A Preliminary Study of Photodynamic Therapy Using Verteporfin for Choroidal Neovascularization in Pathologic Myopia, Ocular Histoplasmosis Syndrome, Angioid Streaks, and Idiopathic Causes

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Objective: To evaluate short-term safety and the effects on visual acuity and fluorescein angiography of single or multiple sessions of photodynamic therapy with verteporfin for choroidal neovascularization (CNV) not related to age-related macular degeneration (AMD), including pathologic myopia, the ocular histoplasmosis syndrome, angioid streaks, and idiopathic causes.

Design: A nonrandomized, multicenter, open-label, dose-escalation phase 1 and 2 clinical trial.

Setting: Four ophthalmic centers in Europe and North America providing retinal care.

Participants: Thirteen patients with subfoveal CNV due to pathologic myopia, the ocular histoplasmosis syndrome, angioid streaks, or idiopathic causes.

Methods: Standardized protocol refraction, visual acuity testing, ophthalmic examinations, color photographs, and fluorescein angiograms were used to evaluate the results of photodynamic therapy treatments with verteporfin. Follow-up ranged from 12 weeks for patients who were treated once to 43 weeks for patients who were treated up to 4 times.

Results: Verteporfin therapy was well tolerated in patients with CNV not related to AMD. No deterioration in visual acuity was observed; most patients gained at least 1 line of vision. Reduction in the size of leakage area from classic CNV was noted in all patients as early as 1 week after verteporfin therapy, with complete absence of leakage from classic CNV in almost half of the patients. Improvement in visual acuity after verteporfin therapy was greatest (+6, +8, and +9 lines) in 3 patients with relatively poor initial visual acuity (between 20/200 and 20/800). Up to 4 treatments were found to have short-term safety even with retreatment intervals as short as 4 weeks.

Conclusions: Treatment of CNV not related to AMD with verteporfin therapy achieves short-term cessation of fluorescein leakage from CNV in a small number of patients without loss of vision. Further randomized clinical trials including a larger number of patients are under way to confirm whether verteporfin therapy is beneficial for subfoveal CNV not related to AMD.


CHOROIDAL neovascularization (CNV) is a leading cause of loss of central vision in developed countries. Choroidal neovascularization disrupts the anatomy of the retinal pigment epithelium–photoreceptor complex, leaks serum and sometimes blood, and is often accompanied by irreversible scar formation that is associated with a loss of photoreceptors.1,2 Choroidal neovascularization is encountered most often in patients with age-related macular degeneration (AMD), but also occurs as a consequence of other causes such as pathologic myopia, the ocular histoplasmosis syndrome, angioid streaks, or idiopathic causes.

For more than 25 years, thermal laser photocoagulation has been the only accepted treatment to reduce visual loss related to CNV. The Macular Photocoagulation Study Group has demonstrated the benefit of laser treatment over the observation of selected cases of extrafoveal and juxtafoveal CNV due to various causes other than AMD. When the CNV extends beneath the center of the fovea, the thermal laser treatment may limit scotoma size, but central visual function can be reduced immediately as a result of concomitant damage to the overlying neurosensory retina.3
PATIENTS AND METHODS

The methods have been described previously for patients with AMD.17,18 Briefly, the study protocol and all amendments adhered to the regulatory groups responsible for the respective clinical centers, including the Drug Law, the European Good Clinical Practice Guidelines, the US Food and Drug Administration, the Swiss Interkantonale Kontrollstelle fur Heilmittel, and the German Ethics Committee, and were approved by the local institutional review board of each participating center. Each patient signed a written consent statement before entering the study. Best-corrected visual acuity was measured on a Bailey-Lovie chart using a standardized refraction protocol at baseline and at weeks 1, 4, and 12 after each treatment. Patients were included when it was determined by fluorescein angiography and confirmed by the Wilmer Photograph Reading Center at the Johns Hopkins University School of Medicine, Baltimore, Md, that they had specific characteristics of CNV. All centers used similar 35-mm film retinographic equipment to produce standardized stereoscopic color fundus photography and fluorescein angiography corresponding to the same protocol used during the Macular Photocoagulation Study trials.19 The CNV lesion had to be no greater than 9 Macular Photocoagulation Study disc areas and show a pattern of classic CNV, although occult CNV could also be present. A total of 142 patients were enrolled in this phase 1 and 2 trial, of whom 13 had CNV not related to AMD. The results from these 13 patients without AMD are reported in this article.

