Photodynamic Therapy of Subfoveal Choroidal Neovascularization With Verteporfin

Fluorescein Angiographic Guidelines for Evaluation and Treatment—TAP and VIP Report No. 2

Treatment of Age-Related Macular Degeneration With Photodynamic Therapy (TAP) and Verteporfin in Photodynamic Therapy (VIP) Study Groups

Objective: To describe fluorescein angiographic guidelines for the use of verteporfin therapy in patients with subfoveal choroidal neovascularization (CNV) secondary to age-related macular degeneration (AMD) or other conditions based on 2-year vision outcomes from the Treatment of Age-Related Macular Degeneration With Photodynamic Therapy (TAP) Investigation and Verteporfin in Photodynamic Therapy (VIP) Trial.

Methods: Three multicenter, double-masked, placebo-controlled randomized clinical trials at 28 ophthalmology clinical centers in Europe and North America involving prospectively identified patients with best-corrected visual acuity (Snellen equivalent) of approximately 20/20 to 20/200, subfoveal CNV secondary to AMD or pathologic myopia with evidence of CNV, and a lesion greatest linear dimension of 5400 µm or less. Fluorescein angiography was to be performed on all patients at enrollment and at regular 3-month follow-up visits through 2 years. The initial treatment laser spot size and all subsequent treatment decisions were based on the investigator’s interpretation of these fluorescein angiograms. Photographic materials forwarded to the Wilmer Photograph Reading Center were reviewed by masked graders.

Main Outcome Measures: Baseline angiographic features, including lesion composition and size, morphologic response to treatment during follow-up (eg, absence of leakage), and reliability (κ values) of grading selected characteristics based on a 10% regrading of baseline visits.

Results: Terms and examples of different lesions and lesion components are provided to assist recognition of fluorescein angiographic characteristics of choroidal neovascular lesions that were important in determining when and where to apply verteporfin therapy. The κ statistics for agreement of identification of lesion characteristics by the Wilmer Photograph Reading Center for these trials ranged from 0.70 to 0.85.

Conclusions: Ophthalmologists should consider interpreting fluorescein angiographic images of subfoveal lesions with terms provided to follow recommendations regarding which patients are most likely to benefit from verteporfin therapy based on results from the TAP Investigation and VIP Trial.

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Photodynamic Therapy with verteporfin (Visudyne; Novartis Ophthalmics AG, Basel, Switzerland) has been shown to reduce the risk of moderate and severe vision loss in selected patients with subfoveal choroidal neovascularization (CNV) due to age-related macular degeneration (AMD) and increase the chance of stable or improved visual acuity in patients with subfoveal CNV due to pathologic myopia. Analyses showed that the magnitude of the treatment effect varied according to the baseline composition and size of the choroidal neovascular lesion in patients with AMD. A variety of vision outcomes supported the recommendation that this therapy be considered specifically for the following groups: (1) AMD patients with predominantly classic lesions (in which the area of classic CNV occupies at least 50% of the area of the entire lesion); (2) AMD patients with occult with no classic subfoveal CNV, particularly, but not exclusively, in the presence of either a smaller lesion size or lower levels of visual acuity; or (3) patients with subfoveal CNV due to pathologic myopia or other causes in which the natural history was judged to be similar to lesions due to AMD or pathologic myopia. In contrast, no beneficial effect of verteporfin therapy on reducing the risk of moderate or severe visual acuity loss at 12 or 24 months was noted in AMD patients with minimally classic CNV (in which the area of classic CNV occupied >0% but <50% of the area of the entire lesion), although exploratory analyses have suggested that the therapy might...
be beneficial for a minimally classic lesion that has a relatively smaller size with a relatively lower level of visual acuity.

Given the current results of the verteporfin photodynamic therapy trials, the recognition of lesion components and the estimation of their proportions are critical for the appropriate selection of eyes for treatment with verteporfin therapy. To assist ophthalmologists in the application of these results, this article describes the guidelines followed by the Treatment of Age-Related Macular Degeneration With Photodynamic Therapy (TAP) Investigation and the Verteporfin in Photodynamic Therapy (VIP) Trial Study Groups for interpreting the fluorescein angiograms of subfoveal choroidal neovascular lesions. The angiographic eligibility criteria that ophthalmologists used to enroll patients into the TAP Investigation and VIP Trial are reviewed. Review of photographs before enrollment by the Wilmer Photograph Reading Center at The Johns Hopkins University School of Medicine, Baltimore, Md, was not performed, since the investigators who designed the study believed that the study results more likely could be extrapolated to clinical practice, where instituting a “prior review” would be logistically difficult to coordinate with patient care and a potentially unnecessary expense. Instead, training and evaluation of study ophthalmologists by the Wilmer Photograph Reading Center investigators were performed using the guidelines presented in this article. Interpretation of angiographic patterns and classification of lesions by their composition at baseline, as used in the TAP Investigation and VIP Trial, are therefore presented to provide guidance to ophthalmologists on how to apply these guidelines to the interpretation of lesion composition and lesion size in clinical practice. This information also should assist ophthalmologists in determining the laser spot size required to treat a lesion in its entirety. Furthermore, the angiographic patterns of lesions at follow-up, the assessment of whether to re-treat these lesions, and the area of the lesion to re-treat are reviewed so that ophthalmologists can use procedures similar to those adopted in the TAP Investigation and VIP Trial within their clinical practice.

**METHODS**

The patients and methods in the TAP Investigation and VIP Trial have been described previously. In brief, for the TAP Investigation, 609 patients were enrolled at 22 clinical centers during December 1996 through October 1997. The principal visual acuity criterion for enrollment was a best-corrected visual acuity letter score of 73 to 34 (an approximate Snellen equivalent of 20/40 to 20/200) after a protocol refraction. For the VIP Trial, 120 patients with pathologic myopia and 339 patients with AMD were enrolled at 28 centers from February 1998 through September 1998. The principal visual acuity criterion for enrollment was a best-corrected visual acuity letter score of 50 or better (an approximate Snellen equivalent of 20/100 or better after a protocol refraction).

