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

Results of Retreatments in a Phase 1 and 2 Study

Ursula Schmidt-Erfurth, MD; Joan W. Miller, MD; Michel Sickenberg, MD; Horst Laqua, MD; Irene Barbazetto, MD; Evangelos S. Gragoudas, MD; Leonidas Zografos, MD; Bertrand Piguet, MD; Constantin J. Pournaras, MD; Guy Donati, MD; Anne-Marie Lane, MPH; Reginald Birngruber, PhD; Hubert van den Berg, PhD; H. Andrew Strong, PhD; Ulrike Manjuris, PhD; Todd Gray, MSPH; Mario Fsadni, MRCOphth; Neil M. Bressler, MD

Objectives: To evaluate safety and short-term visual acuity and fluorescein angiographic effects of photodynamic therapy (PDT) after retreatments with verteporfin for choroidal neovascularization (CNV) in age-related macular degeneration (AMD) that demonstrated fluorescein leakage after at least 1 course of PDT.

Design: Nonrandomized, multicenter, open-label phase 1 and 2 clinical trial using 2 different retreatment dosage regimens.

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

Methods: Standardized protocol refraction, visual acuity testing, ophthalmic examinations, color photographs, and fluorescein angiograms were used to evaluate the results of multiple PDT treatments. Two regimens (regimens 2 and 4) for treatment and retreatment were chosen from 5 used in a single-treatment study. Both regimens used a verteporfin dose of 6 mg/m^2 infused for 10 minutes. However, regimen 2 used a light dose of 100 J/cm^2 applied 20 minutes after the start of the verteporfin infusion, whereas regimen 4 used a light dose of 50, 75, or 100 J/cm^2 applied 15 minutes after infusion commenced. Posttreatment evaluations were planned in 31 participants up to 3 months after up to 2 retreatments given at 2- or 4-week intervals after initial PDT treatment. Similar posttreatment evaluations were planned after retreatments in 5 additional participants who were reenrolled some time more than 12 weeks after an initial PDT treatment.

Results: The average visual acuity change for the 31 participants who had retreatment within 2 to 4 weeks after the initial treatment and a follow-up examination 16 to 20 weeks after the initial treatment was 0.2 lines (range, −4 to 4 lines) in regimen 2 and −1.0 line (range, − 5 to 3 lines) in regimen 4. Similar outcomes were noted in the 5 reenrolled participants. Cessation of fluorescein leakage from classic CNV for at least 1 to 4 weeks could be achieved without loss of visual acuity after at least 2 treatments in 2 (6.5%) of 31 patients. Similar to single-treatment effects, the disappearance of leakage was documented regularly at 1 week after each retreatment. Fluorescein leakage reappeared by 4 to 12 weeks after a retreatment in almost all cases. However, compared with baseline, leakage activity appeared to be reduced after multiple PDT courses. For the 31 patients who had follow-up for 3 months after the last retreatment and had received retreatment 2 to 4 weeks after the initial treatment, progression of CNV beyond the area identified before the retreatment was noted in 10 (48%) of the 21 eyes with classic CNV in regimen 2 and 9 (90%) of 10 eyes in regimen 4. The rate and severity of ocular or systemic adverse events were not increased by multiple applications.

Conclusions: Multiple applications of PDT with verteporfin achieve repetitive, short-term cessation of fluorescein leakage from CNV secondary to AMD, without loss of visual acuity. This strategy can be used in randomized clinical trials investigating the efficacy of verteporfin in PDT for recurrent fluorescein dye leakage from persistent or recurrent CNV, following an initial or subsequent PDT treatment, with maintenance of visual acuity. Retreatments may achieve progressive cessation of leakage and prevent further growth of CNV and subsequent visual loss.

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The affiliations of the authors appear in the acknowledgment section at the end of the article.

CHOROIDAL neovascularization (CNV) due to age-related macular degeneration (AMD) is a major cause of severe, irreversible central vision loss in people older than 65 years in the western world.[1-3] The only proven therapy for CNV at this time is laser photocoagulation.[4-7] With its nonselective thermal tissue destruction, laser photocoagulation can eradicate surrounding choriocapillaries, retinal pigment epithelium (RPE), and adjacent photoreceptors, leading to an absolute scotoma at the

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SUBJECTS AND METHODS

This study was a nonrandomized, multicenter, open-label clinical trial using 2 retreatment regimens and different retreatment intervals. All protocols and amendments for this study adhered to the guidelines established by the regulatory groups responsible for the respective clinical centers (including the following: the Drug Law, the European Good Clinical Practice Guidelines, the United States Food and Drug Administration, the Swiss Interkantonale Kontrollstelle für Heilmittel, and the German Ethics Committee), and approved by the local institutional review boards of each treating center. All participants signed a written informed consent form following an oral informed consent discussion with a study investigator, detailing the potential benefits and risks of initial and repeated treatments.

INCLUSION-EXCLUSION CRITERIA

Two sets of patients were identified for a retreatment protocol. One set of patients underwent retreatment 2 to 4 weeks after the initial PDT treatment. A second set of patients had participated in a single-treatment regimen and were reenrolled in a retreatment protocol sometime beyond 12 weeks but less than 6 months, after their initial treatment, if they met the criteria for retreatment at that time. Major inclusion criteria for participants in each group before their first treatment with verteporfin included best corrected visual acuity of 20/40 or worse, evidence of subfoveal CNV secondary to AMD with some classic CNV, lesion size less than or equal to 9 Macular Photocoagulation Study (MPS) disc areas, and greatest linear dimension less than or equal to 5400 µm. The main inclusion and exclusion criteria are listed in **Table 1**. Criteria for retreatment or reenrollment included the following: (1) evidence of fluorescein leakage from classic or occult CNV, (2) greatest linear dimension of leakage from CNV of less than 6400 µm (diameter of 12 MPS disc area circles), (3) no adverse event judged to be due to previous PDT, and (4) no other additional ocular abnormality associated with visual loss identified since the first PDT. Criteria for reenrollment also required fluorescein leakage from classic CNV.

RETREATMENT PROTOCOL

The first set of patients were given retreatment 2 to 4 weeks after their first PDT treatment. Following the first retreatment, follow-up fluorescein angiography was obtained and evaluated for CNV leakage 1 and 4 weeks after retreatment. If leakage had reappeared, an additional course of retreatment was applied at 2- or 4-week intervals, and a final evaluation was performed 12 weeks after the last retreatment. For the second set of patients, who were reenrolled, up to 3 additional courses of retreatment were to be instituted if indicated. In this group of patients, the second and third retreatments were scheduled at 4-week intervals, and final evaluation was performed 12 weeks after the last retreatment.