PATIENTS WITH CNV NOT RELATED TO AMD

Choroidal neovascularization was judged to be associated with AMD when the patient was older than 50 years and when drusen or other retinal pigment epithelial abnormalities commonly associated with AMD were seen on the photographic documentation. Choroidal neovascularization was considered to be secondary to pathologic myopia when features such as tilted optic nerves, lacquer cracks, and staphylomatous abnormalities were found in addition to refractive changes. The ocular histoplasmosis syndrome was diagnosed when one or more typical histoplasmosis spots were present.20 Choroidal neovascularization was considered to be idiopathic in the absence of any pathologic features associated with CNV such as large drusen, histoplasmosis spots, angiod streaks, or pathologic myopia.

EVALUATIONS

At follow-up, the CNV evaluation was done by the Wilmer Photograph Reading Center according to a grading system developed to assess both the size of the CNV lesion and the presence or absence of leakage from the classic and occult CNV components. The grading was performed without knowledge of the patient's refraction or visual acuity status at screening or during follow-up. A grading system was devised to assess semiquantitatively the effect of verteporfin therapy on the extent (area) of fluorescein leakage from the CNV lesions at each follow-up visit compared with that seen at baseline. Leakage from classic and occult CNV was assessed without any knowledge of verteporfin therapy dosage. The extent of fluorescein leakage for classic CNV and, separately, for occult CNV, was graded as follows: (1) "progression" (leakage from CNV beyond the area of the lesion noted at baseline, regardless of the amount of leakage noted within the area of the lesion identified at baseline); (2) "moderate leakage" (area of CNV occupying the extent of fluorescein leakage for classic CNV and, separately, for occult CNV, was graded as follows: (1) "progression" (leakage from CNV beyond the area of the lesion noted at baseline, regardless of the amount of leakage noted within the area of the lesion identified at baseline); (2) "moderate leakage" (area of CNV occupying...
(50% of the area of CNV noted at baseline and no progression); (3) “minimal leakage” (area of CNV occupying <50% of the area of CNV noted at baseline and no progression); and (4) “absence of leakage” (no CNV within the area of the lesion noted at baseline and no progression). These gradings were based only on the lesion area, not other fluorescein features such as the amount of fluorescence or the area of leakage extending beyond classic CNV or a fibrovascular pigment epithelial detachment.

The laser spot size used was calculated based on the greatest linear dimension of the lesion (in millimeters) as measured on the fluorescein angiogram. This value was multiplied by 1000 to transform the units into microns and then divided by a factor of 2.5 to correspond to the optical magnification of the fundus camera. A 300-µm safety margin was included around the lesion.

PHOTODYNAMIC THERAPY WITH VERTEPORFIN

A total of 142 patients with CNV were enrolled in this phase 1 and 2 trial, of whom 13 had CNV not related to AMD. At the beginning of the trial, each patient received a PDT treatment starting with a 10-minute intravenous infusion of liposomal verteporfin at 6 mg/m² of the dye per estimated body surface area. It was followed by 689-nm laser irradiation 30 minutes after the start of verteporfin infusion, using a slitlamp system coupled to a diode laser (Coherent, Palo Alto, Calif). The first 3 of these 142 patients were treated with a light dose of 50 J/cm², delivered at a light intensity of 600 mW/cm². In the absence of any adverse event at the 1-week follow-up, the light dose was increased to 75 J/cm² for the next 3 patients, then to 100 J/cm², and finally to 150 J/cm².

