Photodynamic Therapy With Verteporfin for Choroidal Neovascularization Caused by Age-related Macular Degeneration

Results of a Single Treatment in a Phase 1 and 2 Study

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Objective: To evaluate the safety and short-term visual and fluorescein angiographic effects of a single photodynamic therapy treatment with verteporfin with the use of different dosage regimens in patients with choroidal neovascularization (CNV) from age-related macular degeneration.

Design: Nonrandomized, multicenter, open-label, clinical trial using 5 dosage regimens.

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

Participants: Patients with subfoveal CNV caused by age-related macular degeneration.

Methods: Standardized protocol refraction, visual acuity testing, ophthalmic examination, color photographs, and fluorescein angiograms were used to evaluate the effects of a single treatment of photodynamic therapy with verteporfin. Follow-up was planned through 3 months in 97 patients and for less than 3 months in 31 other patients.

Results: The mean visual acuity change (and range of change) from baseline at the follow-up examination at week 12 after a single treatment with regimens 1 through 5 was −0.2 (−3 to +2), −0.9 (−9 to +5), −1.6 (−9 to +2), +0.4 (−8 to +7), and +0.1 (−8 to +9) lines, respectively. Only the highest light dose (150 J/cm²) in regimens 2 and 3, which produced angiographic nonperfusion of neurosensory retinal vessels, caused marked vision loss. Some cessation of fluorescein leakage from CNV was achieved without loss of vision when the light dose used was less than 150 J/cm². Systemic adverse events were rare. Cessation of fluorescein leakage from CNV was noted in all regimens by 1 week after photodynamic therapy. Fluorescein leakage from at least a portion of the CNV reappeared by 4 to 12 weeks after treatment in almost all cases. Progression of classic CNV beyond the area of CNV identified before treatment was noted in 42 (51%) of the 83 eyes with classic CNV followed up for 3 months after a single treatment. Eyes in which the area of any CNV leakage at 12 weeks was less than at baseline had a significantly better visual acuity outcome (+0.8 line) than eyes in which CNV leakage progressed (−0.8 line).

Conclusions: Photodynamic therapy with verteporfin achieved short-term cessation of fluorescein leakage from CNV without loss of vision or growth of classic CNV in some patients with age-related macular degeneration. Except for nonperfusion of neurosensory retinal vessels at a light dose of 150 J/cm², no other adverse events were of concern. Randomized clinical trials to investigate whether this new modality can preserve vision in patients with CNV secondary to age-related macular degeneration are justified.

PATIENTS AND METHODS

The study was a nonrandomized, multicenter, open-label trial that used 5 dose regimens. The protocol and all amendments were reviewed by the US Food and Drug Administration, the local ethics committee in Germany, and the Interkantonale Kontrollstelle für Heilmittel in Switzerland, and approved by an internal review board at each participating institution. Each patient signed a written consent statement after receiving a full verbal and written explanation of the study, including the potential benefits and risks of treatment.

STUDY POPULATION

The main inclusion and exclusion criteria are listed below.

Inclusion Criteria

- Clinical signs of CNV from any cause
- CNV under the geometric center of the foveal avascular zone (subfoveal)
- Some classic CNV (occult CNV could, but need not, be present)
- Greatest linear dimension of entire CNV 5400 µm in diameter or less
- Nasal side of CNV at least 300 µm from temporal border of optic nerve
- For CNV lesions recurring after standard laser therapy, foveal center must not have been included in area treated by laser
- Best-corrected visual acuity of 20/40 or worse
- 50 years of age or older

Exclusion Criteria

- Tears of RPE at screening
- Vitelliformlike detachment of RPE
- Central serous retinopathy
- Drusenoid pigment epithelial detachment alone
- Additional retinovascular diseases compromising visual acuity of study eye
- Use of investigational drugs, systemic corticosteroids, cytokines, or photosensitive drugs in past 3 months
- Substantial hepatic, renal, or neurologic disease
- Class III or IV cardiovascular disease (New York Heart Association functional status criteria)
- Porphyria, porphyrin sensitivity, hypersensitivity to sunlight or bright artificial light
- Any treatment for malignant disease
- Any acute illness during screening or fever on day of treatment before verteporfin infusion
- Uncontrolled hypertension
- Ocular surgery within 3 months before study treatment

Standardized protocol refraction was performed and visual acuity of each eye was determined on retroilluminated modified Bailey-Lovie charts according to a modified protocol of the Submacular Surgery Trials. Color fundus photography and fluorescein angiography were obtained according to a standardized protocol adapted from the Macular Photocoagulation Study (MPS) Group. Photographic features were identified on the basis of definitions used in MPS reports. Photograph Reading Center staff confirmed angiographic eligibility before enrollment for the first 61 treated patients. Subsequent patients were enrolled on the basis of the investigator’s determination of eligibility; color photographs and fluorescein angiograms were reviewed by the Reading Center afterward to confirm eligibility retrospectively. Of the 128 patients in this study, 31 received multiple treatments, and data from these patients are included up until a retreatment. Data on retreatments are included in a separate report.

EVALUATIONS

Standardized protocol refractions, visual acuity determinations, complete ophthalmic examinations, color fundus photography, and fluorescein angiography were performed at baseline (between 1 and 7 days before the day of treatment) and at follow-up weeks 1, 4, and 12. Visual acuity testing without refraction was also performed on the day of treatment and 1 day after treatment. Additional testing was carried out at week 2 if any ocular adverse event was noted at week 1 or at any time between visits, if judged to be clinically indicated. In addition, each patient underwent measurement of vital signs, a physical examination, and an electrocardiogram at baseline and at week 12. Laboratory testing, including a complete blood cell count, measurement of serum cholesterol, triglyceride, urea nitrogen, creatinine, electrolyte, calcium, phosphorus, glucose, protein, albumin, and bilirubin levels, liver function tests, and urinalysis, was performed at baseline and at weeks 1 and 12.