PHOTODYNAMIC THERAPY

Two of 5 dosage regimens that were used in a single-treatment study,[16] termed regimens 2 and 4 (**Table 2**), were used in this retreatment study. Regimen 4 showed the best mean visual acuity change in a single-treatment study.[16] Liposomal benzoporphyrin derivative was reconstituted to a final volume of 30 mL. A verteporfin dose of 6 mg/m^2 was used for retreatments in all participants. The infusion was always given over a 10-minute period. The light dose was 100 J/cm^2 for regimen 2, and 50, 75, or 100 J/cm^2 for regimen 4. The size of the spot to irradiate the retina was determined in a manner similar to that of the single-treatment regimen.[16] In brief, the greatest linear dimension of the CNV lesion on a 35-mm fluorescein angiogram negative was determined with a transparency that was overlaid on the film. Assuming a magnification of 2.5 for the cameras used to obtain the angiograms, the greatest linear dimension of the lesion on the retina was calculated by dividing the length on the angiogram by 2.5. An additional distance of at least 300 µm, but no more than 500 µm, was added to this dimension to increase the chance that the lesion was covered entirely by the spot size. While projecting the fluorescein angiogram, after visualizing the lesion with a contact lens and a slitlamp system coupled to a diode laser (Coherent, Palo Alto, Calif), the aiming beam (the size of which corresponded to that of the 689-nm beam to be used for photosensitizing) was placed over the lesion, and irradiation began 15 or 20 minutes after the start of the intravenous infusion of verteporfin (ie, 5 or 10 minutes after the end of the 10-minute infusion). Patients were then instructed to wear protective sunglasses and to avoid bright sunlight for 1 week.

EVALUATIONS

Snellen-equivalent visual acuity was determined on retroilluminated Bailey-Lovie charts following a standardized refraction and visual acuity protocol modified from the Submacular Surgery Trials.[17] Color fundus photographs and fluorescein angiograms were obtained and evaluated following a standardized protocol adapted from the MPS Group. In brief, the CNV lesion was evaluated after enrollment by graders who participated in the MPS investiga-

area of treatment.[6,7] Consequently, laser treatment has been beneficial in a selected few cases that do not involve the foveal center [4,5] or that are relatively small when subfoveal.[6-8]

Photodynamic therapy (PDT), a modality used safely in tumor therapy, was evaluated for vascular photothrombosis experimentally using benzoporphyrin derivative, or verteporfin, in rabbit models, and results had shown that subretinal vessels could be occluded without altering the adjacent retina.[9,10] Subsequently, use in experimental CNV in primate studies was shown to be effective.[11,12] Benzoporphyrin derivative photosensitizer was complexed with low-density lipoproteins or formulated as a liposomal preparation.[9-14] A number of investigations showed that photodynamic occlusion of the choriocapillaris underlying normal retina did not alter intact photoreceptors significantly[10-12] and that PDT with verteporfin was able to effectively occlude experimental CNV with only minimal damage to surrounding RPE and photoreceptors.[11-13] In addition, repeated PDT treat-

tions, using definitions of angiographic interpretation standardized by the MPS Group,[18] and who were masked to the regimen used or to any other clinical data such as visual acuity or biomicroscopic findings not seen on color fundus photographs. Angiograms obtained at follow-up were evaluated for leakage from classic or occult CNV as well as any adverse events. Leakage following treatment was graded separately for classic and occult CNV. For each pattern of CNV, leakage was compared with that at the baseline visit at the time of enrollment into the retreatment study. The extent of fluorescein 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) *minmal 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 fluorescein features such as the amount of fluorescence or the area of leakage extending beyond classic CNV or a fibrovascular pigment epithelial detachment. The Photograph Reading Center reviewed angiographic eligibility retrospectively after enrollment and retreatments.

Statistical analysis was performed using a 2-way analysis of covariance (ANCOVA) with baseline lesion size as covariate using SAS statistical software (SAS Institute Inc, Cary, NC).

SAFETY PARAMETERS

Safety evaluation was based on visual acuity measurements, with a change of at least 3 lines considered to be clinically significant, and the semiquantitative evaluation of fluorescein leakage described above. In addition, significant visual acuity loss of 6 lines or more or occlusion of retinal vascular arterioles or venules would have stopped any additional retreatments. Lack of these events was required in at least 3 patients (and sometimes 6, depending on local institutional review board safety concern with the first 3 patients in a group) before progressing to another regimen. The photographic reading center also graded the extent of subretinal hemorrhage, RPE atrophy, and arteriolar, venular, and/or capillary retinal nonperfusion.

Adverse events were captured by case record forms and reading center forms (ie, forms used to document ocular adverse events identified on stereophotography or angiography). Systemic events or events noted by the investigator were reported immediately by personal communication and noted on case record forms.

Table 1. Main Inclusion and Exclusion Criteria*

Inclusion criteria
Clinical signs of CNV due to 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 diameter
Nasal side of CNV ≥500 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 y of age
Exclusion criteria
Tears of the RPE at screening
Vitelliformlike detachment retinal pigment epithelium
Central serous retinopathy
Drusenoid pigment epithelium detachment alone
Additional retinovascular diseases compromising visual acuity of study eye
Use of investigational drugs, systemic steroids, cytokines, or photosensitive drugs in past 3 mo
Significant hepatic, renal, or neurologic disease
Class III or IV cardiovascular disease (New York Heart Association functional status criteria)
Porphyria, porphyrin sensitivity, or hypersensitivity to sunlight or bright artificial light
Any treatment for malignant neoplasms
Any acute illness during screening or fever on day of treatment before verteporfin infusion
Uncontrolled hypertension
Ocular surgery within 3 mo before study treatment

**CNV indicates choroidal neovascularization; RPE, retinal pigment epithelium.*

Table 2. Treatment Regimens 2 and 4 and Duration of Follow-up

Treatment Regimen No.	Verteporfin Dose, mg/m²	Planned Duration of Infusion, min	Light Dose, J/cm²	Time of Light Application After Start of Verteporfin Infusion, min	No. of Patients
2*	6	10	100	20	21
4	6	10	50, 75, or 100	15	10

**Five additional participants were enrolled to receive a retreatment sometime beyond 12 weeks after the first treatment. Of these 5 patients, 4 received 2 photodynamic therapy (PDT) treatments. One of these 4 patients did not return beyond 1 week after the first retreatment; 1 patient died of chronic heart disease 4 weeks after the first treatment. The fifth participant had a second retreatment 12 weeks after the first retreatment, and a third retreatment 4 weeks after the second retreatment, with follow-up through 12 weeks after this third retreatment.*

ments in normal monkey eyes demonstrated dye dose–dependent recovery of the RPE and choriocapillaries with minimal damage to photoreceptors.[15] Based on these experimental results, a phase 1 and 2 trial was initiated to evaluate safety and short-term visual and fluorescein angiographic effects of PDT in patients with subfoveal CNV.[14] In a single-treatment protocol, each participant received a single PDT course with the light dose escalated and the timing of the light exposure modified to try to identify a maximum tolerated dose and a minimum effective dose. Using 6 or 12 mg/m² of verteporfin administered intravenously, followed by illumination of the lesion with nonthermal light at 689 nm, cessation of fluorescein leakage could be achieved without loss of visual acuity when the light dose used was less than 150 J/cm².[16] However, persistent absence of leakage was not achieved at some point between weeks 4 and 12, even at the highest light dose.[16] When the effective serum concentration at the time of light irradiation was increased by shortening the time between infusion and irradiation

