Photodynamic Therapy with Verteporfin (Visudyne): Impact on Ophthalmology and Visual Sciences

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Recently, the Treatment of Age-Related Macular Degeneration with Photodynamic Therapy (TAP) Study Group reported that photodynamic therapy with verteporfin (Visudyne; Ciba Vision, Bülach, Switzerland) can reduce the risk of vision loss in patients with subfoveal choroidal neovascularization (CNV) due to age-related macular degeneration (AMD). This is a review of the circumstances leading to the design of the TAP Investigation, the findings of that investigation, and the impact of those findings on clinicians and researchers in ophthalmology and vision sciences.

Limitations of Treatment for CNV in AMD through the 1990s

The TAP Investigation was designed to determine whether photodynamic therapy with verteporfin could reduce the risk of vision loss in patients who have subfoveal CNV in AMD. The investigation was initiated because of the many limitations of treatment for CNV in AMD through the 1990s. Specifically, CNV, or the ingrowth of new vessels from the choriocapillaris with subsequent fibrosis and destruction of the outer retina and inner choroid, which usually extends under the center of the foveal avascular zone (i.e., is subfoveal) in patients with AMD, is the leading cause of severe central vision loss in people more than 65 years of age in the United States and throughout the Western world. Occasionally, laser photocoagulation of subfoveal CNV can reduce the risk of severe visual acuity loss, compared with no photocoagulation, by confining the lesion to a small area of damaged retina using thermal laser. In comparing this laser treatment with observation 2 years after entry into randomized clinical trials, the Macular Photocoagulation Study Group reported that the proportion of patients in whom severe vision loss developed (approximately 20%) was approximately half the proportion of those in whom such loss developed without treatment. However, this treatment is beneficial only for relatively small lesions, because the photocoagulation damages viable neurosensory retina overlying the treated CNV. Unfortunately, most patients with subfoveal CNV do not benefit from laser photocoagulation, because the lesions are too large or have poorly demarcated boundaries that require treatment of a relatively large area of the macula to ensure that treatment covers the entire area of the lesion.

The risk of severe visual acuity loss after laser treatment of such a large area of subfoveal CNV in AMD (in an eye that has had no prior laser photocoagulation) is as great or greater than the risk without treatment.

Potential of Photodynamic Therapy in the Treatment of CNV in AMD

Because of the limitations of laser photocoagulation for subfoveal CNV and because CNV in AMD is an important public health problem, other treatments that may be less destructive but are still able to slow down visual loss from CNV are under evaluation in an effort to improve the visual outcome in this condition. One such treatment is photodynamic therapy with verteporfin, a benzoporphyrin derivative monoacid ring A, the only drug, to date, to have a therapeutic benefit in large-scale randomized clinical trials, although other photosensitizers are under investigation. Photodynamic therapy is a two-step process. The first step requires the intravenous infusion of a photosensitive drug, in this case, verteporfin. The second step is activation of the drug by nonthermal light at the wavelength absorbed by the photosensitizer used and in the presence of oxygen. The activation probably results in the formation of cytotoxic oxygen species such as singlet oxygen and free radicals, which can damage cellular structures. This damage may lead to platelet activation and subsequent thrombosis and occlusion of choroidal neovascularization within the treated area. After studies reported that photosensitizers could be retained preferentially in tumors and that photodynamic therapy could lead to tumor death by occlusion of the tumor vasculature and direct cytotoxic effects, investigators hypothesized that photodynamic therapy may be particularly useful in the selective destruction of CNV to confine the lesion from growing and thereby reduce the risk of progressive visual damage without causing significant destruction to viable neurosensory retina overlying the CNV. Verteporfin was believed to be a good photosensitizer for treatment of CNV, not only because of its potential selectivity for neovascular lesions, but also because of its pharmacokinetics, which include rapid clearance within the first 24 hours after infusion to reduce the chance of generalized photosensitivity of a patient after treatment.

