominantly classic lesion (and are included among the 7 of 89 eyes in Figure 4 that converted to this lesion composition), and 6 (22%) maintained a visual acuity (approximate Snellen equivalent) of at least 20/50. For the remaining 18 eyes, the visual acuity (approximate Snellen equivalent) decreased to a level of 20/50⁻¹ or worse. In 5 of these 18 eyes, the lesion composition was minimally classic at the time of visual acuity loss and remained minimally classic through the 24-month examination or last available fluorescein angiogram. In the remaining 13 of 18 eyes that decreased to a lower level of visual acuity, the lesion composition either remained occult with no classic lesion at the time of visual acuity decrease (10 eyes) or converted to a minimally classic lesion composition and then reverted back to an occult with no classic lesion with a visual acuity deterioration to a level of 20/50⁻¹ or worse (3 eyes).
The visual acuities (approximate Snellen equivalents) at the first documentation of this lower level of visual acuity while the lesion composition was occult with no classic CNV ranged from 20/50−1 to 20/100+2 for 10 eyes and 20/200 or worse in 3 eyes. The median time of visual acuity loss to 20/50−1 or worse was 6 months. The time of visual acuity loss for the 10 eyes that decreased to 20/50−1 to 20/100+2 at the first documentation of a lower level of visual acuity included 3 eyes at the 3-month examination, 4 eyes at the 6-month examination, 1 eye at the 9-month examination, and 2 eyes at the 12-month examination. At the time of the first documentation of a lower level of acuity for these 10 eyes, the lesion size was no greater than 9 MPS disc areas in 6 of these eyes. For the other 3 eyes in which the first documentation to a lower level of visual acuity was 20/200 or worse, the documentation was at the 12-month examination for 1 eye and the 24-month examination for the other 2 eyes.

For patients with subfoveal lesions composed of occult with no classic CNV associated with presumed recent disease progression with a larger size (>4 MPS disc areas) and higher levels of visual acuity (approximate Snellen equivalent, ≥20/50), in which verteporfin therapy does not appear to be beneficial and in whom pegaptanib injections may not be considered, continued monitoring for a situation in which verteporfin therapy or initiation of pegaptanib treatments might be considered, rather than cessation of follow-up, appears indicated. As shown in Figure 4, some of these lesions may convert to predominantly classic lesions (3 [11%] of 27) or remain occult with no classic CNV associated with lower levels of visual acuity (18 [67%] of 27), so verteporfin therapy might reduce the risk of vision loss. Furthermore, some of these lesions may go through a stage of converting to a minimally classic lesion and then reconvert to an occult with no classic lesion composition.

Some caveats to this analysis are apparent. First, one cannot know how many patients in the TAP Investigation who initially developed a predominantly classic lesion composition had lesions that had converted from occult with no classic CNV before entering the study; therefore, one does not know if the beneficial effect of verteporfin therapy observed in the TAP Investigation, which may have included patients who had predominantly classic lesions without converting from an occult with no classic composition, applies to occult with no classic lesions in the VIP Trial that converted to predominantly classic lesions. Similarly, one cannot know how many patients in the VIP Trial had relatively large occult with no classic lesions with higher levels of visual acuity that had deteriorated to a lower level of visual acuity before the patient entered the study. Consequently, one cannot be certain if patients with occult with no classic lesions who had lower levels of visual acuity when they entered the VIP Trial and received treatment would have similar beneficial responses to verteporfin therapy to those who initially have both larger lesions and higher levels of visual acuity and deteriorate to lower levels of visual acuity for which they then receive treatment. Nevertheless, in our opinion, there is no biological rationale to suggest that the same results observed in the TAP Investigation and VIP Trial could not be obtained for patients with occult with no classic lesions with higher levels of visual acuity and larger lesions that convert to predominantly classic compositions or for patients with lesions that remain occult with no classic CNV but develop lower levels of visual acuity.

Second, this analysis may underestimate the number of lesions that convert to a minimally classic or predominantly classic composition because angiograms were reviewed by photograph reading center graders at only 3-month intervals. If such a conversion occurred between these visits and rapidly progressed to a lesion composed predominantly of scarring or at a visit when an angiogram was not available, it would not be documented as a lesion that converted to a predominantly classic composition.
Third, these results are based on specific interpretations of lesion compositions on fluorescein angiography. Although these interpretations were shown to be reliable and reproducible by trained photograph graders at a central photograph reading center,

6,10 these interpretations may not be as reliable and reproducible when performed by ophthalmologists.11

Fourth, the results of these analyses would be stronger if the study population totaled more than 89 eyes at baseline. The interpretation of these findings is based on relatively small numbers, as noted in Figure 4. However, to our knowledge these data represent the largest amount of information available to date in which visual acuity, following a detailed protocol refraction and visual acuity measurement as well as centralized grading of color photography and fluorescein angiography, was available every 3 months for up to 2 years in a cohort followed up prospectively at multiple clinical centers. With these caveats in mind, this information may be of assistance to physicians who treat patients with subfoveal CNV and an occult with no classic lesion composition and provides further insight into understanding the natural history of occult with no classic lesions that develop with presumed recent disease progression.

In conclusion, for patients with AMD who had subfoveal occult with no classic CNV and presumed recent disease progression, conversions to predominantly classic composition were rare (4 [6%] of 62). In addition, careful monitoring rather than cessation of follow-up of an occult with no classic lesion with presumed recent disease progression with both a relatively larger size and a higher level of visual acuity seems warranted if treatment is not given because conversion to predominantly classic lesions or deterioration to lower levels of visual acuity, when verteporfin therapy might be considered or initiation of pegaptanib treatments might be reconsidered, can occur within 6 months. Since conversion to dominantly classic composition or deterioration to visual acuity worse than (approximate Snellen equivalent) 20/50−1 in this situation may occur up to at least 24 months after initial diagnosis, monitoring may be indicated as long as the lesion has not become too large or the visual acuity too poor before the conversion or deterioration to suggest that the effects of verteporfin therapy or pegaptanib injections would no longer be meaningful to the patient. These recommendations may change as results of other trials evaluating treatments for neovascular AMD are obtained.

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REFERENCES