Table 3. Summary of Baseline Characteristics*

Characteristic	Regimen 2 (n = 21)	Regimen 4 (n = 10)
Sex		
Female	13 (62)	7 (70)
Male	8 (38)	3 (30)
White race	21 (100)	10 (100)
Age, y		
<60	0 (0)	1 (10)
60-70	9 (43)	3 (30)
>70-80	8 (38)	5 (50)
>80	4 (19)	1 (10)
Median	73.7	72.8
Median BP, mm Hg		
Systolic	140.0	140.7
Diastolic	80.0	78.7
Proportion of lesions with classic CNV		
Classic CNV only, no occult CNV	10 (48)	3 (30)
Lesion ≥50% classic CNV plus occult CNV	2 (10)	3 (30)
Lesion <50% classic CNV plus occult CNV	6 (28)	4 (40)
No classic CNV, occult CNV only	3 (14)	0 (0)
CNV lesion location		
Subfoveal	21 (100)	9 (90)
Probably subfoveal	0 (0)	1 (10)
CNV secondary to AMD	21 (100)	10 (100)
Lesion size, MPS DA		
Mean (SD)	5.8 (3.7)	4.3 (2.7)
Median	5.0	3.5
Minimum	1.0	2.0
Maximum	16.0	9.0
Visual acuity, study eye		
20/40-20/80	9 (43)	5 (50)
20/100-20/200	8 (38)	5 (50)
<20/200	4 (19)	0 (0)
Mean	20/125	20/80
Fibrosis, % of lesions†		
0-25	18 (86)	9 (90)
26-50	2 (10)	0 (0)
>50	1 (5)	1 (10)

*Data are given as number (percentage) of patients, unless otherwise indicated, and do not include the 5 reenrolled patients. MPS DA indicates Macular Photocoagulation Study Group disc area; AMD, age-related macular degeneration; CNV, choroidal neovascularization; and BP, blood pressure.

†Because of rounding, percentages may not total 100.

as well as by increasing the dye dose or the infusion rate, the recurrence of CNV leakage was not reduced. In contrast, this strategy led to loss of selective damage to CNV, with occlusion of neurosensory retinal vessels accompanied by visual loss at a light dose of 150 J/cm^2.[16]

Therefore, an amendment to the single-treatment protocol was instituted on November 6, 1995, to determine if various retreatment protocols (ie, repeated PDT with verteporfin at different times of light administration relative to the beginning of intravenous infusion of verteporfin, at different light doses, and at different intervals after initial PDT treatment) were safe (ie, not causing significant systemic adverse events, visual acuity loss, or retinal adverse events) and efficacious (ie, stopping fluorescein leakage again after it had recurred following a previous treatment with verteporfin). Our study reports on the safety and short-term effects of repeated PDT courses with verteporfin on visual acuity and fluorescein angiographic outcomes.

Table 4. Visual Acuity Change From Baseline for Patients Receiving Multiple PDT Treatments With Regimen 2*

PDT Treatment	No. of Patients	Visual Acuity Change by Time After Most Recent PDT Treatment, Mean (Range)	
		Week 1	Week 4
First	16	−0.25 (−5 to +4)	−0.3† (−2 to +3)
Second	16	+1.3 (−2 to +5)	+0.7‡ (−3 to +5)
Third	12§	+1.2 (−2 to +5)	+0.3 (−3 to +5)
Last follow-up‖	16	+0.1 (−4 to +4)	

*PDT indicates photodynamic therapy.

†Four participants were retreated before week 4 and are not included in the week 4 mean or range for the first treatment. Also, the 5 reenrolled patients are not included.

‡No visual acuity data are available at this visit for 1 participant.

§Four participants did not receive a third treatment.

‖Last follow-up was week 16 after baseline for participants who had 2 treatments and week 20 for participants who had 3 treatments.

Table 5. Visual Acuity Change From Baseline for Patients Receiving Multiple PDT Treatments With Regimen 4*

PDT Treatment†	No. of Patients	Visual Acuity Change by Time After Most Recent PDT Treatment, Mean (Range)	
		Week 1	Week 4
First	10	+1.2 (−3 to +5)	+1.1 (−2 to +3)
Second	10	+0.8 (−3 to +3)	0 (−5 to +5)
Last follow-up‡	9§	−1.0 (−5 to +3)	

*PDT indicates photodynamic therapy.

†Two patients had a third PDT treatment with no change from baseline in visual acuity for both patients 1 week later; 4 weeks after the third treatment, visual acuity change from baseline was +1.0 and 0 for the 2 patients.

‡Last follow-up was week 16 after baseline for participants who had 2 treatments and week 20 for participants who had 3.

§One patient had no final follow-up assessment because of hip replacement surgery, which was unrelated to treatment.

RESULTS

Thirty-six patients with subfoveal CNV secondary to AMD were treated with multiple courses of PDT using verteporfin. Up to 4 treatments in total were performed, with 2 PDT regimens and 2 different retreatment intervals (2 and 4 weeks). In 1 subgroup of patients, retreatments were started after completion of a single-treatment protocol.

BASELINE FEATURES AND ADHERENCE TO PROTOCOL

The baseline visual acuity and lesion size for the patients receiving multiple courses of PDT with verteporfin are listed by regimen in **Table 3**. The average initial visual acuity was lower for regimen 2. These participants also were more likely to have smaller lesions or lesions that had classic CNV only (no occult CNV) at baseline.

Three participants in regimen 2 and no participant in regimen 4 had occult, but not classic, CNV at baseline. Two participants in regimen 2 had light administered at 30 minutes, instead of 20 minutes, after the start of verteporfin infusion for the first treatment (but not for