Based on preclinical studies, a phase I and II investigation was designed to evaluate the safety of verteporfin therapy for the treatment of patients with CNV and to determine the effects of this therapy on fluorescein leakage from CNV. This investigation showed that an initial treatment of photodynamic therapy with verteporfin could cause short-term cessation of fluorescein leakage from CNV without angio-
graphic damage to retinal blood vessels (Fig. 1 and Fig. 2) or loss of vision.\[^{17}\] In most cases, fluorescein leakage from CNV became apparent by 12 weeks after this initial treatment, even in subjects who had received the maximum tolerated light dose (in which nonselective damage to sensory retinal blood vessels with visual loss had occurred). The investigators suspected that this reappearance of leakage probably would be accompanied by subsequent growth of the neovascular lesion with progressive vision loss. Therefore, the investigators considered evaluating a treatment strategy that would try to confine the neovascular lesion and reduce the chance of vision loss by periodically applying photodynamic therapy with verteporfin to an eye with subfoveal CNV. Subsequently, the safety and fluorescein angiographic effects of multiple treatments of verteporfin therapy were evaluated.\[^{18}\] These studies suggested that repeated treatments could consistently cause short-term cessation of fluorescein leakage from CNV without angiographic damage to the overlying retinal blood vessels and without short-term visual acuity loss after each treatment. However, because fluorescein leakage from CNV typically was noted by 12 weeks after a retreatment, although often involving an area smaller than was noted before treatment, investigators believed that periodic retreatments for an unknown length of time might be required if verteporfin therapy were to be beneficial in reducing vision loss from CNV.
RESULTS OF RANDOMIZED CLINICAL TRIALS EVALUATING VERTEPORFIN THERAPY

Based on the phase I and II investigation, two identically designed phase III randomized clinical trials (the TAP Investigation), sponsored by CibaVision and QLT PhotoTherapeutics (Vancouver, British Columbia, Canada), were initiated at 22 clinical centers in Europe and North America in December 1996.1 The study objective was to determine whether photo- dynamic therapy with verteporfin could safely reduce the risk of vision loss in patients with subfoveal CNV in AMD. Participants included patients with fluorescein angiographic evidence of subfoveal CNV lesions due to AMD measuring 5400 μm or less in greatest linear dimension (because of spot size limitations of the laser devices used to activate the verteporfin) and classic CNV. Classic CNV is defined by a fluorescein angiographic pattern consisting of an area of bright fluorescence in the early phase of the angiogram with fluorescein leakage at the periphery of that area in the mid- and late-phase frames. Investigators believed that this pattern probably would be associated with a relatively high risk of losing vision without treatment within 1 to 2 years after study entry. Other patterns of fluorescein leakage from CNV noted at the level of the retinal pigment epithelium are termed occult CNV. The best-corrected visual acuity was to be approximately 20/40 to 20/200 measured on a retroilluminated distance visual acuity test chart (Lighthouse, Long Island, NY).

Six-hundred nine patients were enrolled through September 1997 and were randomly assigned (2:1) to verteporfin (6 mg/m² body surface area) or placebo (5% dextrose in water) administered by intravenous infusion of 30 ml during 10 minutes. Fifteen minutes after the start of the infusion, a laser light (Coherent, Palo Alto, CA or Zeiss, Jena, Germany) at 689 nm delivered 50 J/cm² at an intensity of 600 mW/cm² during 83 seconds using a spot size with a diameter 1000 μm larger than the greatest linear dimension of the CNV lesion. This choice of a spot size 1000 μm larger than the largest linear dimension was chosen to increase the chance that the lesion would be treated in its entirety and to compensate for any slight movements of the study eye during the light application under topical anesthesia. Follow-up examinations were scheduled every 3 months (±2 weeks), and retreatment with the same regimen used at baseline was to be applied if fluorescein leakage from classic CNV, occult CNV, or both was identified by the treating ophthalmologist on the follow-up angiogram. The spot size at follow-up was to be 1000 μm larger than the largest linear dimension of any areas of CNV leakage on the follow-up fluorescein angiogram (even if those areas were noncontiguous or did not involve the foveal center) and any blood or serous detachment of the retinal pigment epithelium contiguous to that leakage. All patients, treating ophthalmologists, vision examiners, and fundus photograph graders were masked to the treatment assignment. Although the TAP Investigation consisted of two trials (to comply with regulatory agency requirements that two randomized clinical trials confirm a statistically significant benefit for a primary outcome), because the two trials ran concurrently (except that 10 of the clinical centers from Europe and North America were assigned to one trial and the other 12 clinical centers to the other trial), and because baseline characteristics, completeness of follow-up, and outcomes were similar for the two studies, the TAP Data and Safety Monitoring Committee recommended, with agreement by the TAP Study Group, that the scientific presentation of the results combine the data sets from both studies.

