Guidelines for Using Verteporfin (Visudyne®) in Photodynamic Therapy to Treat Choroidal Neovascularization due to Age-related Macular Degeneration and Other Causes: Update 2004

Verteporfin Roundtable 2003 Participants

A complete list of participants in the Verteporfin Roundtable 2003 is available on page XXXX. Original Guidelines by Verteporfin 2000 and 2001 Roundtable Participants and Principal Investigators of the TAP Investigation and VIP Trial listed in Retina 2002;22:6–18.

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The Roundtable organized to originally create and subsequently update these guidelines were supported by Novartis AG, Basel, Switzerland, and QLT Inc., Vancouver, British Columbia.
**Keywords:** Age-related macular degeneration, choroidal neovascularization, guidelines, photodynamic therapy, randomized clinical trials, verteporfin therapy.
Summary

Guidelines originally were published in 2002 based on best available scientific data as well as consensus of expert opinion in absence of controlled clinical trial data to: (1) assist ophthalmologists with selection of patients for whom photodynamic therapy with verteporfin (Visudyne®, Novartis AG), termed “verteporfin therapy”, should be considered, and (2) offer suggestions regarding initial treatment, follow-up, and additional courses of treatment at follow-up. Consensus was based on results of these trials and expert opinion. Additional input and advice were received from representatives on behalf of the American Society of Retina Specialists, the Macula Society, and the Retina Society, as well as principal investigators of randomized clinical trials evaluating verteporfin therapy. As additional information was published in the peer-review literature since 2002 relevant to clinical care, revisions to the originally published guidelines are provided. Patient selection criteria include the following: (1) in cases due to age-related macular degeneration (AMD), lesion composition either (a) predominantly classic choroidal neovascularization (CNV), or, (b) occult with no classic CNV with presumed recent disease progression, or, possibly (c) relatively small minimally classic lesions; (2) CNV location subfoveal or so close to the foveal center that conventional laser photocoagulation treatment almost certainly would extend under the center; (3) etiology of CNV from AMD, pathologic myopia, or other causes in which the outcome without treatment is likely to be worse than with treatment; (4) vision at a level where further loss would be recognized as detrimental to the quality of life of the patient. Criteria do not include lesion size except for AMD patients with either a minimally classic lesion composition (where treatment usually should be considered only for relatively smaller lesions) or occult with no classic lesions (where treatment should be consider usually for
relatively smaller lesions or those larger than 4 MPS disc areas with a relatively lower or poorer best-corrected visual acuity). Criteria also do not include patient age, history of systemic arterial hypertension or prior laser photocoagulation. Therapy should be initiated ideally within one week of the initial fluorescein angiogram on which the clinical decision to treat is based. Patients should return for follow-up at least as often as every 10 to 14 weeks after any initial or subsequent treatment to determine if there is fluorescein leakage from CNV. Additional courses of treatment should be considered as often as every 10 to 14 weeks if fluorescein leakage from CNV is noted at that time. Additional courses of treatment could be deferred if the biomicroscopic and fluorescein angiographic appearances of the lesion are unchanged and show minimal fluorescein leakage, especially when there is no subretinal fluid or fluorescein leakage from CNV underlying the center of the foveal avascular zone. Patients should avoid exposure of skin or eyes to direct sunlight or bright indoor light for 48 hours after treatment or until resolution of any swelling or discoloration from extravasation. Follow-up of relatively larger minimally classic lesions and occult with no classic lesions that initially do not undergo therapy appears indicated to consider therapy if a predominantly classic lesion develops, or in the case of occult with no classic lesions, if visual acuity declines slightly to a lower (poorer) level of visual acuity without a marked increase in lesion size. Additional revisions of these guidelines may be required as new data become available.

**Summary statement**

Update to recommendations providing guidelines regarding the role of verteporfin therapy in the management of choroidal neovascularization due to age-related macular degeneration and other causes are provided from a consensus of retina specialists,
based on results of randomized clinical trials and expert opinion on this therapy, with additional input and advice from representatives on behalf of the American Society of Retina Specialists, the Macula Society, and the Retina Society, as well as investigators of randomized clinical trials evaluating verteporfin therapy.
Introduction

Verteporfin (Visudyne®, Novartis AG) is the first light-activated drug shown in large randomized clinical trials to reduce the risk of moderate and severe vision loss compared with no treatment in patients with choroidal neovascularization (CNV).1-8 The results of the Treatment of Age-related macular degeneration with Photodynamic therapy (TAP) Investigation, composed of two phase III clinical trials in AMD patients, and the Verteporfin In Photodynamic Therapy (VIP) Trial, composed of one trial in AMD patients and one in patients with pathologic myopia, showed that these benefits were sustained through at least 24 months of follow-up, with no additional safety problems identified with even longer follow-up in the TAP Investigation.5 In addition, among patients presenting with predominantly classic or occult with no classic lesions, verteporfin-treated patients were more likely to have improved visual acuity. For predominantly classic lesion, 6% of treated patients at 12 months and 9% at 24 months experienced moderate vision improvement (at least 3 lines of vision gain) following verteporfin therapy compared with 2% at 12 months and 4% at 24 months of patients who received placebo.2 For occult with no classic lesions associated with presumed recent disease progression, 5% at 24 months experienced moderate vision improvement following verteporfin therapy compared with 1% who received placebo.6 For occult with no classic lesions and minimally classic lesions in these trials, this reduced risk of vision loss appeared greater in lesions with smaller size.9,10 These vision outcomes were substantiated further by fluorescein angiographic outcomes in which eyes treated with verteporfin showed a greater chance of reduction in lesion growth and absence of leakage from CNV.1-8
When these treatment guidelines were published in 2002,\textsuperscript{11} it was agreed that the protocols used for patient selection, initial treatment, follow-up, and additional courses of treatment at follow-up had demonstrated verteporfin therapy to be safe and effective in selected patients. However, the guidelines for patient selection and clinical management outside the confines of controlled clinical trials needed to be discussed. Two roundtable discussion groups, sponsored by Novartis Ophthalmics and QLT Inc., were held on July 8–9, 2000 and on March 30–April 1, 2001 to discuss how the scientific data currently available and consensus of expert opinion in the absence of strong scientific data can be applied to clinical practice. The meeting objective was to reach a consensus on guidelines for using verteporfin therapy to treat CNV due to AMD and other causes. The meeting was attended by leaders in ophthalmology from around the world, including retina specialists who were Principal Investigators in the TAP Investigation or the VIP Trial, or both, or who had clinical experience with verteporfin therapy. The results of that meeting were published as guidelines in 2002. Since that time, additional data were published in the peer-review literature that were judged worthy of incorporation into updated guidelines.\textsuperscript{9,10,12-16}