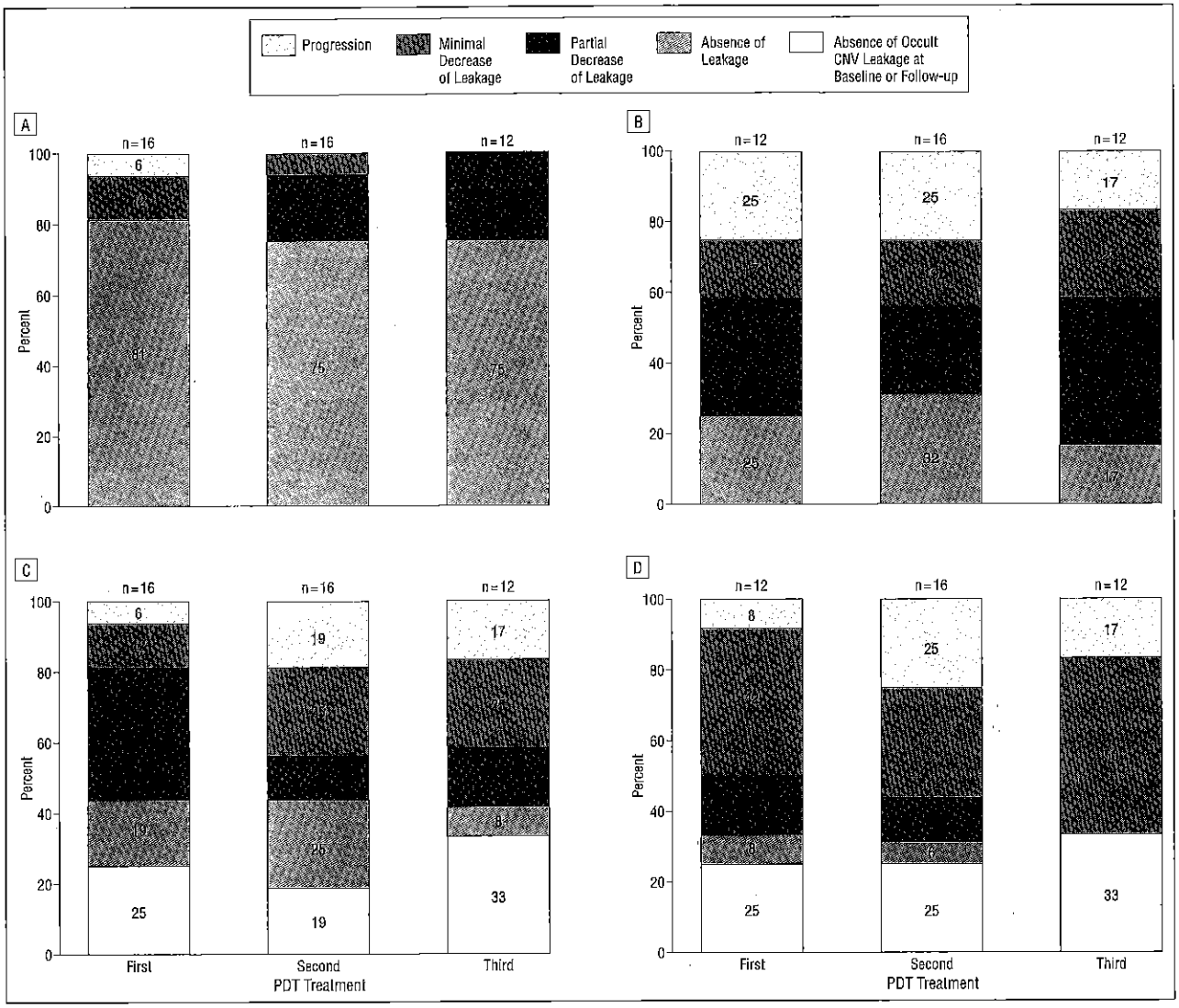


Figure 1. *Grading of fluorescein leakage in patients with age-related macular degeneration receiving multiple photodynamic therapy (PDT) treatments with regimen 2. Classic choroidal neovascularization (CNV) at week 1 (A) and week 4 (B); occult CNV at week 1 (C) and week 4 (D). Four participants underwent retreatment before week 4 and are not included in the week-4 first treatment.*

any retreatment) because of technical difficulties with the laser system. One patient in regimen 4 had no follow-up at 8 weeks after initial therapy (ie, 4 weeks after a retreatment) because of a hip fracture, which was judged to be unrelated to treatment. Another patient in the same regimen had light administered at 20 minutes, instead of 15 minutes, after the start of the infusion for the first treatment (but not any retreatments).

For the 5 participants who were re-enrolled to receive a retreatment sometime beyond 12 weeks after the first treatment, 4 patients received 2 retreatments of PDT. One of these 4 patients did not return beyond 1 week after the first reretreatment, and another died 4 weeks after the first treatment. That death was judged to be due to chronic heart disease, which was confirmed by results of postmortem examination. A fifth participant underwent retreatment 12 weeks after the first treatment, and a second retreatment 4 weeks later, with follow-up through 12 weeks after the second retreatment.

Since the present trial was designed as a safety and not as an efficacy trial, the patients were not randomized to different retreatment regimens. As a result of the small numbers of patients in the subgroups, the influence of different baseline characteristics could not be evaluated statistically.

CHANGES IN VISUAL ACUITY AFTER TREATMENT

Table 4 shows the changes in visual acuity for the patients undergoing retreatment with regimen 2 and light dose of 100 J/cm^2. Four of these patients did not have fluorescein leakage 4 weeks after the second PDT treatment to warrant additional retreatment. The mean visual acuity remained stable after the first treatment, with a mean change of –0.25 lines. Even after a second or third PDT application, visual acuity was not reduced. On the contrary, after repeated treatments at short intervals of 2 and 4 weeks, visual acuity showed an average increase of 1.8 and 1.2 lines, respectively. Twelve weeks after the last retreatment for the 16 participants in regimen 2 (ie, 20 weeks after the initial treatment for participants re-

