Photodynamic Effects on Choroidal Neovascularization and Physiological Choroid

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PURPOSE. To evaluate the effect of photodynamic therapy (PDT) on perfusion and vascular integrity of choroidal neovascularization (CNV) and collateral physiological choroid.

METHODS. In a prospective clinical trial, patients with subfoveal CNV were treated with PDT and verteporfin. Indocyanine green angiography (ICG-A), using a confocal laser scanning system with tomographic sections, was performed continuously 1 week before and 1, 4, and 12 weeks after and a mean long-term follow-up of 16.5 months after the final PDT. Vascular changes were localized tomographically and quantified on the level of the CNV and collateral choroid according to early lesion size, late hyperfluorescence, and persistence or recurrence. Data were analyzed separately for 38 eyes in a single- and 12 eyes in a multiple-treatment regimen.

RESULTS. CNV lesions were significantly reduced in size and late hyperfluorescence. However, 54% of lesions primarily demonstrated persistence, typically of the choroidal feeding complex, which was only detectable by ICG-A. Regrowth from the feeding vessel occurred regularly, but did not reach baseline dimensions. Collateral choroid exposed to photoactivation exhibited choriocapillary occlusion. Progressive recanalization was documented within 4 to 12 weeks after both single and multiple PDT. Residual changes in the choroidal filling pattern often persisted during long-term follow-up.

CONCLUSIONS. Tomographic ICG-A after PDT reveals persistence of CNV and/or the feeder vessel and a reduction in perfusion within the entire photosensitized area, including the surrounding choroid. Repair mechanisms occur slowly in neovascular and normal choroidal structures. (Invest Ophthalmol Vis Sci. 2002;43:830–841)

Although the pathophysiology of age-related macular degeneration (AMD) remains unclear, studies show that choroidal neovascularization (CNV) is central to progressive and irreversible vision loss. The concept of photodynamic therapy (PDT) using a sensitizing agent such as verteporfin appears to fulfill the premise of an efficient and selective inactivation of CNV. Clinical studies of a single course of verteporfin therapy show short-term cessation of leakage from CNV. However, the high proportion of recurrent CNV suggests that repeated applications are the only effective strategy to achieve persistent absence of leakage. The Treatment of AMD with PDT (TAP) investigation showed that verteporfin therapy offers significant benefits in visual acuity, contrast sensitivity, and fluorescein angiographic outcomes, which was sustained for up to 2 years.

Although the clinical outcomes of verteporfin therapy have been established, the knowledge of how PDT acts at the target vascular site—including the choroidal neovascular complex and the surrounding choroid—is less clear. Conventional fluorescein angiography (FA) initially shows homogenous choroidal hypofluorescence, suggesting the complete disappearance of the CNV. Subsequently, there appears to be a high rate of de novo lesion recurrence. Although these findings may be pathognomonic, they cannot be explained by visual acuity tests or by the means of ophthalmoscopy and FA alone. However, indocyanine green angiography (ICG-A) has been shown to offer an alternative to FA to elucidate vaso-occlusive effects, changes in perfusion, and vascular repair mechanisms.

This study reports an ICG-A pilot trial in patients with subfoveal CNV, using high-resolution confocal laser scanning to take tomographic section images during a single- and a multiple-treatment regimen of PDT. Characteristic ICG-A patterns after PDT were defined qualitatively and quantitatively in 38 eyes that received a single PDT course and a separate group of 12 eyes that were treated repeatedly within a short interval. The size of the early-phase vascular net and late-phase hypofluorescence, presumably consistent with leakage activity of CNV, were monitored. Collateral choroidal changes were analyzed based on the presence or recovery of posttreatment hypofluorescence. The crucial problem of recurrence was investigated by tomographic evaluation of primary CNV occlusion and the origin of recurrence and or persistence.

PATIENTS AND METHODS

The overall study was a prospective, nonrandomized, open-label phase I and II trial performed in multiple centers in the United States and Europe. The protocol and all amendments for both the overall study and this ancillary, prospective, single-center ICG-A study complied with the provisions of the Declaration of Helsinki and the recommendations of other governing bodies and the local ethics committee. All participants signed a written informed consent form after an oral informed consent discussion that detailed the potential use and individual risks of an ICG-A examination.

Inclusion Criteria

Patients with clinical signs of CNV, regardless of cause, were eligible. The CNV had to involve the geometric center of the foveal avascular zone and demonstrate evidence of a classic component by conventional FA. The greatest linear dimension (GLD) of the entire lesion could not exceed 5400 μm. Best corrected visual acuity was measured on Early-Treatment Diabetic Retinopathy Study (ETDRS) charts and had to be 20/40 or worse.