PDT REGIMENS

The size of the treatment spot was calculated by means of the baseline fluorescein angiogram. The greatest linear dimension of the neovascular lesion was measured. This dimension was divided by 2.5 to account for the magnification of the camera systems used, to yield a size of the lesion on the retina. Initially the dimension was divided by 3.0 on the basis of the MPS protocol, but this was found to be in error, and the method was modified for the PDT studies. A 600-µm border was added to the dimension on the retina to provide at least a 300-µm border at all edges. In some cases, the resulting treatment border at a given edge was greater than 300 µm, but it was always less than 500 µm. The treatment spot was selected on the basis of the available laser link settings (400–4000 µm) and magnification of the contact lens, according to the manufacturer of the lens.

The initial study treatment regimen involved intravenous infusion of verteporfin (6 mg/m², or approximately 0.15 mg/kg), followed by irradiation 30 minutes after the start of dye infusion (regimen 1) with 689-nm conventional thermal laser therapy and that are able to improve the visual outcome of this disease.

One of these treatments, photodynamic therapy (PDT), involves injection of a photosensitizer, usually intravenously, followed by irradiation of the photosensitized tissue by non-
light delivered by an ocular photoactivation diode and laser link slitlamp (Coherent Inc, Palo Alto, Calif), as described in a previous study.14 The delivered irradiance was kept constant at 600 mW/cm². Treatment protocol amendments were made to evaluate different dose regimens that might increase the persistence of the PDT effect on fluorescence leakage from CNV after a single treatment. These regimens are summarized in Table 1. In the first 3 treatment regimens, the light dose (fluence) was escalated from 50 to 75 to 100 to 150 J/cm², with a minimum of 3 patients at each light dose. In regimen 4, the 150-J/cm² light dose was not included because of nonselective sensory retinal vessel nonperfusion seen after PDT with this light dose in regimens 2 and 3. In regimen 5, lower light doses of 12.5 and 25 J/cm² were included, as well as 50 J/cm².

On the day of treatment, the patient was weighed and the verteporfin solution was prepared as 6 mg/m² or 12 mg/m². The verteporfin solution and intravenous tubing were wrapped in aluminum foil to protect the verteporfin from light. The verteporfin was infused by means of a syringe pump followed by 3-mL flush of 9% dextrose solution. Irradiation was performed at a specified time after the start of verteporfin infusion with the use of the selected contact lens, and the duration of irradiation ranged from 21 to 250 seconds depending on the light dose used. The first 45 participants underwent cardiac monitoring during PDT with a 2-lead rhythm strip, and vital signs were measured periodically. Initially, patients underwent retrobulbar injection of anesthetic of the study eye to ensure akinesia. This was discontinued after it was used in approximately 50 patients, when it was judged to be unnecessary. After the procedure, patients were instructed to avoid bright sunlight as much as possible for 7 days, and to wear special sunglasses with a low (4%) transmittance during that time.

SHORT-TERM EFFICACY AND SAFETY PARAMETERS

Two measures were used to assess short-term efficacy and safety: (1) the extent of fluorescence leakage from the CNV (classic and occult) and (2) stabilization of the best-corrected visual acuity at 12-week follow-up compared with baseline. A grading system was devised to semiquantitatively assess the effect of PDT on the extent (area) of fluorescence leakage from the CNV lesions at each follow-up visit compared with that seen at baseline. Fluorescence leakage from classic and occult CNV was assessed without any knowledge of the PDT dosages. The extent of fluorescence leakage for classic CNV and, separately, for occult CNV, was graded as (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 lesion area and not on other fluorescence features such as the amount of fluorescence or the area of leakage extending beyond classic CNV or a fibrovascular pigment epithelial detachment. The Reading Center also graded the extent of subretinal hemorrhage, RPE atrophy, and retinal arteriolar, venular, and capillary nonperfusion.

Best-corrected visual acuity was obtained primarily as an indicator of safety, not efficacy, given the absence of a control group, the short period of follow-up, and the known variability in the natural course of the disease. A change in visual acuity of 3 or more lines was considered to be clinically significant. However, changes in visual acuity and angiographic leakage were used to compare the results among the regimens. This exploratory analysis was used to select the treatment regimen for the subsequent randomized, placebo-controlled trial.

Data on adverse ocular events were obtained from the following 2 source documents: case record forms and Reading Center forms. Case record forms captured general systemic and ophthalmologic adverse events noted by the treating ophthalmologist that would not be captured by color fundus photographs or fluorescein angiograms. The Reading Center forms noted adverse events observed on fundus photographs and fluorescein angiograms.

STATISTICAL METHODS

The different grades of cessation of fluorescein leakage from CNV were evaluated descriptively by treatment regimen and within subgroups. Treatment regimens were compared by Fisher exact test to assess differences in the degree of absence of leakage by visit. Two-by-two contingency tables were generated by collapsing the categories of leakage extent for each treatment regimen.

The comparisons performed included the proportion of patients with absence of leakage vs the proportion of patients with some leakage or progression; the proportion of patients with minimal leakage or absence of leakage vs the proportion of patients with moderate leakage or progression; and the proportion of patients with no progression vs the proportion of patients with progression.

Summary statistics (mean, median, and SD) were generated for the change from baseline in visual acuity by treatment regimen and within subgroups. Further exploratory comparisons using analysis of variance methods were performed to assess the relationship between visual acuity outcomes and baseline characteristics such as baseline visual acuity, baseline lesion size, baseline lesion component, and baseline lesion status. Patients who received the 150-J/cm² light dose in regimens 2 and 3 were excluded from these subgroup analyses, since this light dose was found to be unsafe and above the maximum tolerated dose. All summary statistics and statistical tests were performed with the SAS system. All tests were 2 sided, and all P values of .05 or less were considered to be statistically significant.