The current guidelines on patient selection criteria for initial treatment, follow-up monitoring, and decisions regarding when to consider additional courses of treatment at follow-up, as discussed in 2003, are presented in this document to assist ophthalmologists in the identification of patients for whom verteporfin therapy should be considered and to provide suggestions for follow-up of these patients. These guidelines were produced from a draft of consensus points reached at the Roundtables following review by some Principal Investigators of the TAP and VIP Study Groups, with additional
input and advice from representatives on behalf of the American Society of Retina Specialists, the Macula Society, and the Retina Society.

**Patient Selection Criteria**

Treatment outcomes are strongly influenced by patient selection. Therefore, identifying those patients most likely to benefit from verteporfin therapy is important. Patient selection is also essential so that those who are unlikely to benefit from treatment are recognized and counseled as such. An algorithm (Figure 1) is presented to summarize the selection criteria in the following section.

The phase III TAP Investigation studied patients with subfoveal CNV due to AMD with evidence of some classic CNV on fluorescein angiography at baseline. In this investigation, verteporfin therapy was shown to reduce the risk of moderate and severe vision loss compared with placebo therapy (Table 1). However, a greater treatment benefit was observed in patients with predominantly classic subfoveal CNV, particularly, but not exclusively, in the absence of occult CNV. These differences in treatment benefit for predominantly classic compared with minimally classic lesions may be due in part to the larger size of minimally classic lesions compared with predominantly classic lesions at baseline, and in part to the large size of predominantly classic lesions without occult CNV compared with predominantly classic lesions with occult CNV. The AMD arm of the VIP Trial showed that verteporfin therapy reduced the risk of moderate and severe vision loss compared with placebo therapy in patients with occult with no classic CNV and presumed recent disease progression, particularly for cases presenting *either* with smaller lesions or lower levels of best-corrected visual acuity (Table 2). The pathologic myopia arm of the VIP Trial showed that verteporfin therapy increased the chance of
stable or improved vision compared with placebo in the treatment of subfoveal lesions (not necessarily predominantly classic) due to pathologic myopia (Table 2). Therefore, when selecting which patients should be considered for verteporfin therapy, the following guidelines should be considered as part of the initial evaluation. These criteria are not applicable after the initial treatment, when deciding whether or not to retreat with verteporfin therapy. (For criteria regarding retreatment, see Treatment and Follow-up Procedure, item # 4. “When should patients receive retreatment with verteporfin therapy?”)

1. How should lesion composition influence patient selection in patients with AMD?

a. Predominantly Classic CNV

Verteporfin therapy is recommended to treat eyes that present with a subfoveal lesion that is predominantly classic CNV (area of classic CNV occupying ≥50% of the area of the entire lesion at baseline) (Table 1). Subgroup analyses from the TAP Investigation showed a larger treatment benefit for lesions that were predominantly classic CNV with no occult CNV (Table 1). However, eyes with lesions composed of predominantly classic CNV with an occult CNV component also showed a benefit (Table 1 and Table 3 footnote). Furthermore, predominantly classic lesions without occult CNV were smaller, on average, than those with classic CNV,3 possibly contributing to the differences in treatment benefit suggested within these subgroups. Therefore, treatment with verteporfin therapy is recommended in predominantly classic CNV with or without evidence of occult CNV, and for both smaller and larger lesions (Figures 2 and 3).9
b. Minimally Classic CNV

For patients with AMD who have subfoveal lesions that are minimally classic (area of classic CNV occupying <50% but >0% of the area of the entire lesion at baseline), the best evidence at this time indicates that the therapy is not of value for this lesion composition (Table 1). However, exploratory analyses suggest that smaller minimally classic lesions may have a treatment benefit as well (Figures 2 and 3). Also, a small randomized clinical trial (the Verteporfin In Minimally Classic or VIM Trial) suggested that either a reduced fluence light dose or standard fluence light dose for photodynamic therapy with verteporfin reduced the risk of vision loss for minimally classic lesions no greater than 6 MPS disc areas compared with a placebo treatment. Of note, when the minimally classic cases within the TAP Investigation that met the VIM Trial eligibility criteria were evaluated, no treatment benefit was noted. Based on the totality of the information described above, a consensus of experts suggests there may be individual situations in which an ophthalmologist may wish to consider treatment for minimally classic lesions if all other criteria for treatment are met. For example, treatment might be considered for a relatively small minimally classic lesion. Also, treatment could be considered for an eye with minimally classic CNV when several examinations have shown that the proportion of classic CNV in this eye is increasing and approaching 50%. (If increasing beyond 50%, becoming a predominantly classic lesion, then verteporfin therapy should be recommended.)