Main Outcomes

Ninety-four percent of each group completed the month 12 examination. Visual acuity, contrast sensitivity, and fluorescein angiographic outcomes were better in the verteporfin-treated patients than in the placebo-treated group at every follow-up visit through the month 12 examination. At the month 12 examination, 156 (39%) of 402 eyes assigned to verteporfin compared with 111 (54%) of 207 eyes assigned to placebo (P < 0.001) had moderate vision loss or worse (loss of ≥15 letters or approximately three or more lines on an eye chart compared with baseline). At this follow-up, verteporfin-treated eyes had a low mean number of contrast sensitivity letters lost compared with patients given placebo (1.3 versus 4.5, P < 0.001). These treated eyes also were less likely to show progression (growth) of classic CNV beyond the area of the lesion at baseline (46% versus 71%, P < 0.001), have fluorescein leakage from classic CNV (77% versus 88%, P = 0.002), and have a lesion size more than six disc areas (41% versus 73%, P < 0.001), even though most lesions in both groups were less than this size at the time of study entry for the participant.

Subgroup Analyses

In subgroup analyses, the visual acuity benefit was clearly demonstrated when the area of classic CNV occupied 50% or more of the area of the entire lesion (termed predominantly classic CNV lesions), especially when there was no occult CNV. Specifically for the predominantly classic CNV lesions, 33% of the 159 verteporfin-treated eyes compared with 61% of the 84 placebo-treated eyes (P < 0.001) had moderate vision loss or worse at the month 12 examination. These benefits were even greater in predominantly classic CNV lesions without occult CNV.

No difference in visual acuity between verteporfin-treated patients and controls was noted when the area of classic CNV was more than 0% but less than 50% of the area of the entire lesion (termed minimally classic CNV lesions). However, minimally classic CNV lesions receiving verteporfin therapy were less likely to show progression of classic CNV beyond the area of the lesion at baseline, to have fluorescein leakage from classic CNV, and to have a lesion size more than six disc areas compared to those receiving placebo. These positive outcomes using angiographic surrogate end points did not correspond to a visual acuity benefit at the month 12 examination.

Safety

Few ocular or other systemic adverse events associated with verteporfin treatment were judged to be clinically relevant. The results suggested that treated patients should be warned of the possibility of adverse events at the injection site, infusion-related back pain, photosensitivity reactions, and transient visual disturbances. Adverse events at the injection site (such as pain, edema, hemorrhage, or inflammation) were noted in 13.4% of verteporfin-treated patients compared with 3.4% of patients given placebo. Infusion-related back pain was noted only in verteporfin-treated patients (2%). Photosensitivity reactions, noted only in verteporfin-treated patients (3%) were generally transient mild to moderate sunburns due to direct sunlight exposure shortly after drug administration, usually
within 24 hours of administration. Transient visual disturbances in 18% of verteporfin-treated patients compared with 12% of placebo-treated patients included reports of abnormal vision, decreased vision, and visual field defects that the treating ophthalmologist judged were not due to the impact of the natural course of CNV in AMD on vision. Two percent of patients assigned to verteporfin and 2% of those given placebo had died by the month 12 examination; no deaths were judged to be related to treatment. Verteporfin-treated patients did not experience development of more subretinal hemorrhage, fibrosis, or atrophy of the retinal pigment epithelium than did placebo-treated patients.

**Impact on Ophthalmology and Visual Sciences**

Thus, the TAP Investigation provides strong evidence that photodynamic therapy with verteporfin can safely reduce the risk of vision loss for at least 1 year in patients with subfoveal lesions in AMD that are predominantly classic CNV, especially in the absence of occult CNV. This vision benefit, which probably represents a potential improvement on the quality of life for patients who should be considered to receive this therapy, represents the culmination of basic scientists working on compounds for photodynamic therapy, vision scientists providing preclinical data essential to designing clinical trials, clinical researchers evaluating the safety and potential efficacy of various treatment regimens, investigators in clinical trials determining the precise risks and benefits of verteporfin therapy using methods adapted from prior well-designed clinical trials, sponsors willing to provide the support for these investigations, and patients willing to volunteer to participate in these clinical trials. Given the public health impact of CNV in AMD, these results probably will have a large impact on ophthalmology and visual sciences.