ARCH OPHTHALMOL / VOL 117, SEP 1999

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an absorption peak near 690 nm.\textsuperscript{22,23} It has been demonstrated to be an effective photosensitizer in vitro and in several in vivo systems.\textsuperscript{22-26} Photodynamic therapy with verteporfin was used for photothrombosis of ocular neovascularization in different animal models and has been shown to provide occlusion of subretinal vessels without significant alteration of overlying photoreceptors.\textsuperscript{16,17} Preclinical studies have shown that verteporfin localizes to experimental CNV,\textsuperscript{27} and that PDT with the use of verteporfin can occlude experimentally induced CNV, with cessation of fluorescein leakage seen angiographically and thrombotic occlusion of vessels seen histologically.\textsuperscript{19,21} By controlling the verteporfin dose, light dose, and timing of irradiation, the effect can be selective to the CNV, with minimal effects on the surrounding retina and choroid.\textsuperscript{19,21} In animal models, once cessation of fluorescein leakage from CNV is observed, a fibrotic scar develops in 4 to 7 weeks.\textsuperscript{28} The use of PDT in normal monkey retina, with the same therapeutic measures, showed absence of perfusion of the choriocapillaris acutely, followed by reperfusion.\textsuperscript{18,19,21,28} Similarly, the retinal pigment epithelium RPE was damaged acutely after PDT. However, by 4 to 7 weeks after PDT, the RPE had repopulated the treatment area, demonstrating variable pigmentation but normal basal infoldings, indicating some degree of normal function. The neural retina was essentially normal by 4 to 7 weeks after treatment.\textsuperscript{28} These preclinical studies established preliminary safety and efficacy of PDT with verteporfin to treat CNV. Furthermore, they identified treatment parameters that could be used in clinical trials.

The present study was initially designed to assess the safety of PDT and to determine the maximum tolerated dose of PDT with verteporfin to treat CNV. It was later expanded by a number of treatment protocol amendments to make comparison evaluations on dosimetry. This report presents data on the effects of a single treatment of PDT with verteporfin on 128 patients with subfoveal CNV secondary to AMD. Follow-up was planned through 3 months in 97 patients and for less than 3 months in 31 patients. The remaining 13 patients who participated in this study (not included in this report) had CNV from causes other than AMD; these data are included in a separate report (in preparation). Photodynamic therapy with verteporfin will be known in the future as “verteporfin (Visudyne) therapy.”

One hundred twenty-eight patients with CNV caused by AMD were treated with at least a single course of PDT, including 31 patients who later received multiple courses of PDT with regimen 2 or 4. In cases with multiple treatments, only data up to the second PDT treatment are presented; retreatments are reported in a separate communication. The distribution of patients and the duration of follow-up are shown in Table 1.

### BASELINE PATIENT CHARACTERISTICS

The baseline characteristics of the 128 patients in the study are given in Table 2. One case in regimen 4 and two cases in regimen 5 were judged not to be subfoveal lesions by the Photograph Reading Center. Lesion characteristics listed were based on interpretation of the Photograph Reading Center, not the enrolling ophthalmologist. In the eye to be treated, most patients (79.7%) had a baseline visual acuity better than or equal to 20/200. The mean and median baseline visual acuities were both 20/125. The mean baseline lesion size was 5.1 MPS disc areas (DAs), with a range of 1 to 16 MPS DAs (1 MPS DA is 1.775 mm\textsuperscript{2}, assuming a ×2.5 magnification). Eighty-one (63.3%) of the CNV lesions manifested classic CNV in which the area of classic CNV was 50% or more of the area of the lesion. Of these lesions, 41 (32.0%) had no occult CNV. Ten (7.8%) of the baseline lesions were judged to have no classic CNV on review by the Reading Center. In 93.0% of the lesions, fibrosis was judged to be 50% of the lesion or less.

Since this trial was designed primarily as a safety trial and not as an efficacy trial, patients were not randomized to different regimens. Baseline characteristics were compared among groups to determine any differences in patient
characteristics that could confound results. These comparisons identified large differences in sex distribution among regimens 1, 4, and 5: regimens 1 and 5 included more men (34; 68%) and regimen 4 included more women (17; 77%). Otherwise, there were no significant differences among the 5 regimens in the patient variables assessed.

PROTOCOL DEVIATIONS

Withdrawals

As seen in Table 1, six patients withdrew from the study before their week-12 assessment or before enrolling in a retreatment protocol. One patient in regimen 1 withdrew after a single PDT treatment because of pain associated with the fluorescein injections, as well as an unwillingness to travel to the clinic for follow-up. One patient in regimen 4 withdrew between weeks 8 and 12 because of the death of a spouse. Another patient in regimen 4 missed the final follow-up visit because of a left hip fracture. For regimen 5, one patient refused to return by week 1; two additional patients refused to return after the week-4 follow-up visit.

Adherence to Light Administration

Three patients assigned to regimen 2 had light administered such that regimen 1 actually was performed; they are included under regimen 1 data. Two other patients assigned to, and listed under, regimen 1 had light administration 39 and 55 minutes late because of technical difficulties with the laser. One patient assigned to regimen 4 had light administered such that regimen 2 was performed, and this patient is included under regimen 2 data.

Adherence to Eligibility Criteria

Ten patients had no classic CNV and were excluded from the analysis of classic CNV. Three patients (see Table 2) had CNV that was judged not to be subfoveal by the Reading Center staff, but were still included in the final analysis. One patient had a baseline visual acuity better than 20/40 but was still included in the final analysis.