In lesions where the proportion of classic CNV is approximately 50%, it may be difficult to make a clear distinction between a predominantly classic and a minimally classic lesion. In this situation, the expert opinion suggests that an ophthalmologist may wish to consider treatment with verteporfin therapy since the small risk of harm is
probably outweighed by the potential benefits, especially if the lesion is relatively small. Alternatively, some ophthalmologists may wish not to consider treatment because of insufficient evidence to make a definitive recommendation in this circumstance.

c. **Occult CNV With No Classic CNV**

Results from the AMD arm of the VIP Trial indicated that verteporfin therapy could reduce the risk of moderate and severe vision loss for patients with AMD who have subfoveal lesions that are occult CNV with no classic CNV and presumed recent disease progression (Table 2). Presumed recent disease progression was defined as the presence of blood from CNV, or growth of the lesion (at least a 10% increase in the greatest linear dimension of the lesion) within the last 12 weeks, or deterioration of best-corrected visual acuity (at least 5 letters or approximately one line) within the last 12 weeks. Subgroup analyses suggested that a greater benefit was achieved in patients presenting with *either* smaller lesions (no greater than 4 MPS disc areas) or lower levels of visual acuity (letter score less than 65, an approximate Snellen equivalent of 20/50<sup>-1</sup> or less) (Table 2). Based on these results, verteporfin therapy should be considered for the treatment of patients with subfoveal lesions from AMD composed of occult CNV with no classic CNV who are presumed to have recent disease progression, particularly for *either* smaller lesions (Figures 2 and 3) or lower levels of visual acuity (Table 2). For larger lesions (greater than 4 MPS disc areas), therapy usually should be considered only if visual acuity has deteriorated to a lower level (approximately 20/50<sup>-1</sup> or less). The available data do not permit making a recommendation for treatment of occult with no classic lesions that are greater than 9 MPS disc areas on presentation. Expert opinion
suggests that treatment might be considered for such patients with rapidly decreasing levels of best-corrected visual acuity.

2. **How should lesion composition influence patient selection in patients with pathologic myopia?**

Lesion composition should not influence patient selection in patients with pathologic myopia as it has not been shown to influence any outcome following verteporfin therapy in these patients.7,8

3. **How should the size of the lesion influence patient selection?**

In the opinion of the Roundtable participants, as well as the TAP and VIP Study Group,9 treatment of predominantly classic lesions in AMD should not be restricted by the size of the lesion if all other criteria for treatment are met. The TAP Investigation showed that lesion size did not appear to affect the treatment benefit in predominantly classic lesions (Table 4). In the clinical trials, the eligibility criterion for lesion size was restricted to lesions with a greatest linear dimension on the retina of up to 5400 µm (the diameter of a 9 MPS disc area circle). The prototype lasers used could not create spot sizes on the retina larger than 6400 µm with most contact lenses. Furthermore, when designing the TAP Investigation, investigators were reluctant to include very large lesions because these tended to have worse baseline visual acuity; hence it may have been difficult to demonstrate benefit if the chance of additional vision loss was small. With the level of knowledge as it stood at the time of trial design, larger lesions were suspected of being at greater risk of harm from the therapy than smaller lesions. The clinical trials data for predominantly classic lesions described above show that these concerns currently have
no supporting evidence. The laser equipment now available has been upgraded to allow for larger treatment spot sizes as the therapy appears relatively safe and effective for selected cases regardless of lesion size. For lesions composed of occult CNV with no classic CNV with presumed recent disease progression, or minimally classic lesions, therapy could be considered when the lesion is relatively small (less than 4 MPS disc areas). For larger minimally classic lesions (greater than 4 MPS disc areas), therapy usually should not be considered, although data suggests that for occult with no classic lesions with presumed recent disease progression, therapy might be considered if visual acuity has deteriorated to a lower level (approximately 20/50<sup>-1</sup> or less).

4. How should the location of the lesion influence patient selection?
Verteporfin therapy is indicated for CNV that extends under the geometric center of the foveal avascular zone, that is, CNV in a subfoveal location. Based on expert opinion, verteporfin therapy should be considered for juxtafoveal lesions that are so close to the fovea that conventional laser photocoagulation almost certainly would extend under the center of the foveal avascular zone if all other criteria are also met. For the few lesions judged to be subfoveal when enrolled by an ophthalmologist in the TAP Investigation but graded as juxtafoveal by Reading Center graders, verteporfin therapy appeared to be beneficial.<sup>17</sup>

5. How should visual acuity influence patient selection?
Visual acuities required for enrollment in the TAP Investigation (letter score of 73 to 34, equivalent to 20/40 to 20/200) and VIP Trial (letter score of 50 or better, equivalent to 20/100 or better) were obtained using a strict protocol for refraction and visual acuity
determination by certified Visual Acuity Examiners undergoing annual recertification using modified Early Treatment Diabetic Retinopathy Study (ETDRS) charts 1, 2, and R. These visual acuity letter scores usually do not accurately reflect Snellen visual acuities obtained in routine practice.18 “Office” visual acuity does not adequately define the lowest level of visual function for which verteporfin therapy should routinely be considered. In addition, baseline visual acuity did not affect the magnitude of the treatment benefit to a statistically significant degree (Table 4). The results from the controlled clinical trials also showed that verteporfin therapy is beneficial in preserving contrast sensitivity (Table 3)4 at a level that would be expected to have a favorable impact on daily activities.19 At present, the lowest level of visual acuity for which verteporfin therapy should routinely be considered is not known. However, Roundtable participants as well as the TAP and VIP Study Group Principal Investigators believe, based on subgroup analyses and expert opinion, it is reasonable to consider treatment, provided that all other criteria for verteporfin therapy are met, if a patient’s vision is at a level where further loss of visual function would be recognized as detrimental to their quality of life. Again, as mentioned above, lesions composed of occult with no classic CNV presenting with higher levels of visual acuity (approximately 20/50 or better) should only be considered for therapy when the area of the lesion is relatively small (no greater than 4 MPS disc areas). The National Coverage Policy for Ocular Photodynamic Therapy with Verteporfin also states that the United States Health Care Financing Administration "does not believe that visual acuity should be a determinant of whether or not a patient is eligible for verteporfin treatment . . . The determination of whether or not there is any visual function worth preserving will be left to the patient's treating physician".20
6. **What criteria should not influence patient selection?**