The treatment regimen was then modified, in particular the injected dose of verteporfin was doubled and the interval between drug injection and laser irradiation was decreased. The light dose of 150 J/cm² was terminated because there was closure of retinal vessels at this light dose in some cases using these regimens. Light-dose escalation was repeated thereafter, up to a maximum of 100 J/cm². To treat recurrences and assess the safety of multiple treatments, 42 patients received up to 4 PDT treatments.

SAFETY PARAMETERS

The effect of verteporfin therapy on the extent (area) of fluorescein leakage from CNV lesions at each follow-up visit was compared with that seen at baseline. Safety evaluation was based on 2 parameters: best-corrected visual acuity and semiquantitative evaluation of fluorescein leakage. Lack of severe visual acuity loss and lack of serious adverse events on fluorescein angiography were required in at least 3 patients before a higher treatment regimen was performed. Additional retreatments were stopped if there was visual acuity loss of 6 or more lines, or nonperfusion of retinal arterioles or venules as judged by the Wilmer Photographic Reading Center. The extent of subretinal hemorrhage, RPE atrophy, and arteriolar, venular, or capillary retinal nonperfusion was graded by the Wilmer Photographic Reading Center. Adverse events were recorded using case record forms. Serious general systemic events and ocular adverse events noted by the investigator were reported immediately by personal communication. Ocular adverse events identified on stereophotography or angiography were recorded by the Wilmer Photographic Reading Center and confirmed by an investigator.

for this indication, as well as to optimize the treatment parameters in humans. The cause of CNV was AMD17,18 in all but 13 patients in this trial. The aim of this study is to describe the visual acuity, anatomic (including angiographic) results, and safety in the group without AMD.

RESULTS

BASELINE FEATURES AND ADHERENCE TO PROTOCOL

Thirteen patients with subfoveal CNV from pathologic myopia (n = 10), ocular histoplasmosis syndrome (n = 1), angioid streaks (n = 1), or idiopathic causes (n = 1) were enrolled (Table). Six of these patients were women. This group had a mean (±SD) age distribution of 53.1 (±14.6) years. Best-corrected visual acuity at screening ranged from 20/50 to 20/800. A myopic refraction was present in 12 of 13 patients, with a mean spherical equivalent of –8.3 (±5.9) diopters (D) (range, –0.5 to –18 D). Classic CNV with no evidence of occult CNV occurred in 11 patients. The other 2 patients had fluorescent patterns, indicating both classic and occult CNV.

Eight patients were treated once, 2 patients were treated twice, 1 patient was treated 3 times, and 2 patients were treated 4 times. As a consequence, the follow-up planned through 12 weeks after the initial treatment ranged from 12 to 43 weeks, depending on the number of treatments received. Retreatments, if given, were applied 4 to 21 weeks after any previous PDT treatment, with the final follow-up at 12 weeks after the last treatment. Because of the relatively large number of treatment parameters associated with this PDT study and the small sample size of this group, the 13 patients without AMD were assigned individually to one of several treatment parameters according to when they were enrolled in the study. There was no loss to follow-up of any of these patients without AMD during the trial.

CHANGES IN VISUAL ACUITY AFTER TREATMENT

One week after a single PDT treatment, visual acuity improved an average of 2.3 (±2.1) lines. Greatest visual acuity improvement (+6, +8, and +9 lines) was noted in 3 patients with an initial visual acuity between 20/200 and 20/800. Increase in mean visual acuity was 2.6 (±3.0) lines at the last follow-up (Figure 1). Four patients had no improvement of their vision at the last follow-up examination. No patient had deterioration in visual acuity.
Fluorescein angiography indicated that all patients had some decrease in the extent of CNV leakage 1 week after PDT, with nearly half of the patients having complete absence of leakage at this follow-up examination. At the last follow-up examination, 12 patients had minimal leakage within the area of the CNV lesions identified at baseline. Only 3 patients showed progression of CNV leakage beyond the area of the lesion at baseline. One patient showed no CNV leakage at the last follow-up examination.