CHANGES IN VISUAL ACUITY AFTER TREATMENT

The study was designed primarily as a safety trial. In each regimen, the light dose was escalated to determine a maximum tolerated dose before visual acuity changes, ocular adverse events, or systemic adverse events were noted. Dose escalation in regimen 1 did not result in any signs of toxicity but also did not result in cessation of fluorescein leakage from the CNV by week 12. Therefore, additional regimens were investigated with changes in the verteporfin dose, the rate of verteporfin infusion, or the timing of light irradiation, to assess the effect on vision and fluorescein leakage from the CNV. At the highest light dose used (150 J/cm²) in regimens 2 and 3, PDT-related vision losses were observed in 3 patients. Subsequently, patients were not treated at this light dose. The adverse events related to this highest light dose are discussed in further detail in the “Safety” section below.

Table 3 summarizes the changes in visual acuity from baseline for treatment regimens 1 through 5. Overall, of the 127 patients who had an assessment at week 1, the mean change in visual acuity was +0.7 line. Interestingly, in 18 patients (14.2%) visual acuity improve-

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>1 Course of PDT Received (n = 97)</th>
<th>≥2 Courses of PDT Received (n = 31)</th>
<th>Total (N = 128)</th>
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<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>40 (41)</td>
<td>20 (65)</td>
<td>60 (46.8)</td>
</tr>
<tr>
<td>Male</td>
<td>57 (59)</td>
<td>11 (35)</td>
<td>68 (53.1)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>96 (99)</td>
<td>31 (100)</td>
<td>127 (99.2)</td>
</tr>
<tr>
<td>Asian</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60</td>
<td>3 (3)</td>
<td>1 (3)</td>
<td>4 (3.1)</td>
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<tr>
<td>60-69</td>
<td>20 (21)</td>
<td>12 (39)</td>
<td>32 (25.0)</td>
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<tr>
<td>70-79</td>
<td>47 (48)</td>
<td>13 (42)</td>
<td>60 (46.8)</td>
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<td>≥80</td>
<td>27 (28)</td>
<td>5 (16)</td>
<td>32 (25.0)</td>
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<tr>
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<td>74.5</td>
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<tr>
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<td>140.0</td>
<td>140.0</td>
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<tr>
<td>Diastolic</td>
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<td>80.0</td>
<td>80.0</td>
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<tr>
<td>Type of CNV</td>
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<tr>
<td>Classic only</td>
<td>28 (29)</td>
<td>13 (42)</td>
<td>41 (32.0)</td>
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<tr>
<td>Classic and occult; ≥50% classic</td>
<td>35 (36)</td>
<td>5 (16)</td>
<td>40 (31.2)</td>
</tr>
<tr>
<td>Classic and occult; &lt;50% classic</td>
<td>27 (28)</td>
<td>10 (32)</td>
<td>37 (28.9)</td>
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<tr>
<td>No classic</td>
<td>7 (7)</td>
<td>3 (10)</td>
<td>10 (7.8)</td>
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<td>CNV lesion location</td>
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<tr>
<td>Subfoveal</td>
<td>93 (96)</td>
<td>30 (97)</td>
<td>123 (96.1)</td>
</tr>
<tr>
<td>Not subfoveal</td>
<td>3 (3)</td>
<td>0 (0)</td>
<td>3 (2.3)</td>
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<td>CNV secondary to:</td>
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<tr>
<td>AMD</td>
<td>92 (95)</td>
<td>31 (100)</td>
<td>123 (96.1)</td>
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<td>AMD and myopic degeneration</td>
<td>3 (3)</td>
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<td>3 (2.3)</td>
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<td>AMD and OHS</td>
<td>2 (2)</td>
<td>0 (0)</td>
<td>2 (1.6)</td>
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<td>Lesion size, MPS DA</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>5.1 (2.7)</td>
<td>5.3 (3.4)</td>
<td>5.1 (2.9)</td>
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<tr>
<td>Median</td>
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<tr>
<td>Minimum</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Maximum</td>
<td>12.0</td>
<td>16.0</td>
<td>16.0</td>
</tr>
<tr>
<td>Visual acuity, study eye</td>
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<tr>
<td>&gt;20/40</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>20/40-20/80</td>
<td>39 (40)</td>
<td>14 (45)</td>
<td>53 (41.4)</td>
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<tr>
<td>20/100-20/200</td>
<td>36 (37)</td>
<td>13 (42)</td>
<td>49 (38.3)</td>
</tr>
<tr>
<td>20/250-20/640</td>
<td>21 (22)</td>
<td>4 (13)</td>
<td>25 (19.5)</td>
</tr>
<tr>
<td>Mean</td>
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<td>20/125</td>
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<td>Fibrosis, % of lesion</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>No fibrosis</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>0-25</td>
<td>70 (72)</td>
<td>27 (87)</td>
<td>97 (75.8)</td>
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<tr>
<td>26-50</td>
<td>19 (20)</td>
<td>2 (6)</td>
<td>21 (16.4)</td>
</tr>
<tr>
<td>&gt;50</td>
<td>7 (7)</td>
<td>2 (6)</td>
<td>9 (7.0)</td>
</tr>
</tbody>
</table>

*Unless otherwise specified, data are given as number of patients, with percentages of patients allocated to 1, or 2 or more, courses of photodynamic therapy (PDT) and of the total number of patients included in parentheses. AMD indicates age-related macular degeneration; BP, blood pressure; CNV, choroidal neovascularization; MPS DA, Macular Photocoagulation Study Group disc area; and OHS, ocular histoplasmosis syndrome.
ment was 3 lines or more. Of the 118 patients with an assessment at week 4, the mean change in visual acuity was +0.2 line, and of the 91 patients with a week-12 assessment, the mean change in visual acuity was −0.5 line. The difference in mean visual acuity change at week 4 between regimen 3 (−1.6 lines) and regimen 4 (+1.1 lines) was statistically significant (P = .002).