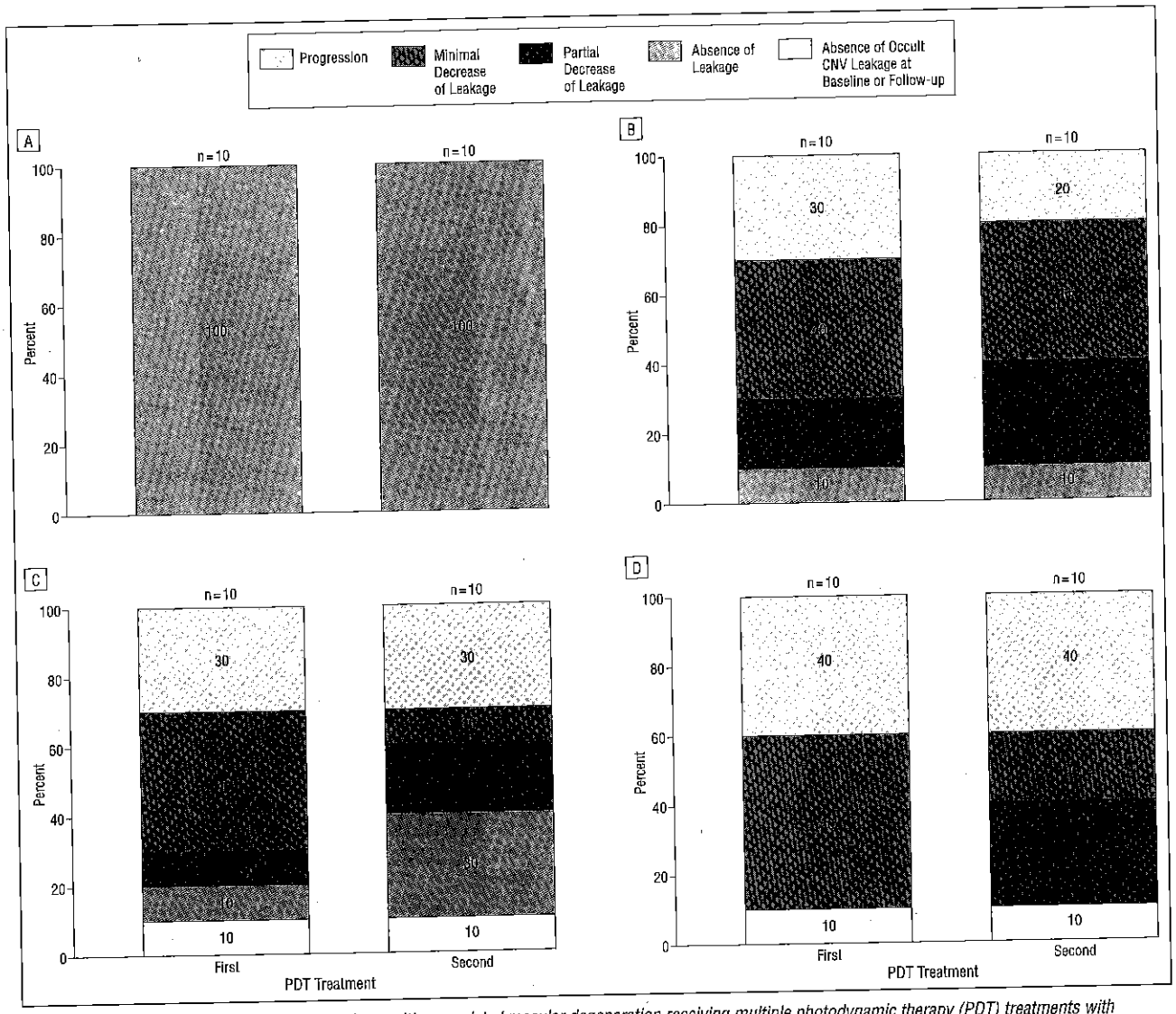


Figure 2. *Grading of fluorescein leakage in patients with age-related macular degeneration receiving multiple photodynamic therapy (PDT) treatments with regimen 4. Classic choroidal neovascularization (CNV) at week 1 (A) and week 4 (B); occult CNV at week 1 (C) and week 4 (D). Two patients undergoing evaluation after a third PDT treatment are not included; at week 1, both patients had complete absence of leakage; at week 4, 1 patient had progression and 1 patient had partial absence of leakage.*

ceiving 2 retreatments, and 16 weeks after the initial treatment for participants receiving only 1 retreatment), the average visual acuity was essentially unchanged (+0.1 lines) from baseline.

Another 5 participants were treated with regimen 2, with retreatments provided at 2 and 4 weeks after enrollment. For these participants, visual acuity improved by 1.8 lines 1 week after the first treatment and by 2.8 lines 1 week after the second treatment (3 weeks after the initial treatment). Following a third treatment 4 weeks after the initial treatment, the 5 patients had a change of 0.4 lines in visual acuity at 16 weeks after the initial treatment (ie, approximately 12 weeks after the third treatment).

Table 5 shows the changes in visual acuity for the 10 patients retreated with regimen 4. Visual acuity was unchanged or improved by approximately 1 line at 1 and 4 weeks after each treatment. Twelve weeks after the last retreatment, average visual acuity decreased by 1 line.

For the 5 participants reenrolled for retreatment sometime beyond 12 weeks after the initial treatment, visual acuity changed 1 week after retreatment, compared with that at 12 weeks after the initial treatment, ranging from −2 to 1 lines (median, 0 lines). For the 1 patient in this group who received 3 retreatments, visual acuity change from baseline at 12 weeks after the third retreatment was −2 lines.

CHANGES IN FLUORESCEIN LEAKAGE AFTER RETREATMENT

Figure 1, **Figure 2**, and **Figure 3** show the grading of fluorescein leakage following treatments and retreatments for regimens 2 and 4. Fluorescein leakage from classic CNV is shown in Figures 1, part A, and 2, part A (1 week after each treatment course) and Figures 1, part B, and 2, part B (4 weeks after each treatment course). Figure 3 shows fluorescein leakage from classic CNV at 12 weeks after the last retreatment. Fluorescein leakage was absent 1 week after the first treatment in almost all participants in regimen 2 (Figure 1, A) and in all participants in regimen 4 (Figure 2, A). Most participants

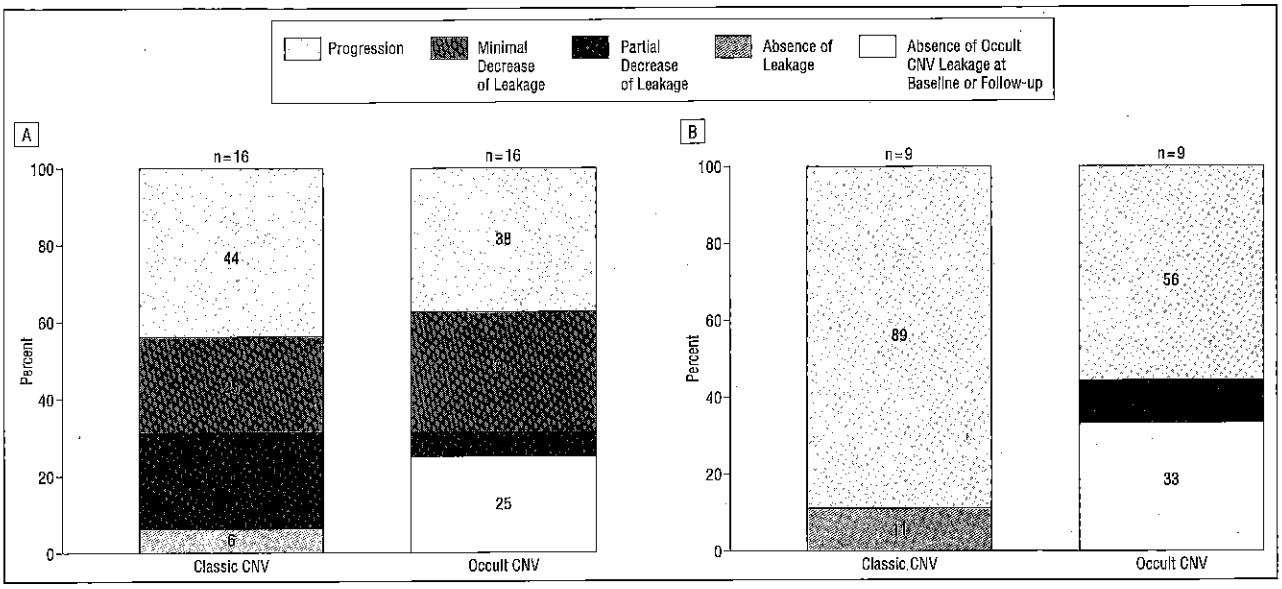


Figure 3. *Grading of fluorescein leakage from choroidal neovascularization (CNV) at 12 weeks after the last retreatment in patients with age-related macular degeneration receiving multiple photodynamic therapy treatments. Regimen 2 (A) and regimen 4 (B).*

did not have progression of classic or occult CNV at 4 weeks after the initial treatment or any retreatment (**Figure 4**).

The angiographic appearance after each retreatment followed the same pattern with subsequent treatments. Independent of the regimen, cessation of leakage from classic CNV at week 1 was achieved with each additional PDT course (Figures 1, A, and 2, A). Multiple applications, even applied at short intervals, produced the same effect on leakage as that obtained with a single treatment.