SAFETY AND ADVERSE EVENTS

Verteporfin treatment did not cause any systemic photosensitivity complications, and no skin photosensitivity reactions were reported after an initial treatment or multiple course(s) of therapy.

No clinically relevant visual acuity loss of 3 or more lines was noted in any of the 13 patients at any time during the trial. At the last follow-up examination, no patient had any loss in visual acuity and 5 of 13 patients had moderate improvement in visual acuity (≥3 lines) compared with baseline values. At the last follow-up examination, 2 of the 5 patients who received retreatments had no change in visual acuity and 3 had improved visual acuity, compared with baseline.

The treatment was well tolerated. One patient was hospitalized for diverticulitis, which was judged not to be related to PDT treatment. The Wilmer Photograph Reading Center reported no major ocular adverse events such as retinal vessel nonperfusion.

TWO SELECTED CASE REPORTS

Case 1

A 59-year-old man with −13.25-D spherical equivalent myopia was referred for subfoveal CNV. At baseline, the best-corrected visual acuity in the affected right eye was 20/800. A thin layer of blood obscuring the full extent of the neovascular complex could be seen both clinically, on the color photograph (Figure 2), and by fluorescein angiography. The patient received a single PDT treatment with the following treatment parameters: verteporfin, 6 mg/m² of body surface area, with a light dose of 75 J/cm² applied 20 minutes after the start of verteporfin injection. Blood cleared rapidly and visual acuity improved during follow-up. At the last follow-up examination, 2 of the 5 patients who received retreatments had no change in visual acuity and 3 had improved visual acuity, compared with baseline.

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nation (12 weeks after treatment), the patient gained 9 lines of visual acuity with a final best-corrected visual acuity of 20/100 OD, and fluorescein angiography showed staining but no leakage in the late phase within the area of CNV noted at baseline.

Case 2

A 33-year-old man with –18-D spherical equivalent myopia was referred for evaluation of subfoveal CNV. He had a history of vision loss and metamorphopsia of 6.5 years. At baseline, the best-corrected visual acuity in the affected right eye was 20/64. One week after a first PDT treatment with verteporfin (6 mg/m² of body surface area) and a light dose of 50 J/cm² applied 20 minutes after the start of injection, his vision improved to 20/50 OD (+1 line compared with baseline) and CNV leakage was graded as minimal leakage (Figure 3). Visual acuity improved to 20/40 OD (+2 lines compared with baseline) 4 weeks after treatment. After 12 weeks, CNV leakage was graded as moderate leakage (Figure 3), and visual acuity decreased to 20/160 (~4 lines compared with baseline). A second PDT treatment was given 21 weeks after the first treatment. After 1 week, best-corrected visual acuity reached 20/100 (+2 lines compared with 12 weeks; ~2 lines compared with baseline). Fluorescein angiography showed CNV leakage 4 weeks after treatment (Figure 4a) and a third treatment was applied 6 weeks after the second treatment. After 4 weeks, best-corrected visual acuity improved again and reached the baseline level of 20/64 OD. Four weeks after the third treatment, a fourth treatment was applied. Visual acuity improved to 20/40 OD 4 weeks after treatment. At the last follow-up examination (12 weeks after the last treatment), visual acuity was 20/50 OD (+1 line compared with baseline), although fluorescein angiography still showed CNV leakage (Figure 4b).

COMMENT

This phase 1 and 2 trial was designed to evaluate the safety of PDT with verteporfin for subfoveal CNV. The small number of patients with CNV not related to AMD in this trial experienced no significant safety concerns. Furthermore, no patient lost 1 line or more of visual acuity at the last follow-up examination. Most patients gained at least 1 line of vision. In 1 patient, visual acuity improved 9 lines progressively over time by the 12-week examination after a single treatment. This patient was also the only one not to have leakage from CNV throughout follow-up.