The following features at baseline did not affect the magnitude of the treatment benefit in the TAP Investigation or VIP Trial, and therefore were judged not to be relevant in the decision-making process regarding initiation of verteporfin therapy.

   a. **Patient age**

   There should be no age cut-off for treatment with verteporfin therapy. Clinical data from the TAP Investigation and VIP Trial indicate that beneficial outcomes after treatment with verteporfin therapy are not influenced by age (Table 4). However, no data are available for pediatric cases.

   b. **Systemic arterial hypertension**

   Hypertension should not be a contraindication for verteporfin therapy as it did not appear to affect beneficial outcomes (Table 4).

   c. **Prior laser photocoagulation that does not extend under the center of the foveal avascular zone**

   Although very few patients with predominantly classic lesions in the TAP Investigation had prior laser photocoagulation with subsequent recurrent subfoveal CNV at baseline, verteporfin therapy appeared to reduce the risk of vision loss for these patients (Table 1 footnote). Therefore, the Roundtable authors would extrapolate these results to recurrent subfoveal CNV lesions and believe these cases should be considered for treatment if they meet all other criteria as specified for new subfoveal CNV. If there is
fluorescein leakage from CNV within the area of prior laser photocoagulation, this area can be included in the area of the lesion to be treated with verteporfin therapy; because the treatment spot in verteporfin therapy is circular, an area of previous laser photocoagulation may often lie within it anyway.

d. Other causes of CNV

Verteporfin therapy was beneficial for AMD patients with subfoveal lesions composed of predominantly classic CNV or occult with no classic CNV. The therapy also was beneficial for patients with pathologic myopia and subfoveal CNV. In CNV not due to AMD or pathologic myopia, treatment should be considered for subfoveal CNV when it is judged that the outcome without treatment (i.e. from the natural course) is likely to be worse than the outcome with treatment. This treatment group would include, for example, CNV caused by angioid streaks.

e. Subfoveal lesions contiguous to the optic nerve

Subfoveal lesions contiguous to the optic nerve should not be a contraindication to treatment. However, since preclinical work has demonstrated that verteporfin therapy can damage optic nerve vasculature, treatment spots should not overlie the optic nerve.\textsuperscript{21} To ensure that the optic nerve is not damaged, the treatment spot should be placed at least 200 µm away from the optic nerve, even if a small area of the lesion is left untreated as a result. Such lesions were eligible for the TAP Investigation and were treated in this fashion.
f. Other conditions

No safety concerns have been reported regarding treatment of CNV in patients who also have retinal vasculopathies such as diabetic retinopathy\textsuperscript{22} or idiopathic parafoveal telangiectasia.\textsuperscript{23} Similarly, no data are available for pregnant or nursing women, or for patients with significant liver disease (Table 5), all of whom were excluded from the TAP Investigation and VIP Trial.

Treatment and Procedures Following Initial Treatment

1. Who should select patients, apply treatment, and perform follow-up?

Ophthalmologists who are experienced in managing patients with macular disease and expert at interpreting fundus biomicroscopic findings, color fundus photographs, and fluorescein angiograms should select patients, initiate treatment, and perform follow-up of patients who have received an initial treatment until the situation has stabilized.

2. When should verteporfin therapy be initiated?

As in the TAP Investigation and VIP Trial, verteporfin therapy should be initiated ideally within one week of the initial fluorescein angiogram on which the clinical decision to treat was based. A lesion is unlikely to grow to any significant degree or bleed within one week and this time-scale ensures a match between the treatment spot size (determined from the fluorescein angiogram) and the lesion size on the day of treatment. On the day of treatment and before initiating therapy, ophthalmologists should confirm with ophthalmoscopy that the lesion has not changed its ophthalmoscopic appearance from the day of fluorescein angiography.
3. When should treated patients return for follow-up?

Patients should return for follow-up at least as often as every 10 to 14 weeks after any initial or subsequent treatment, to determine if there is any fluorescein leakage from CNV.

a. If an additional course of treatment is not judged to be indicated at a follow-up visit, the patient should again return for follow-up at least as often as every 10 to 14 weeks through to at least 6 months from the time of last course of treatment, and possibly up through at least 2 years from the time of the initial treatment. Fluorescein angiography should be repeated at every follow-up visit when an additional course of treatment might be considered.

b. If an additional course of treatment is not judged to be indicated for at least 6 months, then follow-up might be scheduled at 6-month intervals, and eventually 6- to 12-month intervals. If the patient notes visual deterioration between scheduled visits, the ophthalmologist must determine whether or not the patient should return sooner. The patient must always understand that an additional course of treatment may need to be applied at a future follow-up visit.

c. In rare cases, patients may need to return promptly for evaluation if they experience any severe vision decrease soon after treatment.
4. When should patients receive an additional course of verteporfin therapy?

Patients should receive an additional course of treatment as often as every 10 to 14 weeks following a previous treatment if there is any fluorescein leakage from CNV, since the beneficial results obtained came from following such a protocol in which patients received additional courses of treatment as often as every 10 to 14 weeks if fluorescein leakage from CNV was noted. At the present time, there is no evidence to suggest that intervals for additional courses of treatment as often as every 5 to 7 weeks might result in better or worse outcomes. The expert opinion of Roundtable participants recommended that additional courses of treatment could be considered earlier than 10 to 14 weeks if a patient complains of vision loss, has documented visual acuity loss, and fluorescein angiography shows enlargement of CNV compared to angiography obtained prior to the most recent treatment. Additional considerations for withholding additional courses of treatment are discussed below.