At 4 weeks after each PDT course, typical recurrence of leakage was noted, at least in a portion of classic CNV. Recurrence rates with progression (leakage from CNV beyond the borders of the baseline lesion) were 17% (2 of 12 patients) to 25% (3 of 12 patients, to 4 of 16 patients) in regimen 2, and were as high as 30% (3 of 10 patients) in regimen 4. Only 17% (2 of 12 patients) to 31% (5 of 16 patients) of classic lesion components displayed persistent absence of leakage in regimen 2, and even fewer patients presented with completely dry classic CNV in regimen 4 (1 [10%] of 10 patients) (Figures 1, B, and 2, B). Twelve weeks after the last treatment (ie, 16 or 20 weeks after the initial PDT treatment), some participants exhibited progression from classic CNV (9 [44%] of 21 patients in regimen 2 and 8 [89%] of 9 patients in regimen 4; Figure 3). Although the percentages of absence and recurrence of leakage seemed to be similar after each PDT course, with an obvious on-and-off effect, the area of leakage typically decreased during the entire treatment and retreatment follow-up. Leakage at the last visit was typically less than that at angiographic baseline presentation.

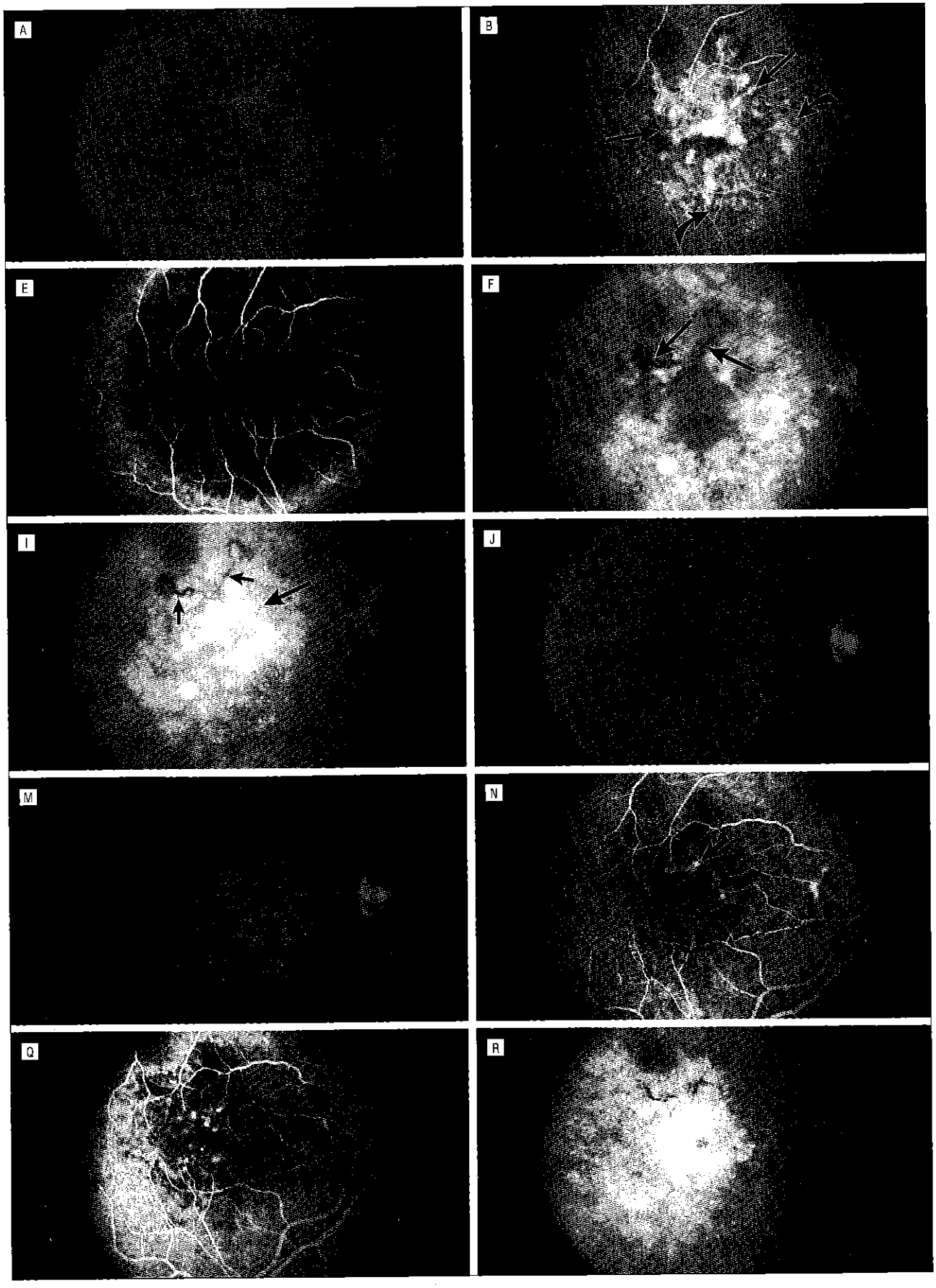
For the 5 participants in regimen 2 who received retreatments at 2 and 4 weeks after the initial PDT treatment, only 1 eye showed leakage from classic CNV at 5 weeks after the initial treatment (1 week after the second treatment). Four weeks after the second treatment, 2 of these 5 participants showed progression from classic CNV, 1 participant showed minimal leakage, 1 participant showed moderate leakage, and 1 participant had absence of leakage.

Of the 5 participants reenrolled sometime beyond 12 weeks, 3 had absence of classic CNV leakage 1 week after retreatment, and 2 had moderate leakage. Four weeks after retreatment, 1 participant had moderate leakage, 2 participants had minimal leakage, and 1 participant had progression. For the 1 eye in this group retreated 2 more times, there was absence of classic CNV leakage 1 week after each retreatment and minimal leakage, but no progression 4 and 12 weeks after the fourth treatment.

In summary, there was no obvious difference in the effects induced by regimen 2 or regimen 4. Absence of leakage was frequent at an early stage, and reappeared continuously thereafter in both groups. Neither regimen achieved a higher rate of long-term complete absence of leakage in classic CNV than that of a single treatment.

The effects of PDT on fluorescein leakage from occult CNV are shown in Figures 1, parts C and D, and 2, parts C and D. Because the diagnosis of occult CNV may be based on late-phase leakage, and since late-phase leakage—particularly at the borders of a treated lesion—was a frequent observation, PDT-related effects on occult components were difficult to grade. Absence of leakage from occult CNV at 1 week after each treatment was found in 19% (3 of 16 patients) to 33% (4 of 12 patients) of angiograms in regimen 2 (Figure 1, C), representing the largest group, and at a lower rate in regimen 4 (Figure 2, C). Progression was present angiographically in 6% (1 of 16) to 17% (3 of 16) and in 30% (3 of 10), in regimens 2 and 4, respectively, at this early posttreatment interval. The rate of progression from occult CNV increased slowly until week 4 in both regimens (Figures 1, D, and 2, D), and was most pronounced 16 to 20 weeks after the initial PDT treatment.