Within 8 days prior to enrollment, certified study photographers performed fluorescein angiography using a standard film-based protocol that emphasizes stereoscopic photographic sequences during the transit and late phases (5 and 10 minutes) of the angiogram. The various cameras used at the TAP and VIP clinical centers and their respective magnifications of the retinal image when captured on 35-mm film are listed in Table 1.

Enrollment criteria, as determined by fluorescein angiography, required evidence of subfoveal CNV due to AMD. At least 50% of the lesion area had to be composed of CNV (classic plus occult, if the latter component was present). Either classic or occult CNV had to underlie the geometric center of the foveal avascular zone (FAZ). The greatest linear dimension (GLD) of the lesion had to be no more than 5400 µm. For the TAP Investigation, some portion of the lesion had to meet the criterion of classic CNV. A component of occult CNV or other components that could obscure the identification of classic or occult CNV (such as blood) within the area of that component could also be present. For AMD patients in the VIP Trial, lesions were to either be composed of occult with no classic CNV with presumed recent disease progression or have some evidence of classic CNV with relatively good visual acuity (approximate Snellen equivalent better than 20/40). For patients with pathologic myopia in the VIP Trial, there were no specific lesion composition criteria, that is, the lesion could have any proportion of classic CNV or occult CNV. After enrollment, photographic materials were forwarded to the Wilmer Photograph Reading Center for an independent evaluation of the baseline lesion features. A drawing of the lesion, including all of its components, was made by projecting the film on a microfilm reader using techniques described previously. All baseline gradings were confirmed by a senior ophthalmologist (S.B.B. or N.M.B.) at the Wilmer Photograph Reading Center.

Patients were assigned randomly to receive verteporfin therapy or placebo in a double-masked fashion and in a ratio of 2:1. Follow-up was scheduled every 3 months (±2 weeks) after the initial treatment for a period of 2 years. At each follow-up visit, patients underwent a protocol refraction, best-corrected visual acuity measurement, contrast sensitivity measurement, ophthalmoscopic examination, stereoscopic color fundus photography, and fluorescein angiography. Retreatment was to be considered at each follow-up visit if there was fluorescein leakage from CNV (classic, occult, or both), as long as the patient had not experienced any serious adverse event that was judged likely to be associated with prior therapy. Procedures for re-treatment were similar to those for the initial treatment, except that re-treatment was performed as long as there was fluorescein leakage from CNV, even if the leakage was not subfoveal or the area to be treated had a GLD that exceeded...
ceed to 5400 µm. Photographic material was also read by graders at the Wilmer Photograph Reading Center who were masked to the patient’s treatment assignment for all follow-up visits in the TAP Investigation except those during months 15 and 21 and all follow-up visits in the VIP Trial except those during months 3, 6, 9, 15, 18, and 21 (unless a serious ocular adverse event in the posterior pole of the study eye at any visit was suspected, in which case that photographic material also was reviewed by the graders).

RESULTS

DEFINITIONS CRITICAL TO FLUORESCIN ANGIOGRAM INTERPRETATION

Several terms used to describe fluorescein angiographic patterns of CNV are critical if ophthalmologists are to apply the results of the TAP Investigation and the VIP Trial to their clinical practice and to determine whether verteporfin therapy may be indicated.

Classic and Occult CNV

The TAP and VIP investigators identified areas of classic and occult CNV using definitions adopted from the Macular Photocoagulation Study (MPS) Group. Relevant information is reiterated herein because ophthalmologists need to be familiar with these definitions to follow the proven treatment protocol for verteporfin therapy.

Classic CNV (Figure 1 and Figure 2) is a bright area of well-demarcated chorioidal fluorescence in the early phase of the angiogram. However, identification of actual new vessels is not necessary or sufficient to define an area as classic CNV. (Visualizing the vessels can be seen in the early-phase frames from fluorescein angiography of occult CNV as well.10) The early appearance of an area of fairly homogeneous and well-demarcated bright fluorescence, however, is critical to identify classic CNV and is unrelated to depigmentation of the overlying retinal pigment epithelium (RPE), as assessed on color fundus photographs. During the mid and late phases, there is progressive leakage of fluorescein that obscures the boundaries of the bright area.

Occult CNV has 2 characteristic patterns. Identification of either pattern within an area of the retina is sufficient to confirm the presence of occult CNV.

The first pattern, termed fibrovascular pigment epithelial detachment (PED) or fibrovascular detachment of the RPE (Figure 3 and Figure 4), is an area of irregular elevation of the RPE, best appreciated on stereoscopic angiography. Unless the overlying RPE is depigmented, a discrete or intensely bright area of early fluorescence is not usually present within this elevated tissue. Rather, an area of stippled or granular hyperfluorescence, which is not at bright as classic CNV, emerges usually within 1 to 2 minutes of fluorescein injection, although it may be discerned in the early-phase frames as well. By the late-phase frames, these areas often intensify in fluorescence to a certain degree and demonstrate persistent staining or leakage beyond the boundaries of fluorescence, elevation, or both as identified in earlier-phase frames. This pattern of occult CNV often has well-demarcated boundaries by differentiation of either the perimeter of elevated vs flat tissue or the perimeter of moderately intense speckled hyperfluorescence.