Photodynamic Therapy

All treatment regimens involved intravenous infusion of verteporfin (Novartis Ophthalmics, Duluth, GA), followed by irradiation 15 to 20 minutes after the start of sensitizer administration with light at 689 nm
delivered by an ocular photoactivation diode and laser-linked slit lamp (Coherent Inc., Palo Alto, CA). The drug dose was either 6 or 12 mg/m² body surface area in the single-treatment regimen and 6 mg/m² in the retreatment group (Table 1). The irradiance delivered was constant at 600 mW/cm². Light doses according to protocol were 50, 75, or 100 J/cm² in the single-treatment group and 100 J/cm² for all participants who were retreated (Table 1). The size of the treatment beam on the retina was based on the GLD of the entire lesion as measured on FA, including a safety margin of 300 μm. Fluorescein angiograms at 3 weeks after PDT were used to determine the need for retreatment in the repeat-treatment group. If leakage persisted or reappeared, two additional courses of PDT were applied at 4-week intervals. The size of the treatment beam included the area of leakage plus the 300-μm safety margin.

Indocyanine Green Angiography

ICG-A was performed using a confocal laser scanning ophthalmoscope (Heidelberg Retina Angiograph; Heidelberg Engineering GmbH, Heidelberg, Germany). ICG-A was performed 1 week before PDT and repeated 1, 4, and 12 weeks after a single course of PDT. In the retreatment group, ICG-A was performed 1 and 3 weeks after the first and second treatments and 4 and 12 weeks after the third course of PDT. For all participants, long-term evaluation was undertaken with ICG-A at a mean interval of 16.5 months (range, 14–18) after their final PDT treatment. A solution of 50 mg ICG (ICG-Pulsion; Medical Systems, Greenvale, NY) reconstituted to 5 mL in aqua ad injectabilia was administered through a cubital vein. An infrared diode laser was used for excitation of ICG at 795 nm, and a barrier filter at 810 nm was used for detection of fluorescence emission. The size of the square scan field was set at $20\times20$° and enlarged to $30\times30$°, if required by the lesion size. Single images were taken in rapid sequence during the first minute. Subsequently, images were obtained at 2, 5, 10, and 20 minutes. A complete tomographic series of 32 images over a 4-mm scan depth was taken at 1 and 20 minutes. Images were digitized in real time in frames of $512\times512$ pixels and were recorded within 32 ms per image.

Analysis of Tomographic Sections

ICG-A analysis was performed separately by two independent investigators. Because a phase II/III trial is not randomized, patients’ names were replaced by numbers, and images were evaluated in random order to avoid any bias. Lesion size was measured in square millimeters by manual planimetry (software version 1.10, package IR1, ver. 1.08; Heidelberg Engineering, Heidelberg, Germany). All ICG-A images of the tomographic sections were screened for distinct delineation of CNV and choroidal effects. The appropriate section demonstrating the focal plane of the lesion was selected from tomographic series, contrast enhanced, and corrected for brightness to achieve optimal high-resolution imaging.

PDT-induced changes were differentiated into effects on the CNV complex and collateral effects within adjacent physiological choroid included in the treated area. The size of the CNV was measured as the area covered by a neovascular net during early-phase ICG-A, and late hyperfluorescence was defined as the area showing increased fluorescence during late-phase ICG-A, consistent with either leakage or staining originating from the underlying choriocapillaris. Hyperfluorescence was measured as hyperfluorescence lesion compared with background, using an identical reference area in each image with a threshold of at least 20% above background fluorescence intensity (identified with the scanning laser ophthalmoscope software fluorescence analysis). Both, CNV size and late hyperfluorescence were determined independently by two masked investigators. Leakage activity appears to be an important factor, because it allows detection of the entire dimension of persistent CNV activity. Changes at the level of the collateral choroid were characterized by the size of the area exhibiting hypofluorescence in early- and late-phase ICG-A. All parameters, including pre-existing hypofluorescence surrounding a lesion, were identically determined before PDT (Table 2).

At 1 week after a PDT application, the site of the initial CNV was screened tomographically for the presence of a detectable residual neovascularization, which was then defined as persistence. In contrast, the presence of a neovascular structure at 4 or 12 weeks with absence at 1 week was referred to as recurrence. Results were analyzed separately for the single- and multiple-treatment groups.