For ophthalmologists, this therapy will add a technique to their treatment armamentarium for some lesions for which there has been no other proven treatment. Because the therapy reduces the risk of vision loss rather than restoring vision, all eye care providers now should have an additional impetus to identify the development of CNV in AMD patients as soon as possible in an attempt to treat patients in whom therapy is beneficial when visual acuity is relatively good. Furthermore, reviewing the therapy with patients will require careful education regarding the risks and benefits, to try to avoid overenthusiastic expectations in patients for whom verteporfin therapy is indicated. Because the lesion components have an impact on the treatment benefit, the ability to identify classic CNV on fluorescein angiography is critical for ophthalmologists using this therapy. In addition, identification of the area of the entire lesion (including recognition of the entire area of any occult CNV, if present) is important to determine whether the lesion is predominantly classic CNV. It is unknown at this time how successful ophthalmologists will be in determining whether a lesion is predominantly classic CNV. However, the TAP Investigation demonstrated that ophthalmologists who were certified through training to identify eligible lesions for the study identified lesions that the Photograph Reading Center graders agreed had some classic CNV 90% of the time and were composed of CNV that comprised 50% or more of the lesion 98% of the time. Thus, it seems likely that similarly trained ophthalmologists should be able to identify cases that would benefit from therapy most of the time.

Those conducting clinical trials must consider the impact of the 1-year results of photodynamic therapy on investigations evaluating other therapies for subfoveal lesions due to AMD with predominantly classic CNV. If the beneficial outcomes reported by the month 12 examination in the TAP Investigation remain the same or increase with longer follow-up, then clinical trials evaluating new treatments for predominantly classic CNV lesions that are subfoveal in AMD could be designed to compare the new treatment to verteporfin therapy and only compare to observation if such a patient refused verteporfin therapy.

Clinical research projects that may be relevant to patient management issues and health policy because of the TAP Investigation results may include determining what proportion of AMD patients are seen by an ophthalmologist with a predominantly classic CNV lesion that is subfoveal and would benefit from verteporfin therapy. Ophthalmologists and health policy experts also may want to know how often and when patients, who initially had a minimally classic or no classic CNV lesion develop lesions that would benefit from verteporfin therapy. These data are unknown at this time; before the TAP Investigation results, there was no reason for investigators to determine this information.

Improvements in this therapeutic approach may be made possible by future clinical trials that determine whether other treatment regimens or other photosensitizers may result in better vision outcomes for predominantly classic CNV lesions or lesions that are not predominantly classic CNV. Although a small proportion of patients enrolled in the TAP Investigation with no evidence of classic CNV (as judged by Photograph Reading Center graders) may have had a treatment benefit, the beneficial effects for this subgroup are imprecise, because this subgroup included only 37 verteporfin-treated patients and 19 placebo-treated patients at study entry. It is not known whether these 56 cases represent the universe of occult CNV lesions without classic CNV, because the enrolling ophthalmologist (but not the Reading Center grader) believed that these cases had some evidence of classic CNV. The Verteporfin In Photodynamic Therapy (VIP) Trial, a companion trial to the TAP Investigation, which includes a large proportion of subfoveal lesions in AMD with occult CNV but no classic CNV, should provide additional information regarding the benefits of this therapy for AMD lesions with compositions different from those enrolled in TAP as well as for subfoveal CNV lesions due to pathologic myopia. Use of this therapy to limit vision loss from other retinal diseases, including vascular tumors such as choroidal hemangiomas, also might be explored further in the future.

The results of the TAP Investigation present additional questions for vision scientists to consider. For example, future investigations that determine why fluorescein angiography results in a pattern of classic CNV versus occult CNV may be helpful in understanding how to improve on the therapeutic benefits and in determining why verteporfin therapy is beneficial for predominantly classic CNV lesions. Clinicopathologic correlation of verteporfin-treated eyes also may provide more information regarding how this therapy works. Clearly, the TAP Investigation results suggest that continued basic science investigations on other photosensitizers and their affects on
ocular tissues may lead to new therapies that will continue to reduce the morbidity from AMD.

**CONCLUSION**

The results of a new treatment, photodynamic therapy with verteporfin for selected patients with subfoveal lesions in AMD with predominantly classic CNV, especially in the absence of occult CNV lesions AMD, show that verteporfin therapy can reduce the risk of moderate vision loss for at least 1 year. Although the therapy is not a magic bullet that can stop or reverse vision loss in all patients with AMD, the benefits are another step in the right direction (joining laser photoagulation and photodynamic therapy for ophthalmologists and vision scientists pursuing investigations intended to reduce the magnitude of vision loss from AMD and its impact on the quality of life of people with this condition. The TAP Investigation should provide encouragement and provide the foundation for future investigations of new treatments for AMD and related conditions by ophthalmologists and vision scientists as the number of people at risk for AMD at least doubles during the next 30 years.

**References**