The second pattern, termed late leakage of an undetermined source, is noted in late-phase frames (Figure 4C) as speckled or punctuate fluorescence with minimal leakage at the level of the RPE that often is associated with fluorescein pooling into the subsensory space. The source of this late leakage, usually apparent within 2 to 5 minutes after injection, does not correspond to an area of classic CNV or a fibrovascular PED in earlier-phase frames. The fluorescent pattern may be similar to an area of fibrovascular PED, in which elevation of the RPE cannot be detected because either the photographs were not obtained stereoscopically or the elevation was too small to detect. The boundaries of this pattern of occult CNV are often poorly demarcated.

Features Obscuring CNV Boundaries

In the TAP Investigation and VIP Trial, features that may obscure the boundaries or extent of either classic or occult CNV were also considered to be part of the lesion to be included in the treatment spot size. These features include hypofluorescence corresponding to blood on color fundus photographs (Figure 5); hypofluorescence not corresponding to blood on color fundus photographs (but presumably due to pigment or fibrous tissue) (see Figure 11 in the article by the Macular Photocoagulation Study Group); hyperfluorescence from fibrous tissue that shows fluorescein staining (not leakage) (rarely noted in cases that otherwise met eligibility criteria for the TAP Investigation or VIP Trial); or hyperfluorescence from a serous PED (Figure 6).

A serous PED (Figure 6) is an area of smooth or regular RPE elevation rather than an irregular elevation as seen in a fibrovascular PED. In the early phase of the angiogram, this smooth RPE elevation shows uniform and bright hyperfluorescence that remains bright with sharp borders in the late-phase frame. In contrast, a fibrovascular PED shows less bright, nonhomogeneous, stippled fluorescence. When any of these “blocking” or “obscuring” features is contiguous to classic or occult CNV, the precise perimeter of the CNV is not visible. Therefore, the CNV may extend beneath this area obscuring CNV boundaries.

Lesion Component vs Lesion

Two other important terms used to assess the CNV process are lesion component and lesion at baseline (Figure 4E and F). Lesion component refers to the constituents of the lesion, which can be CNV (classic, occult, or both) or features that could obscure the boundaries of either classic or occult CNV (thick blood, hypofluorescence not from visible blood, or a serous detachment of the RPE), or hyperfluorescent staining from fibrous tissue. Lesion refers to the complex or area of all lesion components.

Well-Demarcated vs Poorly Demarcated Lesions

The terms well demarcated and poorly demarcated are used to describe the boundaries of the lesion. A choroidal neovascular lesion may be considered well demarcated if the
Figure 1. Subfoveal choroidal neovascularization (CNV), predominantly classic composition with no occult CNV receiving multiple courses of verteporfin therapy. A. Hemorrhage (arrow) surrounding lesion (visual acuity, 20/200). B. Hyperfluorescence under the macula surrounded by a thin rim of hypofluorescence from hemorrhage and hypofluorescence (arrow) in lesion's center from hemorrhage. C. Leakage overlying and at boundaries of hyperfluorescence seen in B, consistent with classic CNV. D-O, Month 3 through 12 visits showing resolution of hemorrhage, hypofluorescence (eg, straight arrows in E) surrounding bright fluorescence (eg, curved arrow in E) with leakage in later-phase frames (eg, curved arrow in F) within area originally receiving therapy. Photodynamic therapy applied to greatest linear dimension (dotted line) of area of leakage until only slight leakage in late phase unchanging from previous visits at months 18 and 24 (P-U) and 20/320 visual acuity.
boundaries of the entire lesion (along all 360° of the lesion boundaries) can be distinguished precisely from the remaining unaffected retina (Figure 1). A lesion is poorly demarcated if any portion of the boundary of the entire lesion cannot be distinguished precisely from the remaining unaffected retina (Figure 4F). Examples of le-
sion components that usually have well-demarcated boundaries are classic CNV, hyperfluorescent staining of fibrous tissue, hypofluorescence from blood, hypofluorescence not from blood, and a serous PED. A fibrovascular PED may or may not have well-demarcated boundaries. An area of late leakage of undetermined source usually will not have well-demarcated boundaries. Whether a lesion has well-demarcated boundaries depends on whether the components that form its entire boundary are well demarcated. Eyes eligible for the TAP Investigation or VIP Trial could have either well-demarcated or poorly demarcated lesion boundaries, as long as all other eligibility criteria were met.

Other Definitions Useful for Interpretation of Trial Results

The TAP Investigation enrolled patients with subfoveal lesions due to AMD; the VIP Trial enrolled patients with subfoveal lesions due to AMD or pathologic myopia. AMD was defined as the presence, in either eye, of at least one medium-size druse (GLD ≥ 63 µm) within 3000 µm of
the foveal center or the presence of RPE abnormalities judged to be consistent with AMD. Pathologic myopia was defined as a spherical equivalent refractive error in the eye with a CNV of −6 diopters or less or the presence of retinal abnormalities associated with pathologic myopia, such as lacquer cracks, tilted optic nerves, or staphylomas associated with an axial length of at least 26.5 mm on ultrasonography.

Recurrent subfoveal lesions could be included in the TAP Investigation or VIP Trial. These were lesions that had been treated by laser photocoagulation in which the laser-treated area did not include the geometric center of the FAZ. The recurrent CNV in these lesions extended under the geometric center of the FAZ. At times, small vessels can be seen emanating from the laser-treated area to the recurrent classic or occult CNV, although distinct vessels can be seen within an area of classic (Figure 7B) or occult CNV without prior laser photocoagulation. A verteporfin treatment was considered to be an individual course of photodynamic therapy.
with verteporfin, whereas verteporfin therapy was considered to be the series of an initial and, as necessary, multiple courses of treatments applied to a lesion over time.