The improvements in visual acuity found in patients without AMD were greater than those seen in patients with AMD. These differences could be explained by the smaller CNV lesion sizes at screening or a healthier RPE-photoreceptor complex surrounding the lesion. Another reason for the improvements observed might be that the classic component of CNV may respond better to PDT than does occult CNV, and most of the patients without AMD had classic CNV without occult CNV at baseline.

As with patients with AMD who participated in this phase 1 and 2 trial, most patients without AMD had leakage from CNV during follow-up. Part of the phase 1 and 2 trial was designed to evaluate the safety of multiple treatments. Hence, a few patients without AMD were treated up to 4 times. Case 2 showed an interesting correlation between PDT and visual acuity improvement. Visual acuity improved shortly after an initial PDT treatment and then decreased during the next 12 weeks when fluorescein leakage from CNV recurred. Visual acuity improved again shortly after each subsequent PDT treatment, and was 1 line better than baseline at the last follow-up examination. This overall visual acuity evolution could be compatible with the natural history of the condition or could be a placebo effect. However, the close correlation between PDT treatment and short-term visual acuity improvement after a long history of vision loss and metamorphopsia suggests that this improvement is not likely to be due to chance alone. Finally, up to 4 treatments were shown to be safe in these patients, including the use of a retreatment interval as short as 4 weeks.

These results have to be considered as preliminary. Indeed, the small sample size and short follow-up time do not allow a definite conclusion on verteporfin safety in patients without AMD. Also, the lack of untreated controls does not allow a clear distinction to be made between short-term visual acuity improvement resulting from the natural history of the disease and that resulting from PDT interventions. Deterioration in visual acuity usually noted in patients with subfoveal CNV from AMD may not be relevant, as the natural history of CNV not related to AMD is better than that of CNV secondary to AMD.

The results from the present study support the need for a randomized, placebo-controlled clinical trial to
Figure 2. Patient with subfoveal choroidal neovascularization related to pathologic myopia receiving a single treatment using photodynamic therapy with verteporfin. Before treatment, color fundus photography shows a pigmented lesion under the center of the foveal avascular zone, with subretinal hemorrhage along the inferotemporal boundary of the lesion, as well as a temporal crescent with somewhat straightened retinal vessels and a blonde fundus (A). Fluorescein angiography shows classic choroidal neovascularization with a bright area of hyperfluorescence in the early phase (B), with leakage in the late phase (C). One week after treatment, note the slightly increased amount of hemorrhage surrounding the lesion (D). Early-phase (E) and late-phase (F) fluorescein angiography shows no fluorescence from choroidal neovascularization and no abnormal fluorescence of the retinal vessels overlying the lesion. Four weeks after treatment, hemorrhage has decreased (G), but fluorescein angiography shows an area of hyperfluorescence (H), with staining of the neovascular lesion in the late phase (I) covering an area smaller than the area of choroidal neovascularization noted at pretreatment. Twelve weeks after treatment, some pigment is seen on red-free black-and-white fundus photography (J). Fluorescein angiography shows fluorescein staining surrounding the hypofluorescence from pigmented area in the early phase (K), with staining of the lesion in the late phase covering an area similar to that seen at baseline (L).
Figure 3. Initial treatment in a patient with subfoveal choroidal neovascularization (CNV) related to pathologic myopia who received multiple treatments using photodynamic therapy with verteporfin. Before treatment, color fundus photography shows a pigmented lesion under the center of the foveal avascular zone (A). Fluorescein angiography shows classic CNV with a bright area of hyperfluorescence in the early phase (B), surrounded by some hypofluorescence corresponding to pigment and blood, with leakage in the late phase (C). One week after treatment, fluorescein angiography shows a small area of retinal pigment epithelium atrophy surrounding the lesion (D), without fluorescence from CNV in the early phase (E) and late phase (F); hyperfluorescence of the retinal pigment epithelium atrophy is seen without any abnormal fluorescence of the retinal vessels overlying the lesion. Four weeks after treatment, retinal pigment epithelium atrophy is still apparent but is not increased (G); fluorescein angiography shows an area of hyperfluorescence (H), with leakage from CNV in the late phase covering an area smaller than that at pretreatment (I). Twelve weeks after treatment, a small hemorrhage is seen on color fundus photography (J). Fluorescein angiography shows hyperfluorescence from CNV in the early phase (K), with leakage from CNV in the late phase covering an area similar to that seen at baseline (L). The patient received subsequent treatments using photodynamic therapy with verteporfin (see Figure 4a and Figure 4b).
Figure 4a. Subsequent treatments in a patient with subfoveal choroidal neovascularization (CNV) related to pathologic myopia receiving multiple treatments using photodynamic therapy with verteporfin. One week after a second treatment, no increased retinal pigment epithelium (RPE) atrophy is noted (A) compared with pretreatment (Figure 3, J). There is an absence of hyperfluorescence from CNV in the early phase, without abnormality to the retinal vessels overlying the treated area (B) or hyperfluorescent staining of RPE atrophy in the late phase (C). Four weeks after the second treatment, hemorrhage has resolved (D). Fluorescein angiography shows an area of hyperfluorescence (E), with leakage from CNV in the late phase covering an area smaller than that at pretreatment and without increased atrophy (F). The patient received a third treatment. One week after the third treatment, no change is seen on color fundus photography (G), and early-phase fluorescein angiography shows no hyperfluorescence of CNV, although choroidal vessels can be visualized along the inferior aspect of the treated area (H). Late-phase fluorescein angiography shows a small area of staining within the hyperfluorescent lesion surrounded by staining of the RPE atrophy (I). Four weeks after the third treatment, a small amount of hemorrhage is noted in the center of the CNV lesion (J); an area of hyperfluorescence is seen on fluorescein angiography (K), with leakage from CNV in the late phase covering an area smaller than that at pretreatment and without increased atrophy (L).
determine whether PDT with verteporfin is beneficial for subfoveal CNV not related to AMD. Such a multicenter, randomized clinical trial, the Verteporfin in Photodynamic Therapy (VIP) Trial, is currently under way and includes 120 patients with subfoveal CNV due to pathologic myopia.22