At the week-12 assessment, regimen 3 showed the largest mean visual acuity loss (1.6 lines), whereas regimen 4 had the largest mean visual acuity improvement (0.4 line). When the patients in regimens 2 and 3 who were treated at the highest light dose (150 J/cm²) in whom arteriolar and venular nonperfusion had occurred, were excluded from the analysis, regimen 4 continued to have the best mean visual acuity change at week 4 (+1.1 lines) and week 12 (+0.4 line). Likewise, when patients who received the highest light dose were excluded, regimen 3 continued to have the worst mean visual acuity change (−1.6 line) at both weeks 4 and 12.

ANGIOGRAPHIC CHANGES IN FLUORESCEIN LEAKAGE AFTER PDT

**Figure 1** summarizes the change in fluorescein leakage from classic CNV for regimens 1 through 5 at weeks 1, 4, and 12 (excluding patients with no classic CNV at baseline). At week 1, some cessation of fluorescein leakage was observed angiographically in all patients (for example, see **Figure 2**). Absence of fluorescein leakage from classic CNV at week 1 occurred in 52% (11 of 21 patients) to 100% (21 of 21 patients), depending on the regimen used. Leakage typically reappeared in a portion of the CNV by week 4 in most patients in all regimens (for example, see Figure 2).

Regimen 4 resulted in the largest proportion of cases with absence of leakage at week 1 (100%; 21 patients) and week 4 (29%; 6 patients). Within regimen 4, the 50-J/cm² light dose was associated with the highest percentage (57%; 4 patients) of patients with absence of leakage at week 4. Otherwise, there was no obvious light dose–response relationship in the ability to stop fluorescein leakage from classic CNV.

The percentages of eyes with minimal leakage and no progression (leakage from CNV beyond the original borders) were comparable among regimens at week 4, with the exception of regimen 5, which appeared to be less effective. The rates of progression by week 4 were comparable among the regimens and ranged from 8% (2 patients) to 23% (4 patients).

At week 12, regimen 4 had a greater percentage of patients (30%; 3 patients) with absence of leakage from classic CNV than other regimens. Regimen 4 also showed the greatest percentage of patients (80%; 8 patients) with no leakage or minimal leakage compared with other regimens. The incidence of progression at week 12 ranged from 20% (2 patients) in regimen 4 to 62% (13 patients) in regimen 5. Cases with some leakage by week 4 were more likely to show progression by week 12.

The effects of PDT treatment on fluorescein leakage from occult CNV at weeks 1, 4, and 12 of follow-up are shown in **Figure 3**. Leakage from occult CNV was qualitatively more difficult to grade. All eyes showed some fluorescence of the treated fibrovascular tissue or retina immediately surrounding the CNV in the late phase of the angiogram (Figure 2). In many cases, this staining was difficult to distinguish from the staining and leaking characteristics of occult CNV. Of note, some eyes with no occult CNV at baseline could be

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**Table 3. Visual Acuity Change From Baseline by Visit and Treatment Regimen**

<table>
<thead>
<tr>
<th>Visual Acuity Change</th>
<th>Regimen 1 (n = 22)</th>
<th>Regimen 2 (n = 37)</th>
<th>Regimen 3 (n = 19)</th>
<th>Regimen 4 (n = 22)</th>
<th>Regimen 5 (n = 28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;3-Line gain, No. (%))</td>
<td>3 (14)‡</td>
<td>5 (18)†</td>
<td>0 (0)</td>
<td>3 (14)</td>
<td>4 (15)†</td>
</tr>
<tr>
<td>No change, No. (%)</td>
<td>18 (81)</td>
<td>21 (57)†</td>
<td>13 (68)</td>
<td>18 (82)</td>
<td>20 (74)</td>
</tr>
<tr>
<td>&gt;3-Line loss, No. (%)</td>
<td>1 (5)</td>
<td>2 (7)†</td>
<td>6 (32)</td>
<td>1 (5)</td>
<td>3 (11)</td>
</tr>
<tr>
<td>Mean (SD) change, lines</td>
<td>+0.7 (1.5)</td>
<td>+0.8 (2.6)</td>
<td>−0.9 (2.9)</td>
<td>+0.9 (2.5)</td>
<td>+1.4 (2.0)</td>
</tr>
<tr>
<td>Range, lines</td>
<td>−3 to +4</td>
<td>−7 to +8</td>
<td>−12 to +2</td>
<td>−3 to +7</td>
<td>−2 to +9</td>
</tr>
</tbody>
</table>

| Week 4 |
|----------------------|-------------------|-------------------|-------------------|-------------------|-------------------|
| >3-Line gain, No. (%)) | 3 (14) | 5 (18)† | 0 (0) | 3 (14) | 4 (15)† |
| No change, No. (%) | 18 (81) | 21 (57)† | 13 (68) | 18 (82) | 20 (74) |
| >3-Line loss, No. (%) | 1 (5) | 2 (7)† | 6 (32) | 1 (5) | 3 (11) |
| Mean (SD) change, lines | +0.1 (1.7) | +0.3 (2.5) | −1.6 (3.2) | +1.1 (2.4) | +0.7 (2.3) |
| Range, lines | −3 to +4 | −7 to +5 | −9 to +2 | −4 to +7 | −4 to +7 |

| Week 12 |
|----------------------|-------------------|-------------------|-------------------|-------------------|-------------------|
| >3-Line gain, No. (%)) | 0 (0)‡ | 1 (6)% | 0 (0) | 4 (36)% | 12 (12)† |
| No change, No. (%) | 18 (85)% | 12 (70)% | 15 (79) | 4 (36)% | 19 (76)% |
| >3-Line loss, No. (%) | 1 (5)‡ | 4 (24)% | 4 (21) | 3 (27)% | 3 (12)% |
| Mean (SD) change, lines | −0.2 (1.4) | −0.9 (3.3) | −1.6 (3.1) | +0.4 (4.5) | +0.1 (3.2) |
| Range, lines | −3 to +2 | −9 to +5 | −9 to +2 | −8 to +7 | −8 to +9 |

* One patient withdrew before week 1.
† Nine patients received multiple photodynamic therapy treatments after week 1, before week 4.
§ Eleven patients received multiple treatments after week 4, before week 12.
‡ One patient withdrew after week 4 assessment; 2 patients received multiple treatments after week 4, before week 12.
|| Nine patients received multiple treatments after week 4 but before week 12; two additional patients missed the week-12 follow-up visit.
¶ Two patients withdrew after week 4.
graded as having progression of occult CNV at follow-up because occult CNV was identified within an area previously occupied by classic CNV.