5. When should additional courses of treatment with verteporfin therapy be discontinued?

Additional courses of treatment with verteporfin therapy should not be given when fluorescein leakage is absent from CNV at a follow-up examination. However, the following additional recommendations should be considered for specific situations:

a. If the entire area of fluorescein leakage cannot be covered by the largest treatment spot on the laser, an additional course of treatment may still be indicated and should encompass as large an area of leakage as possible, as was done in the TAP Investigation and VIP Trial. However, an ophthalmologist should consider discontinuing treatment if a relatively large lesion is associated with a particularly low
level of visual acuity and additional treatment is judged unlikely to prevent further
deterioration, and hence unlikely to have a positive impact on the patient’s quality of
life.

b. In the opinion of the Roundtable participants as well as the TAP and VIP Study
Groups’ Principal Investigators, additional courses of treatment 10 to 14 weeks after
a previous treatment could be deferred up to another 10 to 14 weeks if best-corrected visual acuity was stable or improved, the biomicroscopic and fluorescein
angiographic appearance of the lesion is unchanged or improved with respect to the
preceding pre-treatment examination, and if all of the following criteria also are met:

- There is minimal fluorescein leakage from CNV (<50% of the area treated
  at the previous visit) without progression of fluorescein leakage beyond the
  boundaries of the area treated at the previous visit, especially when the
  fovea is not affected by any leakage within the lesion.

- The lesion has a flat, scar-like appearance.

- There is minimal or no subretinal fluid on biomicroscopic examination.

Some experts have suggested that findings from an optical coherence
tomography could influence this decision; specifically detection of
subretinal fluid through the center of the retina might sway an
ophthalmologist more towards wanting to recommend therapy than if no
subretinal fluid was detected by an OCT exam.

For example, a patient is initially treated at month 0 and retreated at month 3. By
month 6, minimal leakage (<50% of the area treated at month 3) is seen, the
leakage does not involve the fovea, the lesion has a flat, scar-like appearance, and there is no serous detachment; retreatment is applied. At month 9, best-corrected visual acuity is stable and the biomicroscopic and fluorescein angiographic appearance of the lesion is exactly or almost exactly the same as that seen at month 6; additional treatment of the residual, minimal leakage could be deferred. Re-evaluation 3 months later (month 12), or sooner if the patient notes any deterioration, should be conducted and additional treatment at follow-up should be considered if, compared with the level seen at month 6 and month 9, any new leakage is noted, especially if accompanied by decreased vision.

6. Is there any situation where conventional laser photocoagulation should be considered after verteporfin therapy?

Following verteporfin therapy, conventional laser photocoagulation might be considered if a relatively small area of well-demarcated fluorescein leakage, either contiguous or non-contiguous to a lesion previously receiving verteporfin therapy, is confined entirely to an extrafoveal location (i.e., no leakage extends within 200 µm of the center of the foveal avascular zone and the area of fluorescein leakage has well-demarcated boundaries for 360° around its entire perimeter).

7. What photosensitivity precautions should be taken following verteporfin therapy?

Although recommendations made by regulatory authorities may vary between countries, scientific data show that patients should avoid exposure of skin or eyes to direct sunlight or bright indoor light for 48 hours after treatment. Areas of suspected or definite
extravasation during infusion of verteporfin should be thoroughly protected from direct light for at least 48 hours after treatment or until any swelling or discoloration has faded, whichever time interval is greater.

8. What follow-up regimen should be considered for minimally classic lesions or occult with no classic lesions that do not receive treatment?

A retrospective review of the natural history of eyes with subfoveal CNV in which the lesion had a minimally classic composition showed that 40% converted to predominantly classic composition, often within 3 months of initial assessment. In approximately half of the lesions that converted, the lesion size and visual acuity at the time of conversion were at a level where photodynamic therapy with verteporfin was likely to reduce the risk of vision loss compared with continued observation, based on the inclusion criteria and results from the TAP Investigation. These data, while only an approximation of the risk of conversion, would suggest that patients who present with minimally classic lesions, in whom no therapy is recommended initially, should be monitored carefully so that potential conversion to a predominantly classic lesion can be identified promptly. If such a conversion is recognized promptly, verteporfin therapy might be considered at that time since it has been proven to reduce the risk of moderate and severe vision loss in patients with predominantly classic lesions.

In a retrospective review of occult with no classic subfoveal lesions in the VIP Trial, few of these lesions converted to a predominantly classic lesion. Observation with no treatment of such lesions may result in a missed opportunity to reduce the risk of moderate or severe visual acuity loss for smaller lesions or those with a lower level of visual acuity. In contrast, for patients with an occult with no classic lesion associated
with both a larger lesion size and higher (better) level of visual acuity in whom verteporfin therapy usually would not be considered, continued observation, rather than cessation of follow-up, is recommended for two reasons. First, some of the lesions may become predominantly classic with a lesion size and visual acuity for which verteporfin therapy might be considered beneficial. Second, some of the lesions may remain occult with no classic associated with progressive vision loss to a lower level of visual acuity, but still within a visual acuity range and lesion size at which verteporfin therapy would be considered.

9. What is the impact of other medications in place of or as an adjunct to verteporfin therapy?

Add paragraph here based on AAO Macugen results.