Lesion Component Proportions

Only a lesion in which at least 50% of the lesion area was occupied by CNV components was included, because the goal of the TAP Investigation and VIP Trial was to assess the effects of verteporfin therapy on CNV, not a lesion predominantly composed of blood with only a small area of CNV, and not a lesion composed predominantly of a serous detachment of the RPE with only a small area of CNV. In the TAP Investigation, the lesion had to have some evidence of classic CNV. In the VIP Trial, if the lesion included an area of classic CNV in AMD patients, the visual acuity had to be better than a Snellen equivalent of approximately 20/40. If AMD patients in the VIP Trial did not have evidence of classic CNV, then the patient had to have presumed recent disease progression, which included at least one of the following: (1) blood associated with the CNV (not necessarily a lesion component), (2) visual acuity loss of at least one line within the past 12 weeks (intended to be in the setting of CNV at a previous visit before the documented visual acuity loss), or (3) growth of the lesion's GLD of at least 10% within the past 12 weeks.

If classic CNV was present (in either the TAP Investigation or the VIP Trial), the area of classic CNV was assessed relative to the area of the entire lesion at baseline. A lesion had a predominantly classic composition or was termed predominantly classic CNV when the area of classic CNV was at least 50% of the area of the entire lesion (Figure 5) and could have occult CNV (Figure 5) or might not have occult CNV (Figure 1). A lesion had a minimally classic composition or was termed minimally classic CNV when the area of classic CNV was less than 50% but more than 0% of the area of the entire lesion (Figure 7). A lesion had an occult with no classic composition (Figures 3 and 4) when occult CNV was present and there was no classic CNV (area of classic CNV was 0% of the area of the entire lesion). Note that the lesion compositions were not called classic or classic only or occult or occult only. A lesion with classic CNV could have occult CNV (Figure 4D-F); calling such a lesion classic might cause confusion by making one suspect that there was no occult CNV. The term classic only was not used to describe a lesion with classic CNV with no occult CNV, because other components might be present as seen in Figure 1, where, although there is no occult CNV, the lesion components include classic CNV and blood. Calling such a lesion classic only might cause confusion by making one suspect there were no other lesion components. Similar reasoning accounts for avoid-
ing descriptions of occult or occult only for lesions that are occult with no classic CNV. Also avoided is the term mixed CNV to imply a lesion with classic and occult CNV, because the term mixed is not as descriptive as the terms predominantly classic and minimally classic, which have relevance in interpretation and application of photodynamic therapy with verteporfin.

Drawings of patients’ lesion components at baseline were reviewed to determine whether they met the eligibility criteria and to classify lesions that included a component of classic CNV as either predominantly or minimally classic lesions. Only rarely was it necessary to trace these drawings onto a digitizing computer pad to calculate individual lesion component areas. These calculations were made only when graders were not confident that the proportions of an individual component (eg, classic CNV) relative to the area of the entire lesion were obviously either less than or at least 50% of the area of the entire lesion from inspection of the drawings.

Subfoveal Lesion

A subfoveal lesion in these trials contained classic (Figure 1) or occult (Figure 4) CNV that extended under the geometric center of the FAZ. A choroidal neovascular lesion that has any non-CNV component (eg, hypofluorescence corresponding to blood or hyperfluorescent staining of fibrous tissue) under the center of the FAZ (Figure 8) is not considered to be a subfoveal choroidal neovascular lesion unless that component (Figure 1) is surrounded 360° by classic CNV, occult CNV, or a combination of both. This is termed the 360° rule in which it is assumed that CNV underlies the foveal center but is obscured from view.

ELIGIBILITY FOR VERTEPORFIN TRIALS AS DETERMINED BY FLUORESCEIN ANGIOGRAPHY

The guidelines for interpreting fluorescein angiograms of eyes with CNV secondary to AMD discussed herein were used by study investigators to determine the patient’s eligibility for enrollment in the TAP Investigation or VIP Trial. These guidelines should be helpful in clinical practice to select patients who are most likely to benefit from verteporfin therapy. The photographic eligibility criteria of patients from the TAP Investigation and VIP Trial who benefited from this therapy are summarized in Table 2.

Eyes that fulfilled these criteria could have had 1 or 2 types of fluorescein leakage patterns from CNV (classic or classic plus occult for the TAP Investigation, classic or classic plus occult or occult with no classic for the VIP Trial) and up to 4 features that could have obscured the lesion boundaries. The lesions in these eyes could have had well- or poorly demarcated boundaries and extend to the peripapillary area. The presence or extent of subretinal fibrosis on clinical examination or color photographs (Figure 5) was not an exclusion criterion as long as the angiographic criteria, as discussed, were fulfilled. The presence of CNV with scar tissue (fibrous tissue more than 25% of the lesion area on color photographs) was recorded by the Wilmer Photograph Reading Center graders. Subgroup analysis suggested that this baseline feature did not significantly interact with the treatment benefit of verteporfin therapy. Although eyes with CNV and some scarring can meet the angiographic eligibility criteria, eyes with evidence of obvious scarring (Figure 9) often failed to meet one or more of these photographic criteria (eg, GLD >5400 µm or no leakage from classic or occult CNV under the foveal center) or the visual acuity criterion (approximate Snellen equivalent worse than 20/200).