A number of exploratory analyses were performed to evaluate the effects of baseline lesion size, lesion components, and visual acuity on visual and angiographic outcomes. Excluding the patients in regimens 2 and 3 who were treated with the 150-J/cm² light dose, smaller lesions (≤4 MPS DAs) (n = 38) had a mean change in visual acuity of +0.1 line at 12 weeks, whereas lesions larger than 4 MPS DAs (n = 45) had a mean change in visual acuity of −0.6 line. Thirty-six patients with an initial visual acuity of 20/80 or better showed a mean change of −0.9 line compared with patients whose initial visual acuity was 20/200 or worse (n = 21), who showed a mean change of +1.0 line of vision. The difference between the 2 groups was significant (P = .02) despite having similar mean baseline lesion sizes (4.8 and 4.9 MPS DAs, respectively).

The CNV components at baseline also correlated with the visual acuity outcome. At the 12-week assessment, patients with CNV, in whom 100% of the CNV was classic at baseline, gained 0.6 line of vision. In comparison, patients with some occult CNV at baseline lost 0.8 line of vision (P = .045). However, the mean baseline visual acuity was slightly worse for patients with CNV in whom 100% of the CNV was classic than for patients with some occult component (20/164 vs 20/100, respectively). In addition, the mean baseline lesion size was slightly smaller for patients with 100% classic CNV (4.1 MPS DAs) than for patients with some occult CNV (5.1 MPS DAs). These differences may have affected the visual outcome in these patients.

The extent of posttreatment fluorescein leakage from CNV relative to baseline also appeared to be correlated with visual acuity outcome. The 33 patients with lesions that showed a reduced area of leakage from both classic and occult CNV at 12 weeks, compared with baseline, had a mean change in visual acuity of +0.8 line. In comparison, the 49 patients with lesions that developed progression of either classic or occult CNV by 12 weeks lost 0.8 line of vision. This difference was statistically significant (P = .01).

SAFETY

Thirty-eight (29.7%) of the 128 patients receiving a single course of PDT had an adverse event in the treatment eye, as reported by the treating ophthalmologists. Thirty-one of these patients had events that were judged to be possibly, or probably, treatment related. Independent of the relationship to therapy, the highest incidences of adverse events in the treated eyes were as follows: increased subretinal hemorrhage (8.6%), increased fibrosis associated with CNV (8.6%), increased RPE atrophy (3.9%), subretinal hemorrhage (3.1%), eye pain (3.1%), fibrosis (3.1%), branch retinal arteriolar or venular nonperfusion (2.3%), choroidal vessel staining (1.6%), increased hemorrhage (1.6%), and vitreous hemorrhage (1.6%).

Severe vision loss and associated dose-limiting ocular adverse events were examined separately. Treatment with PDT at 50, 75, and 100 J/cm² was found to be safe in all regimens. However, at the highest light dose (150 J/cm²) in regimens 2 and 3, PDT resulted in closure of neurosensory retinal vessels (Figure 4); therefore, enrollment at this light dose was discontinued promptly. Two of the 3 patients who were treated with

Figure 1. Grading of fluorescein leakage from classic choroidal neovascularization at week 1 (A), week 4 (B), and week 12 (C) in treatment regimens 1 to 5 in patients with age-related macular degeneration after a first course of photodynamic therapy.
Figure 2. Baseline and follow-up of single treatment of photodynamic therapy (PDT) with verteporfin with the use of regimen 3 (light dose at 100 J/cm²). Color fundus photograph from initial visit (visual acuity, 20/50) (A) shows fibrovascular tissue with subretinal hemorrhage. Early-phase fluorescein angiogram (B) shows a bright area of hyperfluorescence corresponding to classic choroidal neovascularization (CNV) (straight arrows), with additional hyperfluorescence (curved arrows) corresponding to occult CNV. Both areas demonstrate leakage on late-phase frame (C). One week after PDT (visual acuity, 20/64), color fundus photograph shows darker appearance of fibrovascular tissue (D). Corresponding fluorescein angiogram, early-phase frame (E), shows a hypofluorescent area (straight arrows) corresponding to an area of fibrovascular tissue with an additional area (curved arrows) of relatively less hypofluorescence. Late-phase frame (F) shows persistence of the central hypofluorescent area (straight arrows); the relatively less hypofluorescent area seen in early phase is no longer apparent. Some additional hyperfluorescent area of staining (curved arrows) surrounds hypofluorescence. Four weeks after PDT (visual acuity, 20/50), color fundus photograph (G) shows a central fibrous component surrounded by a reddish hue, possibly corresponding to additional hemorrhage. Corresponding fluorescein angiogram shows some hypofluorescence within the area of previous leakage (H), with absence of leakage from classic CNV and minimal leakage from occult CNV within the area previously occupied by classic and occult CNV seen in the late-phase frame (I). Twelve weeks after PDT (visual acuity, 20/50), color fundus photograph (J) shows complete clearing of subretinal hemorrhage. Corresponding fluorescein angiogram shows minimal leakage from classic CNV (straight arrows) and moderate leakage from occult CNV (curved arrows) in early-phase (K) and late-phase (L) frames, within the area occupied by classic and occult CNV at baseline (B and C).
the 150-J/cm² light dose in regimen 2 had significant loss of vision by 12 weeks, losing 5 and 9 lines of vision, respectively. In regimen 3, two of the 5 patients treated at 150 J/cm² had sensory retinal vessel closure. One of these patients had occlusion of both branch retinal arteries and veins in the posterior pole, which was associated with a loss of 12 lines of vision at week 1 (20/50 to 20/800); visual acuity at week 12 was 20/400 (9 lines lost). The second patient had extensive capillary non-perfusion (≥30% of the treated area), with minimal vision loss of 1 line by 12 weeks. In addition, 1 patient in the 75-J/cm² group in regimen 3, and 1 patient in the 100-J/cm² group in regimen 2, experienced a vitreous hemorrhage. Both patients lost 7 lines of vision by week 12. No ocular adverse events were noted in regimens 4 and 5 for all light doses tested. The remaining events of severe vision loss were without association to any other ocular adverse event.