Conclusions

The availability of verteporfin therapy has expanded the range of treatment options for CNV secondary to AMD and other causes. Treatment guidelines are helpful in maximizing the quality of the management of these conditions. The recommendations contained in this document provide a basis for guidelines regarding the clinical use of verteporfin therapy in the treatment of CNV in 2003. They are based on current data and expert opinion, and revisions may be required as new data regarding verteporfin therapy and other treatment approaches become available and show treatment benefits compared with no treatment. Exceptional cases always will be encountered and, in such circumstances, treating ophthalmologists will have to use their own medical judgement and clinical experience in the interpretation of these guidelines.
Table 1. Evidence Supporting Benefits of Verteporfin Therapy at Month 12\(^1\) and Month 24\(^2\) Examination in the TAP Investigation

<table>
<thead>
<tr>
<th>Visual Acuity</th>
<th>Visit (Months)</th>
<th>Verteporfin n (%)</th>
<th>Placebo n (%)</th>
<th>P</th>
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<td>Loss (Lines)</td>
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<td></td>
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<td>12</td>
<td>156 (39)</td>
<td>111 (54)</td>
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<td>189 (47)</td>
<td>129 (62)</td>
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<td>≥6</td>
<td>59 (15)</td>
<td>49 (24)</td>
<td>&lt;0.006</td>
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<tr>
<td></td>
<td>24</td>
<td>73 (18)</td>
<td>62 (30)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Total Patient Population

Patients with Predominantly Classic CNV*

|               | 12             | 52 (33)           | 51 (61)       | <0.001 |
|               | 24             | 65 (41)           | 57 (69)       | <0.001 |
|               | ≥6             | 19 (12)           | 28 (34)       | <0.001 |
|               | 24             | 24 (15)           | 30 (36)       | <0.001 |

Patients with Predominantly Classic CNV with No Occult CNV

|               | 12             | 21 (23)           | 32 (73)       | <0.001 |
|               | ≥6             | 9 (10)            | 18 (41)       | <0.001 |

Patients with Predominantly Classic CNV with Occult CNV

|               | 12             | 10 (14)           | 10 (25)       | 0.17   |
|               | 24             | 12 (17)           | 14 (36)       | 0.03   |

Patients with Minimally Classic CNV†
In an exploratory analysis of patients with predominantly classic CNV, prior laser photocoagulation was not found to have a statistically significant effect on the treatment benefits of verteporfin therapy. At the month 24 examination, 10 of the 25 verteporfin-treated patients who had received prior laser photocoagulation (40%) had lost at least 15 letters of visual acuity compared with 5 of the 7 patients (71%) who received placebo ($P=0.14$). The percentage of eyes that lost at least 30 letters of visual acuity at the month 24 examinations was also significantly lower in verteporfin-treated patients in the subgroup that had received prior laser photocoagulation. Two verteporfin-treated patients (8%) had lost at least 30 letters of visual acuity at the month 24 examination compared with 3 patients (43%) who received placebo ($P=0.02$). At the month 24 examination in the VIP Trial, in the subgroup of patients presenting with occult with no classic CNV, 5 of the 10 verteporfin-treated patients (50%) who had evidence of prior laser photocoagulation lost at least 15 letters of visual acuity compared with both of the patients (100%) given placebo ($P=0.19$). Two verteporfin-treated patients (20%) had lost at least 30 letters of visual acuity by the month 24 examination compared with both (100%) of the placebo-treated patients ($P=0.03$).

In a retrospective analysis of patients with minimally classic subfoveal CNV due to AMD, the subgroup with small lesions ($\leq$4 MPS disc areas) and lower levels of visual acuity ($\leq$65 letters, equivalent to worse than approximately 20/50 Snellen), 42% of 57 verteporfin-treated patients lost at least 15 letters of visual acuity at the 12 month examination, compared with 63% of 27 patients given placebo. These benefits were
sustained at the month 24 examination.²⁴
### Table 2. Evidence Regarding Outcomes of Verteporfin Therapy at Month 12 and Month 24 Examinations in the VIP Trial

<table>
<thead>
<tr>
<th>Visual Acuity</th>
<th>Change*</th>
<th>Visit (Months)</th>
<th>Verteporfin n (%)</th>
<th>Placebo n (%)</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with AMD with Occult CNV with No Classic CNV&lt;br&gt;≥3 line loss</td>
<td>12</td>
<td>85 (51%)</td>
<td>51 (55%)</td>
<td>0.515</td>
<td></td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>91 (55%)</td>
<td>63 (68%)</td>
<td>0.032</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥6 line loss</td>
<td>12</td>
<td>37 (22%)</td>
<td>30 (33%)</td>
<td>0.07</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>48 (29%)</td>
<td>43 (47%)</td>
<td>0.004</td>
<td></td>
</tr>
<tr>
<td>Patients with AMD with Occult CNV with No Classic CNV presenting either with smaller lesions or lower levels of visual acuity&lt;br&gt;≥3 line loss</td>
<td>24</td>
<td>60 (49%)</td>
<td>48 (75%)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥6 line loss</td>
<td>24</td>
<td>26 (21%)</td>
<td>31 (48%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Patients with AMD with Occult CNV with No Classic CNV presenting with both larger lesions and higher levels of visual acuity&lt;br&gt;≥3 line loss</td>
<td>24</td>
<td>31 (72%)</td>
<td>14 (52%)</td>
<td>0.09‡</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥6 line loss</td>
<td>24</td>
<td>22 (51%)</td>
<td>11 (41%)</td>
<td>0.40‡</td>
</tr>
<tr>
<td>Patients with Pathologic Myopia&lt;br&gt;&lt;1.5 line loss</td>
<td>12</td>
<td>58 (72%)</td>
<td>17 (44%)</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>52 (64%)</td>
<td>19 (49%)</td>
<td>0.106</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥1.0 line gain</td>
<td>12</td>
<td>26 (32%)</td>
<td>6 (15%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>32 (40%)</td>
<td>5 (13%)</td>
<td>0.003</td>
<td></td>
</tr>
</tbody>
</table>
* Values are approximate; there are 5 letters per line.

† Test for treatment effect within subgroups.