A correlation of angiographic effects with visual acuity outcome appeared to show some benefit of retreatments. For many of the patients receiving retreatment,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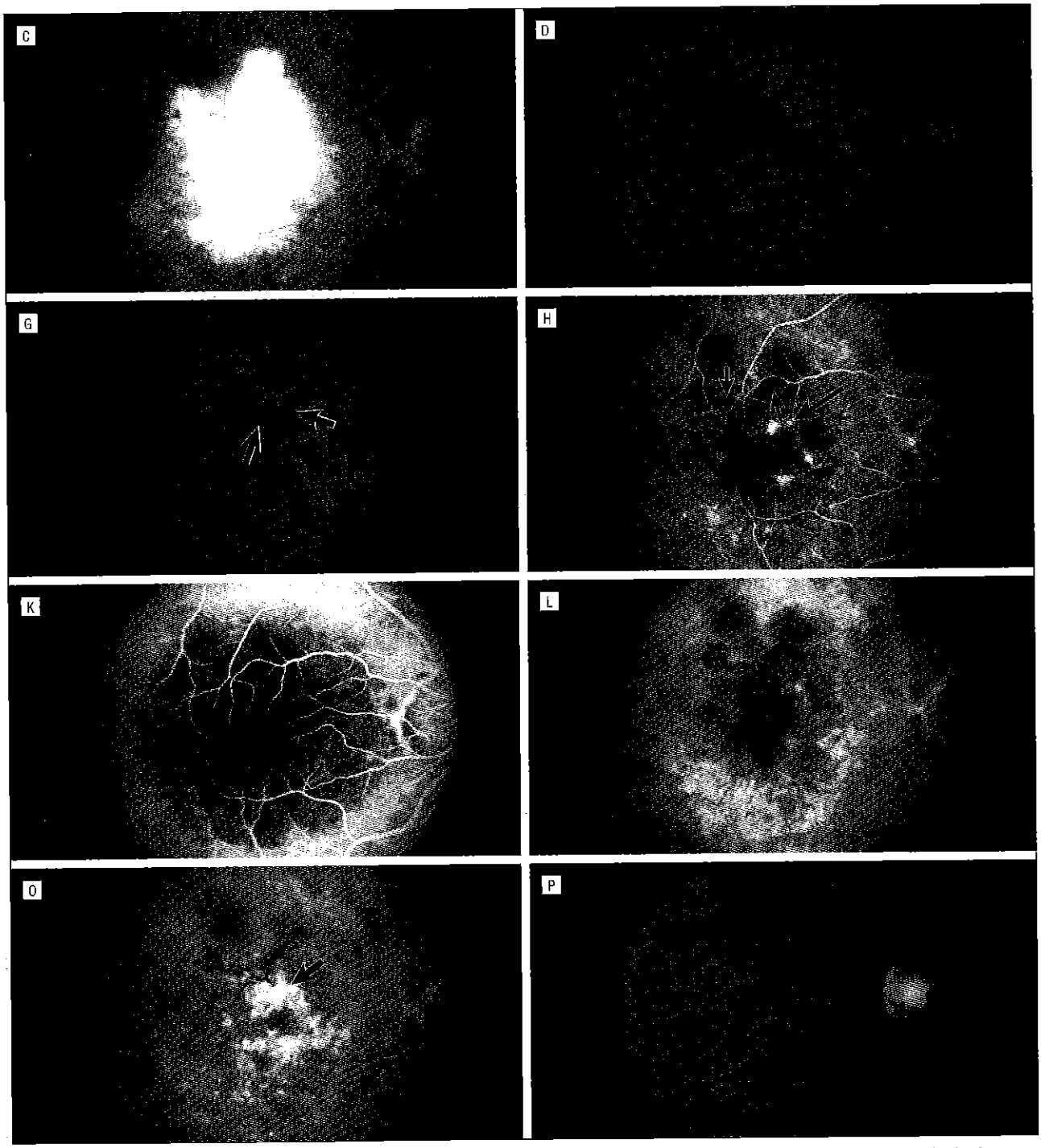

Figure 4. *Baseline and follow-up of multiple verteporfin treatments using regimen 2 (light dose at 100 J/cm²). Initial visit (visual acuity, 20/40) color fundus photograph (A) shows subretinal fluid and hemorrhage overlying choroidal neovascularization (CNV) with drusen temporally as well as a choroidal nevus superotemporally. Early-phase fluorescein angiogram (B) shows bright area of hyperfluorescence corresponding to classic CNV (straight arrows) with additional staining and speckled hyperfluorescence corresponding to occult CNV (curved arrows) that had leakage by the late phase (C). One week after verteporfin therapy (visual acuity, 20/40), color photograph (D) shows less subretinal fluid but a slight increase in subretinal hemorrhage at the superotemporal area of the lesion. Corresponding fluorescein angiogram early-phase frame (E) shows hypofluorescent area of verteporfin therapy. This hypofluorescence is no longer apparent by the late-phase frame (F), which shows absence of hyperfluorescence centrally and along choroidal new vessels superotemporally (arrows) with some persistent staining or leakage from CNV in the pericentral macula. Four weeks after verteporfin therapy (visual acuity, 20/50), little subretinal fluid is seen on the color photograph (G), so that details of the macula appear sharper than at pretreatment (A). Blood within the superotemporal choroidal new vessels is seen (arrows). Corresponding fluorescein angiogram shows absence of fluorescence within superotemporal CNV (small arrows) and some bright areas of hyperfluorescence (large arrow) corresponding to classic CNV in an early-phase frame (H), with leakage by the late-phase frame (I). One week after retreatment with verteporfin (visual acuity, 20/26), color photograph (J) shows less subretinal fluid in macula and persistent visualization of blood within superotemporal portion of CNV. Early-phase fluorescein angiogram (K) again shows hypofluorescence corresponding to verteporfin therapy with slight staining within area of CNV in late-phase frame (L). Four weeks after retreatment (visual acuity, 20/64), color photograph (M) shows no subretinal fluid or hemorrhage. Corresponding fluorescein angiogram shows some bright hyperfluorescence (arrow) in early-phase frame (N) corresponding to classic CNV with some additional leakage in late-phase frame (O), although not as apparent compared with 4 weeks following initial verteporfin therapy (I). Twelve weeks after retreatment (visual acuity, 20/50), color photograph (P) shows slight reaccumulation of subretinal fluid along the temporal aspect of the macula with some hyperfluorescence in the early-phase fluorescein angiogram frame (Q), with leakage from classic and occult CNV in the late-phase frame (R).*

an increase in mean visual acuity seemed to be associated with repeated achievement of absence of leakage from classic CNV. Although a mean change in visual acuity of −0.25 lines was noted after the first treatment, the 21 patients with absence of leakage at 1 week had a mean increase of visual acuity of 1.2 or 1.3 lines (for both regimens). Lesions with only classic CNV components seemed to respond best to retreatments, as demonstrated both angiographically and via visual acuity. This response was most striking in the 5 participants who underwent retreatment at 2-week intervals: visual acuity was improved by 1.8 lines and 2.8 lines after 1 and 2 retreatments, respectively. This group of participants had presented with classic, and no occult, CNV components with a relatively small mean lesion size.