Adverse events for all body systems combined were reported by 42.2% of the 128 patients. The most common adverse events, independent of the relationship to therapy, and other than those noted above, were...
headache in 6 patients (4.7%), asthenia in 4 patients (3.1%), and bronchitis in 4 patients (3.1%). No other adverse events occurred in more than 3 patients (2.3%). Specifically, photosensitivity reactions were not reported by any patients. Adverse events occurring at a site other than the eye, which were considered by the treating ophthalmologist to be possibly, or probably, treatment related, were headache in 2 patients (1.6%), with no other event being reported by more than 1 patient.

This phase 1 and 2 study demonstrated that PDT with verteporfin can lead to cessation of fluorescein leakage from CNV associated with preservation or improvement of vision. After the results from the first few patients were obtained, which showed that cessation of fluorescein leakage from CNV could be achieved without adversely affecting vision, light dose escalation was performed because absence of leakage did not persist at the week 4 assessment. However, even at the highest light dose used (150 J/cm²) in regimen 1, absence of leakage did not persist, although no ocular adverse events were noted.

Rather than increase the light dose further in this first regimen, which would have led to an even longer irradiation time than the 4.2 minutes required to deliver 150 J/cm², it was decided to increase the effective serum concentration of verteporfin. This was accomplished in 2 ways: (1) by shortening the time between infusion and irradiation (regimen 2) and (2) by increasing the verteporfin dose from 6 to 12 mg/m² (regimen 3).

However, at a light dose of 150 J/cm², applied either 20 minutes after a verteporfin infusion of 6 mg/m² (regimen 2) or 30 minutes after an infusion of 12 mg/m² (regimen 3), neurosensory retinal vessel nonperfusion was observed on fluorescein angiography associated with severe visual loss in some cases. While all the lesions treated involved the fovea, some cases with retinal vessel nonperfusion did not lose vision, since the nonselective closure was patchy in its distribution within the treatment area. However, this nonselective effect was clearly undesirable and carried the potential for treatment-associated vision loss. Accordingly, a light dose of 150 J/cm² was considered to be above the maximum tolerated dose when verteporfin, 6 or 12 mg/m², is used with irradiation 20 or 30 minutes after the beginning of a 10-minute verteporfin infusion. Moreover, persistent cessation of fluorescein leakage from CNV was not achieved even at these high light doses when nonselective events occurred. Two of the 4 patients with retinal vessel nonperfusion demonstrated progression (CNV leakage beyond the original borders of the CNV) by week 12.

Retinal vessel nonperfusion in regimen 2 was an unexpected finding at these treatment specifications, since retinal vessel damage at this dose of verteporfin had been rare in preclinical studies with monkeys. The monkey studies, which used a 10- or 30-minute intravenous infusion, were limited to a verteporfin dose of 0.375 mg/kg (approximating 6 mg/m²) and did not produce retinal vessel closure. However, retinal vessel closure was demonstrated in the same monkey model when irradiation was applied early (within 10 minutes) after a bolus verteporfin infusion (30 seconds) at this dose, or at higher verteporfin doses, such as 1 mg/kg (approximately 15 mg/m²). This dose of verteporfin is only 25% higher than

![Figure 3. Grading of fluorescein leakage from occult choroidal neovascularization at week 1 (A), week 4 (B), and week 12 (C) in treatment regimens 1 through 5 in patients with age-related macular degeneration after a first course of photodynamic therapy.](https://archopht.jamanetwork.com/external/figurescopy/117/1/1170F03.jpg?Expires=1571995705&OSSAccessKeyId=q60Q5QXf1lSiN29nMrj5VgE&Signature=ZS3eWnC%2Fv980zUf%2FJiM4Dp%2F6IDv%3D)
that used in regimen 3, although the pharmacokinetics of verteporfin after bolus injection and a 10-minute infusion may differ.

Vitreous hemorrhage occurred in 2 patients after PDT. In both cases, a marked increase in subretinal hemorrhage was noted before breakthrough hemorrhage into the vitreous. This may have represented natural disease progression or may be the result of a relatively large choroidal hemorrhage (secondary to nonselective choroidal vascular closure) with subsequent breakthrough into vitreous. Alternatively, vitreous hemorrhage may just have occurred more often in this study than anticipated in an untreated population of patients with CNV. Additional ocular adverse events, including increased fibrosis and increased subretinal hemorrhage, could be attributable to the natural progression of AMD and unrelated to PDT. Cases of severe vision loss not associated with any other ocular adverse event, such as nonperfusion of retinal vessels, were considered to be part of the natural course of AMD. The causality of adverse events, both ocular and systemic, will be better assessed in the phase 3 trials, in which a placebo group is included.