‡ The placebo-treated group had the better outcome.
Table 3. Contrast Sensitivity Change at Month 12\(^1\) and Month 24\(^2\) Examination in the TAP Investigation and at Month 24 in the VIP Trial

<table>
<thead>
<tr>
<th>Visit (Months)</th>
<th>Contrast sensitivity letters lost</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Verteporfin (letters)</td>
<td>Placebo (letters)</td>
</tr>
</tbody>
</table>

**TAP Investigation: Total Patient Population**

<table>
<thead>
<tr>
<th>Visit (Months)</th>
<th>12</th>
<th>24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verteporfin</td>
<td>1.3</td>
<td>1.3</td>
</tr>
<tr>
<td>Placebo</td>
<td>4.5</td>
<td>5.2</td>
</tr>
<tr>
<td>(P)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**VIP Trial: Patients with Occult CNV with No Classic CNV**

<table>
<thead>
<tr>
<th>Visit (Months)</th>
<th>12</th>
<th>24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verteporfin</td>
<td>3.6</td>
<td>3.7</td>
</tr>
<tr>
<td>Placebo</td>
<td>4.4</td>
<td>6.1</td>
</tr>
<tr>
<td>(P)</td>
<td>0.164</td>
<td>0.004</td>
</tr>
</tbody>
</table>

* In an exploratory analysis of patients with predominantly classic CNV with occult CNV, the mean change in contrast sensitivity score from baseline was almost 0 at the month 24 examination in verteporfin-treated eyes compared with a decrease of approximately 6 letters (approximately two segments of contrast) in eyes receiving placebo.\(^3\)
### Table 4. Selected Subgroup Analyses in the TAP Investigation\(^2\) and VIP Trial\(^6\) at Month 24 Examination

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of Eyes</th>
<th>Loss of $\geq 15$ Letters</th>
<th>$P^*$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Verteporfin</td>
<td>Placebo</td>
<td>Verteporfin</td>
</tr>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td><strong>TAP Investigation: Total Patient Population</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Greatest linear dimension (diameter of MPS disc area circle)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\leq 3$</td>
<td>107</td>
<td>46</td>
<td>41 (38.3)</td>
</tr>
<tr>
<td>$&gt;3$ to $\leq 6$</td>
<td>152</td>
<td>97</td>
<td>68 (44.7)</td>
</tr>
<tr>
<td>$&gt;6$ to $\leq 9$</td>
<td>109</td>
<td>52</td>
<td>65 (59.6)</td>
</tr>
<tr>
<td>$&gt;9$</td>
<td>25</td>
<td>8</td>
<td>14 (56.0)</td>
</tr>
<tr>
<td>Initial visual acuity score in study eye (letters)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>73–54</td>
<td>203</td>
<td>101</td>
<td>114 (56.2)</td>
</tr>
<tr>
<td>53–34</td>
<td>199</td>
<td>106</td>
<td>75 (37.7)</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$&lt;75$</td>
<td>194</td>
<td>87</td>
<td>79 (40.7)</td>
</tr>
</tbody>
</table>
Verteporfin Roundtable 2003 Participants November 6, 2003

<table>
<thead>
<tr>
<th>≥75</th>
<th>208</th>
<th>120</th>
<th>110 (52.9)</th>
<th>78 (65.0)</th>
</tr>
</thead>
</table>

**Systemic hypertension**

| Definite† | 170 | 77 | 80 (47.1) | 52 (67.5) | 0.327 |
| Others    | 232 | 130 | 109 (47.0) | 77 (59.2) |

**VIP Trial: Patients with Occult CNV with No Classic CNV**

<table>
<thead>
<tr>
<th>Lesion size (MPS disc areas)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤4</td>
</tr>
<tr>
<td>&gt;4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Initial number of letters read (approximate Snellen equivalent visual acuity) in study eye</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥65 (≥20/50)</td>
</tr>
<tr>
<td>&lt;65 (≤20/50)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;75</td>
</tr>
<tr>
<td>≥75</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Systemic hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definite†</td>
</tr>
<tr>
<td>others</td>
</tr>
</tbody>
</table>

MPS, Macular Photocoagulation Study.

* Test of interaction between subgroups using a single logistic regression model that includes treatment.

† Definite hypertension was defined as systolic blood pressure of 160 mm Hg or higher or of 140 to 159 mm Hg with a history of hypertension or use of antihypertension medications or diastolic blood pressure of 95 mm Hg or higher or of 90 to 94 mm Hg with a history of hypertension or use of antihypertension medications.
Table 5. Hepatic Impairment and Verteporfin Therapy

- Mild hepatic impairment usually includes transaminase levels up to 5 times the upper normal limit and bilirubin levels up to 1.5 times the upper normal limit.

- The pharmacokinetic properties of verteporfin have been investigated in subjects who had transaminase levels up to 3 times the upper limit of normal and normal bilirubin levels. There were no significant differences in the pharmacokinetic properties between normal subjects and mildly hepatically-impaired subjects.\(^{25}\)

- Verteporfin therapy should be considered carefully in patients with moderate hepatic impairment or biliary obstruction since there has been no experience in these patients.
Figure legends

**Fig. 1.** Algorithm for verteporfin therapy or laser photocoagulation or observation for symptomatic patients with age-related macular degeneration, pathologic myopia, or other causes of choroidal neovascularization in which the natural course is likely worse without treatment.

**Fig. 2.** 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 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 disc area. Reprinted with permission from Elsevier Inc. (*American Journal of Ophthalmology* 2003, 136:407–418).⁹

**Fig. 3.** 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. Reprinted with permission from Elsevier Inc. (*American Journal of Ophthalmology* 2003, 136:407–418).⁹
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    Decision Memorandum.