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The Massachusetts Eye and Ear Infirmary is an owner of a patent covering the use of verteporfin. Should the Massachusetts Eye and Ear Infirmary receive royalties or other financial remuneration related to that patent, Drs Miller and

Figure 4b. The patient received a fourth treatment. One week after the fourth treatment, hemorrhage has resolved within the overlying lesion, although new hemorrhage can be seen just superior to the boundary of the retinal pigment epithelium (RPE) atrophy on color fundus photography (M). Early-phase fluorescein angiography shows no hyperfluorescence of choroidal neovascularization (CNV), although choroidal vessels can be visualized surrounding the treated area (N). Late-phase fluorescein angiography shows a small area of staining within the hypofluorescent CNV lesion, which is surrounded by staining of the RPE atrophy (O). Four weeks (P through R) and 12 weeks (S through U) after the fourth treatment, color fundus photography appears stable (P and S). Note the small area of hyperfluorescence in the early phase (Q and T), with leakage from CNV in the late phase (R and U) covering an area smaller than that at pretreatment; there is little difference between the 4-week (Q and R) and 12-week (T and U) appearance.
Gragoudas would receive a share of same in accordance with the Massachusetts Eye and Ear Infirmary’s institutional Patent Policy and Procedures, which includes royalty-sharing provisions. Drs Sickenberg and Bressler are consultants for CIBA Vision Inc, Duluth, Ga, and QLT Phototherapeutics Inc, Vancouver, British Columbia.

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REFERENCES


From the Archives of the Archives

A look at the past . . .

Dr Conrad Berens, New York, NY: In transplanting the superior oblique for complete third nerve paralysis, it is well to keep in mind the important structures around the trochlear pulley. I had success with the first 3 operations in opening the pulley with a canaliculus knife, as suggested by Peter, but my last 2 (unhappy) experiences made me certain that in freeing the tendon, one should approach the pulley from a cutaneous incision.