Although this study was not designed prospectively to compare the different treatment regimens in terms of efficacy, some exploratory analyses were performed. They suggested that regimen 4, which used a verteporfin dose of 6 mg/m² infused over 10 minutes, with irradiation performed 15 minutes after the start of verteporfin infusion, showed the most favorable mean change in visual acuity at 4 weeks (+1.1 lines). No given light dose had specific advantages in terms of absence of fluorescein leakage from CNV. However, the 50-J/cm² light dose in regimen 4 was associated with the highest percentage of patients with absence of leakage at 4 weeks (57%) and the lowest percentage of patients with progression of classic CNV at 12 weeks. When lower light doses (12.5 and 25 J/cm²) were used in regimen 5, the angiographic outcomes were the least favorable and may represent a minimally effective dose.

The different outcomes among the various regimens with respect to change in visual acuity may represent the varied natural course of this disease. However, the correlation between the extent of CNV leakage at follow-up and the change in visual acuity, determined independently of each other, suggests that a better visual

Figure 4. Baseline and follow-up at week 1 of a single treatment of photodynamic therapy with verteporfin with the use of regimen 3 (light dose at 150 J/cm²) demonstrating loss of selectivity of photodynamic therapy. Color fundus photograph (A) before treatment (visual acuity, 20/50) shows fibrovascular tissue (arrows) that was beneath subretinal fluid. Corresponding late-phase fluorescein angiogram (B) shows fluorescein leakage from classic (straight arrows) and occult (curved arrows) choroidal neovascularization. One week after treatment (visual acuity, 20/800), an early-phase fluorescein angiogram (C) shows neurosensory retinal vessel nonperfusion of both retinal arterioles and venules with persistent nonperfusion in late-phase frames (D). Visual acuity was 20/400 at week 12.
outcome for regimen 4 may be related to an effect of the PDT on the CNV. These factors led to the selection of the 50-J/cm² dose and regimen 4 for some retreatment regimens and phase 3 trials.3,4

Exploratory analyses of the data also suggest that patients with smaller lesions (≤4 MPS DAs) and worse baseline visual acuity (≤20/200) had better visual acuity outcomes. In addition, patients who demonstrated a decreased area of CNV leakage on fluorescein angiography at 12 weeks compared with baseline had a better visual outcome than patients in whom leakage from CNV extended beyond its original borders. This finding suggests that patients who demonstrate stabilization of fluorescein leakage from CNV after PDT may have a beneficial visual outcome if this stabilization can be maintained. Of course, these exploratory analyses should be interpreted with caution, since this study was not designed prospectively to assess these effects.

Week 12 assessment data for regimen 4 may be biased favorably to include the best responders to PDT, since this regimen allowed retreatment of some patients who showed fluorescein leakage from CNV at their week 4 or week 8 visit. Therefore, only patients who did not show fluorescein leakage at these interim visits, and who may be better responders, are included in the week 12 analysis for single treatments. However, comparisons of the visual acuity and angiographic results of the different regimens at week 4 still indicate that regimen 4 has the most favorable mean visual acuity outcome.

In summary, PDT with verteporfin can lead to cessation of fluorescein leakage from CNV for 1 to 4 weeks, with stabilization or improvement of vision for 12 weeks. The data in the present study also suggest that the maximum tolerated light dose is less than 150 J/cm², and that a minimally effective dose is greater than 25 J/cm². Fluorescein leakage, in at least a portion of the CNV, returns in most cases by 4 weeks, with progression in some cases by 12 weeks. The exploratory analyses demonstrating an association between preserved vision and a lesser extent of CNV leakage at 12 weeks suggest that confining the growth of CNV with PDT might result in preservation of vision with PDT compared with no treatment. If multiple courses of PDT are required, studies would have to demonstrate that retreatment of CNV could be accomplished safely. The study presented in the accompanying article by Schmidt-Erfurth et al32 demonstrates that this is true at least in the short term. Randomized, placebo-controlled, clinical trials with longer follow-up, currently in progress by this group, will answer the question of whether PDT with verteporfin can be effective at confining CNV growth and leakage and preserve vision in patients with neovascular AMD.

Accepted for publication April 27, 1999.

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This study was supported by QLT PhotoTherapeutics Inc and CIBA Vision AG.

Presented in part at the annual meetings of the Association for Research in Vision and Ophthalmology, Fort Lauderdale, Fla, April 22, 1996, and May 11, 1997, as well as at the joint meeting of the Retina Society and Club Jules Gonin, Berne, Switzerland, September 4, 1996.

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REFERENCES


Omission in Financial Disclosures. In the Clinical Sciences articles by Miller et al titled “Photodynamic Therapy With Verteporfin for Choroidal Neovascularization Caused by Age-related Macular Degeneration: Results of a Single Treatment in a Phase 1 and 2 Study,” published in the September issue of the ARCHIVES (1999;117:1161-1173); by Schmidt-Erfurth et al titled “Photodynamic Therapy With Verteporfin for Choroidal Neovascularization Caused by Age-related Macular Degeneration: Results of Retreatments in a Phase 1 and 2 Study,” published in the September issue of the ARCHIVES (1999;117:1177-1187); and by the Treatment of Age-related Macular Degeneration With Photodynamic Therapy (TAP) Study Group titled “Photodynamic Therapy of Subfoveal Choroidal Neovascularization in Age-related Macular Degeneration With Verteporfin: One-Year Results of 2 Randomized Clinical Trials—TAP Report 1,” published in the October issue of the ARCHIVES (1999;117:1329-1345), journal omissions of financial disclosure, properly reported at the time of manuscript submission, occurred in the acknowledgment sections on pages 1172, 1187, and 1344, respectively. The following statement should have appeared in all 3 articles: “Drs Sickenberg and Bressler are consultants for CIBA Vision Inc, Duluth, Ga, and QLT Phototherapeutics Inc, Vancouver, British, Columbia.” The journal regrets the errors.