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**Proprietary Interests** (to be completed)
**Glossary**

**Age-related macular degeneration (AMD)** is characterized by drusen and/or retinal pigment epithelium (RPE) abnormalities. The spectrum of the disorder may include RPE atrophy, RPE hyperpigmentation, choroidal neovascularization (CNV), retinal pigment epithelium detachment (PED), and disciform scars.

**Blood as a lesion component** is blood contiguous with CNV that is thick enough to obscure hyperfluorescence from any neovascularization potentially underlying the blood.

**Blood associated with CNV** is preretinal, intraretinal, or subretinal blood judged to be from CNV – not always a lesion component; this finding in a lesion composed of occult CNV with no classic CNV is considered presumed recent disease progression.

**Choroidal neovascularization (CNV)** is an ingrowth of choroidal capillaries through a break in the outer aspect of Bruch’s membrane.

**Classic CNV** is a fluorescent pattern on fluorescein angiography characterized by a well-demarcated area of bright hyperfluorescence in the early phase with leakage through the mid- and late-phase frames which obscures the boundaries of this area.

**Classic CNV with no occult CNV** is a lesion that contains classic CNV but no occult CNV. It is not synonymous with classic CNV only which would be a lesion with classic CNV and no other lesion component such as blood.
**Extrafoveal lesion** is located at least 200 µm from the geometric center of the foveal avascular zone.

**Features which can obscure the boundaries of CNV (classic or occult)** include:

- blood which blocks fluorescence through the late phase of the angiogram,
- blocked fluorescence not corresponding to blood on color fundus photographs (corresponding to either hyperplastic pigment or fibrin or fibrous tissue or blood not apparent on color fundus photographs),
- or serous pigment epithelial detachment (defined as uniform, early, bright hyperfluorescence beneath a smooth, dome-shaped elevation of the retinal pigment epithelium).

**Greatest linear dimension (GLD) on the retina** is obtained by dividing the length of the greatest distance between two points on the boundary of the entire lesion by the magnification of that image relative to the true size of the retina.

**Juxtafoveal lesion** is located 1 to 199 µm from the geometric center of the foveal avascular zone.

**Lesion** refers to the entire neovascular lesion, which is considered to be constituted by the entire complex of lesion components (i.e., classic CNV, occult CNV, and features which can obscure the boundaries of CNV).
Lesion component is an area of the retina definitely or possibly involved by CNV as determined by fluorescein angiography. Lesion components include: CNV (classic or occult), thick blood, blocked fluorescence (due to a pigment or scar that obscures the neovascular borders), and serous detachments of the retinal pigment epithelium.

Minimally classic CNV is a lesion in which the area of classic CNV occupies less than 50% but more than 0% of the area of the entire lesion.

Occult CNV is divided into two fluorescent patterns on fluorescein angiography

a. Fibrovascular pigment epithelial detachment is characterized by irregular elevation of the retinal pigment epithelium that shows stippled or non-homogeneous hyperfluorescence usually within 1 to 2 minutes of fluorescein injection. The boundaries may be well demarcated or poorly demarcated, with persistent staining or leakage of fluorescein in the late phase of the angiogram (by 10 minutes).

b. Late-phase leakage of undetermined source has leakage at the level of the retinal pigment epithelium in late-phase frames, in which the source of the late leakage cannot be determined from earlier phase frames of the angiogram and does not correspond to classic CNV or a pattern of fibrovascular pigment epithelial detachment.
**Occult CNV with no classic CNV** is a lesion with occult CNV and no classic CNV. It is not synonymous with occult CNV only which would be a lesion with occult CNV and no other lesion component such as blood.

**Pathologic myopia** is also referred to as degenerative myopia. It is readily distinguished from physiologic myopia by evidence of axial elongation associated with retinal abnormalities including lacquer cracks, which are fine, irregular linear breaks in Bruch’s membrane, associated with the development of CNV.

**Poorly demarcated lesion** is a lesion in which the demarcation between the boundary of the lesion and retina uninvolved by a lesion component is poorly demarcated (poorly defined). “Poorly defined” is not synonymous with “occult”.

**Predominantly classic CNV** is a lesion in which the area of classic CNV occupies at least 50% of the area of the entire lesion.

**Predominantly occult CNV** is a lesion in which the area of occult CNV occupies at least 50% of the area of the entire lesion. Predominantly occult CNV is not synonymous with minimally classic CNV.

**Presumed recent disease progression** in a lesion composed of occult CNV with no classic CNV is defined as the presence of blood associated with CNV, or growth of the lesion (at least a 10% increase in the greatest linear dimension of the lesion) within the
last 12 weeks, or deterioration of best-corrected visual acuity (at least 5 letters or approximately one line) within the last 12 weeks.

**Recurrent CNV** results from an extrafoveal or juxtafoveal CNV lesion which has had standard laser photocoagulation that did not extend into the foveal center with recurrent CNV that extends under the center of the foveal avascular zone.

**Subfoveal lesion** is a lesion that extends directly beneath the geometric center of the foveal avascular zone.

**TAP Angiographic Grading System** is based on areas of fluorescein leakage and not on other fluorescein features such as the intensity of fluorescence. This system was used in the TAP Investigation and VIP Trial to assess fluorescein leakage from CNV at follow-up.

a. *Progression of leakage*: CNV beyond the area of the entire lesion noted at baseline, regardless of the amount of leakage noted within the area of the original lesion.

b. *Moderate leakage*: area of CNV occupying at least 50% of the area noted at baseline, with no progression.

c. *Minimal leakage*: area of CNV occupying less than 50% of the area of lesion noted at baseline, with no progression.

d. *Absence of leakage*: no CNV within the area of the lesion noted at baseline, with no progression.
**Well-demarcated lesion** is a lesion in which the entire boundary of the lesion is well demarcated (or well defined) from retina uninvolved by any lesion component. “Well-defined” is not synonymous with “classic”.