Initial Treatment

The laser spot size to be used when applying verteporfin therapy to the patient’s eye depends on (1) the identification of all lesion components that affect or are part of the outer boundary of the lesion and (2) the determination of the lesion boundaries. These 2 steps require careful review of the complete angiographic study and, sometimes, a degree of approximation when considering a lesion with poorly demarcated boundaries. To determine the GLD of the lesion on the retina, the first step is to determine the GLD on film by placing a transparent millimeter reticule along the longest axis of the lesion on a representative frame of the fluorescein angiogram film that illustrates the lesion’s boundaries (Figure 10). The lesion’s GLD on the retina is then obtained by dividing the dimension of the lesion measured on the film.
by the camera magnification factor (Table 1). For example, if the angiogram was obtained with a Zeiss fundus camera (model FF2, FF3, or FF4; Carl Zeiss Meditec AG, Jena, Germany) using a 30° field on 35-mm film, the image of a lesion on the film is magnified approximately 2.5 times. No calculations of lesion size on the retina corrected image size based on refractive errors. The GLD of the lesion on the retina would be the GLD of the lesion measured on the film (in millimeters) divided by 2.5. To ensure that the lesion was treated in its entirety, the protocol required that 1000 µm be added to the GLD of the lesion on the retina, and this number was programmed into the laser as the final treatment spot size. The laser equipment is also programmed to take into account the lens magnification of the contact lens used to apply the treatment, such that the final treatment spot size on the retina is as requested in the laser settings. The magnifications of various contact lenses commonly used in verteporfin therapy are listed in Table 3. During light application (for 83 seconds, starting 15 minutes after initiation of verteporfin infusion), the laser spot is centered on the midpoint of the lesion’s GLD. The laser spot is only displaced from this midpoint when it is necessary to avoid light application to the optic nerve: no portion of the treatment spot should be closer than 200 µm to the optic nerve, even if this means that a portion of the lesion will not be exposed to the treatment spot.

The measurement of the GLD of a lesion should not be confused with an estimation of the size of a lesion in MPS disc areas. The latter one, lesion size, is measured in disc areas and might have an impact on whether verteporfin therapy should be considered (eg, smaller lesions appeared to have a better outcome with verteporfin therapy than larger lesions). In contrast, GLD, measured in millimeters, is used to determine the size of the laser spot to be used to activate verteporfin within the lesion to be treated. In the TAP Investigation and the VIP Trial, lesion size was measured in MPS disc areas, where one MPS disc area was defined as an area of 2.54 mm² on a disc diameter of 1.8 mm. Templates were used by the Wilmer Photograph Reading Center with various disc areas to be overlaid on 35-mm-film angiograms, based on the definitions described herein and on the assumption that the camera magnification used in these trials to obtain these angiograms was approximately 2.5. For example, the 1 MPS disc area circle on the template (not the retina) for use on film angiograms in the trials had a diameter of 4.5 mm, occupying an area of 15.9 mm². The 4 MPS disc area circle on the template has an area approximately 4 times the area of the 1 MPS disc area circle and has a diameter of approximately 9.0 mm on the template and covers an area of approximately 63.6 mm². A 4 MPS disc area circle on the retina covers an area of 10.2 mm² on the retina; this circle would have a diameter of approximately 3.6 mm on the retina.

### Table 2. Photographic Eligibility Criteria of Patients Who Benefited From Verteporfin Therapy in the TAP Investigation and VIP Trial

- Evidence of AMD in either eye, with absence of any other fundus disease known to be associated with CNV in the eye to receive therapy
- A subfoveal lesion in which either new or recurrent classic or occult CNV underlies the foveal center (except for lesions that are judged to have subfoveal CNV based on the 360° rule)
- A lesion with predominantly classic CNV (TAP Investigation only)
- A lesion with a GLD ≤5400 µm on the retina
- If classic CNV is present, approximate Snellen equivalent from letter score better than 20/40 (VIP Trial only)
- If occult CNV with no classic CNV, then presumed recent disease progression (VIP Trial only) as evidenced by blood associated with the lesion or at least 5-letter (approximate 1-line) loss within previous 3 months or at least 15% increase in lesion’s GLD on fluorescein angiography within previous 3 months

Abbreviations: AMD, age-related macular degeneration; CNV, choroidal neovascularization; GLD, greatest linear dimension; TAP, Treatment of Age-Related Macular Degeneration With Photodynamic Therapy; VIP, Verteporfin in Photodynamic Therapy.

### Figure 9. A, Lesion in which fibrosis is at least 50% of the entire lesion, demonstrating fluorescein angiographic characteristics typical for such lesions, which generally do not meet criteria for which verteporfin therapy has been shown to be beneficial. Specifically, the greatest linear dimension of the lesion extending to the vascular arcades, based on the early-phase (B) and late-phase (C) frame is far greater than 5400 µm and is associated with a visual acuity so low (visual acuity, approximate Snellen equivalent, 20/500) that reducing the risk of moderate and severe visual acuity loss is not likely to affect the patient’s visual function or quality of life.

### Additional Treatment at Follow-up

In these trials, photodynamic therapy treatment at follow-up was considered as often as every 3 months (±2 weeks) after the initial treatment through the month 21 visit. Additional treatment was recommended if fluorescein leakage from classic or occult CNV, or both, was noted either within (Figure 10E and F) or contiguous to (Figure 10H and I) an area of the lesion on angiography that had received prior photodynamic therapy treatment. After initiation of verteporfin therapy, it becomes increasingly difficult to differentiate classic from occult CNV, but during follow-up it was not necessary to distinguish one CNV component from the other because lesions with leakage from either component were considered for additional treatment (Figure 10H and I). In

**Table 3. Photographic Eligibility Criteria of Patients Who Benefited From Verteporfin Therapy in the TAP Investigation and VIP Trial**

- Evidence of AMD in either eye, with absence of any other fundus disease known to be associated with CNV in the eye to receive therapy
- A subfoveal lesion in which either new or recurrent classic or occult CNV underlies the foveal center (except for lesions that are judged to have subfoveal CNV based on the 360° rule)
- A lesion with predominantly classic CNV (TAP Investigation only)
- A lesion with a GLD ≤5400 µm on the retina
- If classic CNV is present, approximate Snellen equivalent from letter score better than 20/40 (VIP Trial only)
- If occult CNV with no classic CNV, then presumed recent disease progression (VIP Trial only) as evidenced by blood associated with the lesion or at least 5-letter (approximate 1-line) loss within previous 3 months or at least 15% increase in lesion’s GLD on fluorescein angiography within previous 3 months