Statistical analysis was performed for all parameters examined. Readings of the two investigators were averaged. Analysis of deviations indicated individual differences without statistical significance among measurements of identical angiograms by different readers (interindividual variability <5%). The SEM was determined for size and fluorescence intensity. Evaluation was performed with the Wilcoxon rank-sum test; statistical significance was accepted at 0.01.

RESULTS

Photodynamic Effects on the CNV Lesion

Single-Treatment Regimen. Direct effects of PDT within the CNV complex included a change in the size of the neovascular net observed in early-phase ICG-A and in the area exhibiting hyperfluorescence during late-phase ICG-A, consistent with leakage or pathologic staining of fibrous components. A lesion with a distinct neovascular pattern was delineated in all eyes before treatment (Fig. 1A). At 20 minutes, the CNV area was covered by a homogenous plaque of hyperfluorescence that was larger, suggesting leakage of ICG from the neovascular channels into the surrounding tissue (Fig. 1B). At 1 week after PDT, the vascular net was still apparent in half of the patients, but was substantially smaller (Fig. 1C). This area of persistent CNV regularly demonstrated hyperfluorescence and expansion in late-phase ICG-A (Fig. 1D). Four weeks after a single treatment, the membrane seen previously showed increased size in early-phase ICG-A. At 12 weeks, most CNV areas were still

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<thead>
<tr>
<th>Table 1. Patient Distribution in Drug/Light-Dose Regimen</th>
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<tbody>
<tr>
<td>Regimen</td>
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<td>Single treatments ($n = 38$)</td>
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<tr>
<td>Multiple treatments ($n = 12$)</td>
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<tr>
<th>Table 2. Parameters Evaluated by ICG-A</th>
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<tr>
<td>Choroidal neovascular lesion</td>
</tr>
<tr>
<td>Area of neovascular net</td>
</tr>
<tr>
<td>Leakage area originating from a site of early CNV detection</td>
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<td>Collateral choroid</td>
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<tr>
<td>Initial area of hypofluorescence</td>
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<td>Persistent area of hypofluorescence</td>
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identical in dimension and fluorescence intensity with that observed during previous visit, as seen in early- (Fig. 1E) and late- (Fig. 1F) phase ICG-A. The long-term follow-up again demonstrated a well-demarcated vascular net, located within the same area as before treatment (Fig. 1G) with slight enlargement later (Fig. 1H). However, the entire complex was significantly smaller and did not reach the initial size.

Figure 2 summarizes the regression of the size of the CNV lesion and the area of late hyperfluorescence. Before treatment, the mean areas of CNV and hyperfluorescence were 3.51 and 4.53 mm², respectively. As early as 1 week after PDT, the mean lesion size was 0.98 mm² and the hyperfluorescence area was 1.68 mm², a reduction to 28% and 37%, respectively, of the original areas. Both reductions were statistically significant ($P = 0.008$ early-, $P = 0.022$ late-phase ICG-A area). During the following 4 to 12 weeks a moderate progression in growth and hyperfluorescence activity was observed that reached less than half of the baseline of CNV size and hyperfluorescence area. At 3 months, the CNV appeared to stabilize. After a mean of 16.5 months, regression had continued, and the area of CNV and late-phase hyperfluorescence reached a long-term minimum of 0.72 mm² (20.5% of initial size) and 1.11 mm² (24.5% of initial hyperfluorescence area; $P = 0.019$ early-, $P = 0.002$ late-phase ICG-A).

Early- and late-phase ICGA patterns were identical in this group, with both drug doses and with the three different light doses used.

Multiple-Treatment Regimen. PDT applications were repeated at 4-week intervals in a smaller group of 12 patients. Phenomena similar to those in the single-treatment regimen were observed; however, some of the effects appeared to be additive, whereas others were not. As before, CNV was documented in all pretreatment angiograms (Fig. 3A). One week after treatment, the neovascular net became smaller and less
fluorescent (Fig. 3B). CNV then continued to decrease with every additional PDT course (Fig. 3C) and the lesion was smallest 1 week after the third application (Fig. 3D). During the follow-up interval after the final PDT session, lesions recovered and enlarged again without reaching their original sizes (Fig. 3E). Final lesions were generally larger in the retreatment group than in the single-treatment group compared with baseline. The area exhibiting late hyperfluorescence showed stabilization after the final treatment session. Because there was no difference in the angiographic pattern in the single-treatment group in relation to the different light doses used, the increase in size of the neovascular network was probably not related to the unique light dose of 100 J/cm² applied in the retreatment group.