SAFETY AND ADVERSE EVENTS

Of 31 patients who received multiple courses of therapy, 33% (10 of 31 patients) reported adverse events. None of the patients undergoing retreatment lost 6 lines or more of visual acuity from the time of retreatment. The greatest loss from the initial visual acuity (before any PDT treatment) to the last following assessment (before any retreatments) was 6 lines in 1 patient. This patient's CNV lesion had progressed continuously after the third treatment, and the visual acuity loss was probably due to the natural course of the disease. Other reported events included eye pain, itching, lacrimation, asthenia, headache, dizziness, and bradycardia. Other fundus changes recorded in 28 patients by the photograph reading center were increased RPE atrophy in 11 patients (39%), increased fibrosis compared with baseline in 11 (39%), retinal capillary nonperfusion covering less than 30% of lesion area in 4 (14%), and retinal vascular leakage in 3 (10%). A correlation between the number of retreatments and RPE atrophy was not seen. However, there were probably too few patients (n = 14) who received more than 1 retreatment to assess for a correlation adequately. In general, these events were confined to a small portion of the treated area. Retreatment did not result in any arteriolar or venular nonperfusion, or any vitreous hemorrhage.

COMMENT

Our study was performed to determine the ocular safety and short-term effects of repeated PDT using verteporfin to treat subfoveal CNV secondary to AMD. Initially, patients were treated with a single PDT course in a dose-escalation regimen. In most patients, absence of leakage and cessation of CNV growth were temporary. In an attempt to achieve long-term absence of leakage from CNV without visual loss, and thereby potentially stop further growth of CNV and future visual loss, the protocols for our study were designed to determine the safety and effectiveness of repeated PDT treatments for the prevention of recurrent CNV leakage.

Multiple treatments, reproducibly, were able to induce absence of fluorescein leakage from classic CNV without adversely affecting visual acuity. Angiographic effects followed a pattern similar to that of single treatment, ie, no leakage from CNV at week 1, leakage recurring if retreatment was not applied before 4 weeks had elapsed, and further progression of CNV through week 12. On retreatment regimens, leakage was less than before PDT, and visual acuity was maintained for as long as 16 to 20 weeks after initial enrollment. The persistence or progression of occult angiographic leakage, in particular during late-phase angiography, might result from incomplete occlusion of classic CNV with persistence of a portion of the lesion, originate from PDT-induced barrier alterations, or relate to preexisting occult CNV. This was further investigated in an ancillary angiography study using indocyanine green.[19] Multiple treatments, therefore, did not prevent some recurrent leakage in almost every study participant by 12 weeks after the last treatment. However, repeated treatments provided visual acuity stabilization by repeated induction of absence of leakage.

The cause of recurrent CNV remains unclear. The pattern of recurrent leakage with identical localization after each treatment suggests persistence of the feeding vessels or immediate recanalization. If the feeding stem of CNV is not occluded by photothrombosis, regrowth of a neovascular proliferation may occur given a persistent angiogenic stimulation.[20,21] Reopening of transiently occluded vessels may be a consequence of the highly selective nature of PDT with verteporfin. Because PDT-induced thrombosis following isolated endothelial damage can maintain the basic structures of the vascular walls,[9,10] further studies, eg, using indocyanine angiography, may provide additional evidence of the cause of recurrent CNV after PDT.

The analysis of the results from repeated treatments provides some information regarding the timing of PDT intervention. Visual acuity was maintained for as long as 3 months following termination of the retreatment regimens. There were too few cases, and the retreatment study was not designed to determine if an earlier application of retreatments (eg, at 2- or 4-week intervals) would provide any better visual acuity outcome. It does not appear necessary to retreat recurrent CNV leakage with PDT too frequently. Furthermore, as with single treatments, lesion size may play an important role in PDT-related therapeutic benefits.

Retreatments with verteporfin and the relatively high light dose of 100 J/cm^2 could potentially be associated with more progression of RPE atrophy than a single PDT regimen. Such RPE abnormalities could be related to the natural course of AMD. However, the RPE and the choriocapillary layers in AMD are pathogenetically and ultrastructurally an inseparable unit.[22,23] Choroidal neovascularization is often embedded in reactive RPE proliferation.[23,24] Therefore, any efficient manipulation within the CNV invariably could induce some effect on adjacent RPE structures. Atrophy of the RPE may not necessarily be a bad outcome, compared with no treatment. Atrophy of the RPE may promote CNV atrophy directly by reducing the observed secretion of growth factors by activated RPE cells found in CNV.[21] However, if long-term series with multiple treatments are applied, additive damage to the RPE, theoretically, may become a limiting factor for preservation of photoreceptor function. The induction of an effect on the RPE may be useful if intervals between photodynamic interventions are long enough to

allow RPE recovery and regrowth, as seen experimentally in the spontaneous involution of CNV.[25] Therefore, in long-term evaluations of PDT with verteporfin, retreatment should be considered at some point to allow potential RPE recovery, but before too much progressive growth of the CNV lesion has occurred.

The retinal capillary nonperfusion covering less than 30% of the area of the lesion in 14% of cases (4 of 28 patients) almost always consisted of 1 or 2 tiny capillaries. No cases of arteriolar or venular nonperfusion were noted.

Preliminary results from the evaluation of the potential benefit of PDT in the treatment of CNV have demonstrated that a single-treatment regimen may control growth and prevent progression or growth of CNV beyond the area of CNV noted before treatment for as long as 3 months. Multiple treatments were shown in our study to be as safe and as efficient as single treatments in the short term. Consequently, PDT, even applied repeatedly at very short intervals, did not pose any safety concern. The strategy for future trials to evaluate long-term effects of PDT on visual acuity should be based on repeated applications for as long as the chronic disease process is active and leakage reappears. Several double-masked, multicenter, randomized clinical trials are in progress for evaluating the benefit of multiple PDT treatments with verteporfin. These trials use verteporfin and the minimum effective light dose of 50 J/cm^2, as often as every 3 months, with a follow-up of up to 2 years, to determine if this treatment is beneficial compared with no treatment, for subfoveal CNV secondary to AMD.

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From the Retina Department, University Eye Hospital, Lübeck, Germany (Drs Schmidt-Erfurth, Laqua, Barbazetto, and Birngruber); Retina Service, Massachusetts Eye and Ear Infirmary, Harvard Medical School, Boston, Mass (Drs Miller and Gragoudas and Ms Lane); Hopital Ophtalmique Jules Gonin, Lausanne, Switzerland (Drs Sickenberg, Zografos, and Piguet); Department of Oto-Neuro-Ophthalmology, Hopital Cantonal Universitaire de Genève, Geneva, Switzerland (Drs Pournaras and Donati); Laboratory of Air Pollution Studies, Department of Environmental Engineering, Ecole Polytechnique Fédérale de Lausanne, Lausanne, Switzerland (Dr van den Berg); QLT PhotoTherapeutics Inc, Vancouver, British Columbia (Drs Strong and Manjuris); CIBA Vision Inc, Duluth, Ga (Mr Gray); CIBA Vision AG, Bülach, Switzerland (Dr Fsadni); and The Wilmer Ophthalmological Institute, The Johns Hopkins University School of Medicine, Johns Hopkins Hospital, Baltimore, Md (Dr Bressler). *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 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.*

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Corresponding author: Ursula Schmidt-Erfurth, MD, Retina Department, University Eye Hospital, Ratzeburger Allee 160, D-23538 Lübeck, Germany (e-mail: uschmidterfurth@ophtha.mu-luebeck.de).

Reprints: Medical Information, CIBA Vision Ophthalmics, 11460 Johns Creek Pkwy, Duluth, GA 30097 (e-mail: amina.braun@cibavision.novartis.com).

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