Abbreviations: AMD, age-related macular degeneration; CNV, choroidal neovascularization; GLD, greatest linear dimension; TAP, Treatment of Age-Related Macular Degeneration With Photodynamic Therapy; VIP, Verteporfin in Photodynamic Therapy.
Figure 10. Subretinal fluid (visual acuity, 20/80) associated with classic (B, straight arrows) and occult (C, dotted arrows) choroidal neovascularization (CNV) with greatest linear dimension (GLD) (dotted line) of entire lesion (outlined in white). D, E, and F, Minimal fluorescein leakage of classic CNV (E, straight arrows) and moderate fluorescein leakage of occult CNV (F, dotted arrows). G-O, Progression of classic CNV. Dotted line shows GLD of area to be treated. P, Q, and R, Stable lesion with minimal subretinal fluid, a thin flat scar, minimal leakage from CNV. S, T, and U, No subretinal fluid, hyperfluorescent staining but no leakage, with 20/126+2 visual acuity.
addition, any hypofluorescence corresponding to blood on color fundus photographs (Figure 10K) or hyperfluorescence from a serous PED contiguous to classic or occult CNV was included within the area to be retreated. Contiguous hypofluorescence not from blood (even if elevated) or hyperfluorescent staining of fibrous tissue was not included in the area to re-treat (Figure 10T and U). Therefore, the treatment spot size on the retina during follow-up included the GLD of any area of leakage from CNV and contiguous hypofluorescence due to blood or hyperfluorescence due to a serous PED plus 1000 μm. If 2 or more leaking areas were present and separated by either hypofluorescence not from blood or hyperfluorescent staining from fibrous tissue, re-treatment was performed by measuring the GLD across the outer perimeter of these areas so that the treatment laser spot at follow-up would extend across all leaking areas. If the diameter of the area to re-treat exceeded the maximal spot size of the laser delivery system, the treating ophthalmologist positioned the largest possible laser spot to cover the broadest area of leakage judged to pose the greatest risk of additional visual acuity loss.

During follow-up, treated lesions may develop regions within the treatment area that are hypofluorescent (Figure 10E and F) or that stain, rather than leak, at the level of the RPE (Figure 10T and U). These areas may be flat or mildly elevated and appear during the first 2 minutes of the angiogram transit. Later-phase frames of these staining areas may show a modest gain in fluorescein intensity. These staining areas were omitted from re-treatment unless they existed between 2 leaking areas. However, these regions were included in the determination of the total lesion size performed at the Wilmer Photograph Reading Center for each follow-up visit. Therefore, the total lesion size (in contrast to the GLD of the area to receive re-treatment) at follow-up represents the total area of any classic or occult CNV, any features that could obscure the boundaries of classic or occult CNV, and areas of contiguous natural scar such as fibrous tissue staining or mottled RPE atrophy. Using this definition of total lesion size at the month 12 and month 24 follow-up examinations allows one to evaluate the effect of photodynamic therapy on total lesion size; at these follow-up visits, eyes treated with verteporfin therapy had significantly smaller lesions than those given placebo at these follow-up visits (Figure 11).

Although treating ophthalmologists participating in these clinical trials did not differentiate between classic and occult CNV when determining if fluorescein leakage was present from CNV at a follow-up examination, the Wilmer Photograph Reading Center differentiated this leakage for analyses. Furthermore, the area of fluorescein leakage from classic CNV and the area of fluorescein leakage from occult CNV was determined relative to the area occupied by each of these respective components, although only at the baseline examination. When the area of fluorescein leakage from classic CNV or occult CNV extended beyond the area of the entire lesion at baseline (Figure 10H and I), the new area of CNV was considered progression (Figure 10H and I show progression of classic CNV). When the area of leakage of a specific component (either classic CNV or occult CNV) at follow-up occupied an area less than 50% of the area of that same specific component at baseline in the absence of progression, the leakage was considered minimal leakage (Figures 1E and 10E and F show minimal leakage of classic CNV). When the area of leakage at follow-up occupied an area at least 50% of the area at baseline in the absence of progression, the leakage was considered moderate leakage (Figure 10F shows moderate leakage of occult CNV).

Atrophy of the RPE surrounding a lesion, rather than within the original lesion, was defined on fluorescein angiography as a “transmission defect” if it appeared fairly homogeneous (rather than stippled) and flat (rather than elevated). Some eyes in the verteporfin-treated group and the placebo-treated group manifested this surrounding atrophy during follow-up. In a separate analysis in which the area of any surrounding RPE atrophy was added to the total lesion size, verteporfin-treated eyes were more likely to have smaller lesions plus atrophy at follow-up than those given placebo.\textsuperscript{1,2}

An independent lesion is an area of classic CNV, occult CNV, or both, plus any features that could obscure a new area of classic or occult CNV, that develops during follow-up and is not contiguous to an area of previously identified lesion and prior treatment. Independent lesions that developed during follow-up were not treated with verteporfin therapy; the management (observation or laser photocoagulation) was based on the judgment of the individual treating ophthalmologist.