The dynamics of the effects of multiple PDT became obvious, as the mean areas showed over time (Fig. 4). The early detectable lesion decreased, on average, to 37% of its original size after only one course of PDT, to 13% after two courses, and to 3% after three courses. The area exhibiting late hyperfluorescence also decreased each time. Both effects were statistically significant ($P = 0.005; 0.007$). However, both areas increased during the following weeks and months.

Photodynamic Effects within the Physiological Choroid

**Single-Treatment Regimen.** Areas of hypofluorescence were seen in all eyes after treatment during both early- and late-phase ICG-A. Screening of baseline angiograms showed a preexisting area of hypofluorescence surrounding the CNV complex in all eyes (Fig. 1A). This darker area was irregular in fluorescence and shape and persisted throughout the entire examination (Fig. 1B). In contrast to the pretreatment finding, the area of hypofluorescence at 1 week of PDT was substantially larger and more intense, with a round configuration and well-delineated borders (Fig. 1C), and persisted throughout late angiographic frames (Fig. 1D). At 4 weeks, the same area of hypofluorescence persisted in all patients during early-phase
ICG-A, but was less pronounced in the late phase. Collateral hypoﬂuorescence decreased in size and intensity over time (Fig. 1E) particularly in late-phase ICG-A (Fig. 1F). There was no change in the choroidal ﬁlling pattern, compared with baseline in 13 of 38 patients at long-term follow-up (mean, 16.5 months). A small loss in ﬂuorescence within a localized halo surrounding the CNV complex was still detected in the remaining group (Figs. 1G, 1H).

Choroidal hypoﬂuorescence was evaluated regarding the area of reduced ﬂuorescence over time, which is indicative of choroidal perfusion changes. The size of post-PDT hypoﬂuorescence was largest 1 week after PDT and decreased slowly during follow-up (Fig. 5). Early-phase hypoﬂuorescence regularly covered a larger area than the hypoﬂuorescence in the late frames. The mean area of hypoﬂuorescence was, on average, 11.95 mm² during early- and 11.23 mm² during late-phase ICG-A.

The hypoﬂuorescent area was 4.3 times larger than the original size of the CNV determined by ICG-A before treatment. Immediate effects on the neovascular complex, per se (e.g., associated with masking effects), therefore does not account for the extent of hypoﬂuorescence in the surrounding CNV-unrelated physiological choroid. The mean diameter of the round hypoﬂuorescent region (3.826 mm) was identical with the mean diameter of the treatment spot used for photoactivation (GLD, 3.840 mm). Even after as long as 16.5 months, in those eyes that still demonstrated collateral hypoﬂuorescence, the hypoﬂuorescent area covered 7.63 and 5.59 mm² (early- and late-phase ICG-A, respectively), consistent with a persistence of 63.8% and 49.8% of the initial area hypoﬂuorescence (P = 0.004 and 0.005, respectively).

**Multiple-Treatment Regimen.** The area of posttreatment hypoﬂuorescence was always larger than the irregular zone of reduced ﬂuorescence surrounding the lesion before PDT (Fig. 3A). Hypoﬂuorescence was round and homogenous, with larger-caliber vessels seen in early-phase ICG-A (Fig. 3B). Persistent hypoﬂuorescence was documented in all patients after the second (Fig. 3C) and third (Fig. 3D) PDT and subsequently at 3 and 16.5 months. However, the area showing reduced ﬂuorescence became smaller, and the extent of hypoﬂuorescence became less intense within 3 months (Fig. 3E).

Quantitative analysis revealed a 25% enlargement of the hypoﬂuorescent area at the 1-week follow-up after the second PDT treatment, compared with the area measured after the first PDT treatment (10.6 and 9.9 mm² early- versus late-phase ICG-A, respectively) which did not reach statistical signiﬁcance. The size of choroidal hypoﬂuorescence in ICG-A 1 week after the previous treatment was always identical with the size of the treatment spot selected, suggesting an immediate effect of the light exposure. The decrease of this area at 12 weeks after the third PDT was smaller than the more intense resolution of hypoﬂuorescence after a single exposure at that time interval. The dark area remained unchanged in size for up to 4 weeks after the third treatment. Finally, the area with impaired ﬂuorescence became smaller—a slow process in early-phase ICG-A that became faster by late-phase imaging. An area of persistent hypoﬂuorescence covering 6.8 mm² in early-phase ICG-A and 4.0 mm² in late-phase ICG-A was still seen after 16.5 months (Fig. 6).