Reliability of Grading

Grading of photographs was performed by 2 independent graders, masked to treatment assignment, who compared and openly adjudicated their gradings of fluorescein angiographic lesion features at baseline with confirmation by a senior ophthalmologist (S.B.B. or N.M.B.). Any discrepancies between their gradings at follow-up also were openly adjudicated, enlisting a reading center ophthalmologist (S.B.B. or N.M.B.) when the

<table>
<thead>
<tr>
<th>Contact Lens</th>
<th>Magnification of Laser Spot Size on Retina</th>
</tr>
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<tbody>
<tr>
<td>Volk, Area Centralis (Volk, Mentor, Ohio)</td>
<td>1.04</td>
</tr>
<tr>
<td>Haig-Streit 901 Fundus lens (Haig-Streit, Bern, Switzerland)</td>
<td>1.04</td>
</tr>
<tr>
<td>Ocular, Mainster Standard (Ocular Instruments Inc, Bellevue, Wash)</td>
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</tr>
<tr>
<td>Ocular, 3-mirror Universal Long (direct) (Ocular Instruments Inc)</td>
<td>1.08</td>
</tr>
<tr>
<td>Ocular, Fundus lens (Ocular Instruments Inc)</td>
<td>1.08</td>
</tr>
<tr>
<td>Yannuzzi Fundus laser lens (Ocular Instruments Inc)</td>
<td>1.10</td>
</tr>
<tr>
<td>Volk, Trans Equator (Volk)</td>
<td>1.44</td>
</tr>
<tr>
<td>Ocular, Mainster Wide Field (Ocular Instruments Inc)</td>
<td>1.50</td>
</tr>
<tr>
<td>Ocular, Mainster Ultra Field PRP (Ocular Instruments Inc)</td>
<td>1.90</td>
</tr>
<tr>
<td>Volk, SuperQuad 160 (Volk)</td>
<td>1.92</td>
</tr>
<tr>
<td>Volk, Quadra-Aspheric (Volk)</td>
<td>2.01</td>
</tr>
</tbody>
</table>

Table 3. Retinal Magnification of Selected Contact Lenses Used in Verteporfin Therapy

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2 graders could not reach consensus. Subsequently, a sample of 180 visits, representing a random 10% sample of baseline visits, was regraded by reading center personnel and a senior ophthalmologist (S.B.B. or N.M.B.) all of whom were involved in the original grading and masked to the original grading data to examine temporal variability in the grading process. The reliability of the grading classification for selected baseline features, including lesion composition and lesion size at baseline, assessed by the \( \kappa \) statistic, was very good, ranging from 0.70 to 0.85 (Table 4).11

**COMMENT**

Guidelines for the interpretation of fluorescein angiograms of eyes with CNV secondary to AMD were provided by the MPS Group to identify patients eligible for laser photocoagulation. Subsequently, the classification of CNV into classic and occult components has been useful in the description of the natural history of lesions with varying compositions. Because recent data indicate that verteporfin therapy reduces the risk of moderate and severe vision loss in eyes with predominantly classic subfoveal CNV and selected cases with occult CNV with no classic CNV through 2 years of follow-up, it becomes evident that the recognition of these 2 components angiographically is important so that patients who may benefit from this therapy can be identified and treated adequately. Furthermore, because recent data suggest that lesion size might influence the treatment benefit in lesions composed of occult CNV with no classic CNV\(^3\) or in those composed of minimally classic CNV,\(^7\) it is increasingly important to recognize all components of a lesion, determine how well demarcated its borders are, de-

---

**Figure 11.** Distribution of lesion sizes at baseline and with last observation carried forward at month 12 and month 24 for eyes assigned to verteporfin therapy (n=159) or placebo therapy (n=83) from the TAP Investigation of predominantly classic lesions (A, baseline; B, month 12 examination and C, month 24 examination) and for eyes assigned to verteporfin therapy (n=166) or placebo therapy (n=92) from the VIP Trial of occult with no classic lesions (D, baseline; E, month 12 examination; and F, month 24 examination). MPS indicates Macular Photocoagulation Study.
Fluorescein angiography in the TAP Investigation and VIP Trial was performed on 35-mm film, according to a protocol that emphasized stereoscopic images to assist the identification of lesion components and borders. Furthermore, investigators were familiar with camera-field and lens-magnification issues so as to ensure the calculation of proper treatment spot sizes. In routine clinical practice, many physicians use digital cameras to obtain videocapital images. So far, to our knowledge, there has been no study that compares film and digital systems to determine if there are significant differences between these 2 systems in the interpretation of these lesions. If significant differences in the determination of lesion composition or size exist between these 2 photographic systems, then there may be a subsequent impact on the benefits obtained with verteporfin therapy when using one system or the other. If digital techniques are used, the physician should study the monitor carefully and view the transit sequence and late-phase frames to identify the entire extent of the lesion and optimize the selection of patients for verteporfin therapy. Means for measuring the lesion’s GLD on the monitor and for incorporating software that corrects for the camera magnification are necessary to provide the GLD of the lesion on the retina.

As indocyanine green (ICG) angiography was not part of the TAP Investigation or VIP Trial protocol at all centers, decisions regarding patient eligibility, baseline lesion composition and size, and location of treatment at baseline and follow-up were not based on or modified by ICG findings. Modification of the treatment recommendations for verteporfin therapy based on observations with ICG angiography has not been evaluated.

The MPS Group demonstrated that photocoagulation was beneficial in decreasing the risk of severe visual acuity loss in eyes with subfoveal CNV secondary to AMD. Like the TAP Investigation and VIP Trial, the MPS Group reported on subfoveal lesions in which the area of CNV was to be at least 50% of the area of the entire lesion and in which there was to be some area of classic CNV. These types of lesions are known to be associated with a relatively rapid decline in central vision function. The MPS, the TAP Investigation, and the VIP Trial included lesions that had an occult component associated with classic CNV. However, in the MPS, lesions could be included with occult CNV only if the entire lesion had well-demarcated boundaries. The TAP Investigation could include lesions with occult CNV with or without well-demarcated boundaries provided that the GLD of the entire lesion was no larger than 5400 µm and there was some evidence of classic CNV. The VIP Trial could include lesions with occult CNV but no classic CNV with or without well-demarcated boundaries. The inclusion of lesions in photodynamic therapy trials with poorly demarcated boundaries or with occult CNV with no classic CNV has substantially increased the number of patients with neovascular AMD who likely can benefit from treatment.

Although it is sometimes difficult to determine the dimensions of a poorly defined lesion to calculate the treatment spot size, highly trained and skilled graders can interpret fluorescein angiograms of patients with neovascular AMD reproducibly to determine candidacy for initiation of verteporfin therapy (Table 4). Given the rela-

### Table 4. Statistics for Reliability of Grading Selected Baseline Lesion Characteristics From Fluorescein Angiography

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Statistic (95% Confidence Interval)*</th>
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<tbody>
<tr>
<td>Percentage of lesion with classic CNV</td>
<td>0.70 (0.53-0.87)</td>
</tr>
<tr>
<td>Occult CNV (absent, present)</td>
<td>0.88 (0.73-1.00)</td>
</tr>
<tr>
<td>Greatest linear dimension (range of distances)</td>
<td>0.76 (0.63-0.89)</td>
</tr>
<tr>
<td>Meets all photographic eligibility criteria (no, yes)</td>
<td>0.57 (0.34-0.81)</td>
</tr>
</tbody>
</table>

Abbreviations: CNV, choroidal neovascularization; MPS, Macular Photocoagulation Study. *Weighted w when not 2-sided.
tively safe profile of verteporfin therapy to date, it seems reasonable to include all questionable areas of occult CNV involvement within the total lesion size, as was done in the TAP Investigation and VIP Trial.

During follow-up in the TAP Investigation and VIP Trial, patients were considered for additional treatments based on angiographic evidence of fluorescein leakage from CNV. Clinically apparent signs of leakage, such as the presence or extent of subretinal fluid and lipid or blood, did not affect the decision to re-treat. Compared with eyes receiving placebo, verteporfin-treated eyes more often appeared to have a resolution of sensory retinal detachment, as reflected by a resolution of fluorescein leakage, and less blood than at baseline. Whether the inclusion of such factors in the decision to re-treat a lesion in clinical practice will affect final vision outcomes remains unknown. Currently published guidelines based on expert opinion of anecdotal personal experience are slightly different from the criteria considered for additional treatment in the TAP Investigation and VIP Trial. These modified re-treatment criteria suggest stopping treatments when there is no fluorescein leakage from CNV at follow-up or when the lesion appears stable (stable or improved visual acuity and little or no change on fluorescein angiography compared with 3 months previously with little or no subretinal fluid on biomicroscopy, a thin, flat, fibrous scar on biomicroscopy, and little fluorescein leakage from CNV). These guidelines also suggest that physicians should consider discontinuing treatment when the lesion is so large and associated with such a poor visual acuity that both the patient and physician judge that additional moderate or severe vision loss would not likely affect the patient’s quality of life. These modified re-treatment criteria, which to date have not been subjected to evaluation in clinical trials, may or may not result in the beneficial outcomes reported in the TAP Investigation and VIP Trial.

Because fluorescein angiograms at follow-up visits from patients in the TAP Investigation and VIP Trial were evaluated by graders at the Wilmer Photograph Reading Center, the classification of CNV leakage into classic and occult patterns became increasingly difficult in the opinion of the authors (S.B.B. and N.M.B.), perhaps due to the natural evolution of CNV or the effects of verteporfin therapy. Physicians applying this therapy also may find it increasingly difficult to make a distinction between fluorescein leakage typical of classic CNV and occult CNV on fluorescein angiograms following verteporfin therapy. This distinction, however, was not necessary in the trials because additional treatment at follow-up was considered for any area of CNV leakage (either classic or occult) at follow-up visits as often as every 3 months (±2 weeks). At this time, this distinction also is not necessary in clinical practice. However, the differentiation between CNV leakage and staining of RPE alterations or fibrous tissue staining also became increasingly difficult with time, perhaps for the same reasons as with the distinction of type of CNV leakage. Nevertheless, it may be important to distinguish areas of leakage from areas of staining to minimize excess exposure of tissues to verteporfin therapy. The vision benefits recognized in the TAP Investigation and VIP Trial are predicated on treating ophthalmologists who were attempting to make this differentiation during the conduct of these trials, recommending additional courses of verteporfin therapy after initial treatment to eyes with fluorescein leakage from CNV, and restricting treatment at follow-up to areas described herein.

The results from the TAP Investigation and VIP Trial provide guidelines to identify patients with subfoveal CNV who may benefit from verteporfin therapy. Treating ophthalmologists need to differentiate patients with predominately classic CNV from those with minimally classic CNV and those with occult with no classic CNV, as defined by fluorescein angiography, identify the boundaries and size of the lesion, and determine the GLD of the lesion on the retina. They also should be familiar with the laser systems and contact lenses used to apply the therapy. Furthermore, ophthalmologists need to be able to identify fluorescein leakage from CNV at the time of follow-up visits so that appropriate re-treatment can be applied. The recommendations from the TAP Investigation and VIP Trial are based on the patient population recruited for the study and a defined study protocol, and our observations to date may not include all patients who might benefit from verteporfin therapy. For example, in selecting patients who might benefit from initial verteporfin treatment, treating ophthalmologists should not necessarily exclude patients with subfoveal CNV larger than 5400 µm or visual acuity worse than 20/200. Over time, as ophthalmologists have more experience with verteporfin therapy and new data from clinical trials become available, treatment guidelines, including which patients may benefit from the therapy, may be revised. Even these current recommendations from the TAP and VIP Study Groups are subject to further clarification and modification as patients undergoing verteporfin therapy are followed up for longer periods.

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