**Persistence and Recurrence**

When ICG-A images were screened for persistence of CNV in the single-treatment group, 54% of CNV lesions demonstrating neovascular membranes were still detectable in early-phase ICG-A and 69% showed late hyperﬂuorescence in ICG-A at 1 week after PDT (Fig. 7). One week after three consecutive PDT applications, 83% of CNV nets had disappeared in early-phase ICG-A and 50% in the late phase. The recurrence rate after 4 weeks was identical in both treatment groups (87% in the single- and 92% in the multiple-PDT group). During the follow-up, the number of choroidal neovascular lesions identiﬁed by ICG-A decreased. At the ﬁnal visit, 50% of the single- and 58% of the multiple-treatment eyes did not exhibit signs of neovascular disease during early-phase ICG-A or hyperﬂuorescence during late-phase ICG-A.

The pattern of persistent CNV identiﬁed with ICG-A was homogenous and differed markedly from angiographic imaging with fluorescein. Typically, FA revealed CNV with classic and occult components before PDT (Fig. 8A). At the 1-week evaluation, CNV was absent in early-phase FAs in every eye (Fig. 8B). Pretreatment ICG-A demonstrated a feeder vessel, ﬁlling early after dye administration, with the adherent neovascular net (Fig. 8C). Whenever persistence was seen during the 1-week ICG-A follow-up, the patent portion of the CNV was always identiﬁed as the feeding complex (Fig. 8D). Late-phase hyperﬂuorescence originating from this area supported the hypothesis of a persistent neovascular component, as opposed to demarcation of visible physiological choroid (Fig. 8E). Progressive enlargement of CNV regularly proceeded from the localized persistence to form a novel capillary net. This net appeared, regardless of the difference in the internal vascular pattern from the membrane texture seen before PDT (Fig. 8F), but showed less or no hyperﬂuorescence in late-phase ICG-A.

Whenever CNV was detected before treatment (Fig. 9A) and persistence was absent at the 1-week examination (Fig. 9B),
the perfusion blockage was clearly visible at the level of the choroidal communication, including the vessels feeding and draining the CNV. The homogenous hypofluorescent plaque seen during early-phase ICG-A, became irregular during the late phase (Fig. 9C). Multiple hyperflourescent choroidal vessels at the peripheral zone started leaking and demonstrated brightly hyperflourescent leakage pools, whereas the central area of the treatment spot typically remained dark (Fig. 9C). Four weeks after treatment, a newly formed neovascular proliferation was seen sprouting out of the assumed feeder vessel (Fig. 9D).

Visual acuity findings in the phase I and II study based on the entire study population have been described in detail in previous publications. The focus of this study was a qualitative description of the anatomic response observed on the level of neovascular and physiological choroidal vessels. Although the number of patients analyzed does not allow a correlation with visual acuity data, there was a trend toward lower final visual acuity in patients with early and larger persistence of CNV in short-term follow-up ICG-A. Intensity and extent of choroidal hypofluorescence did not correlate with a reduction in visual acuity.

**DISCUSSION**

Photodynamic therapy has recently been shown beneficial for the treatment of the neovascular component of exudative AMD. Selective photothrombosis of the neovascular membrane supposedly underlies the leakage cessation induced by PDT, at least experimentally. However, experience with CNV in humans is limited to clinical observation, presumably indicative of occlusion and subsequent regression of CNV.

ICG-A has been recognized as a sensitive method to identify classic and occult components of CNV, due to improved trans-
mission of the dye. Intravascular ICG, 98% of which is bound by serum proteins, allows distinct imaging of the vascular compartment. Confocal ICG-A further improves the optical and digital resolution to approximately 10 μm in the transverse and 300 μm in the longitudinal direction. The tomographic technique used provides a precise focus on the plane of interest, such as the CNV membrane, and represents an excellent tool for analyzing vascular alteration.

An important finding is that ICG-A showed that verteporfin therapy had a vaso-occlusive mechanism that affected both CNV and the normal choroid. However, occlusion was not complete: The CNV complex remained patent, at least at the feeder-vessel level. Persistent feeder vessels were the origin of newly developing neovascular proliferation—a true recurrence that occurred in approximately one half of the treated patients. In the other 50% of treated eyes, ICG-A directly demonstrated a patent portion of CNV, which represents, by definition, persistence rather than a recurrence. Multiple PDT applications within short intervals reduced the rate of persistence, but did not influence the frequency of recurrence. However, recurrence showed only limited progression with ICG-A. Even a single PDT treatment led to an involution of the recurrent membrane at a smaller final size than that at baseline.

Evidence of true choroidal occlusion and detection of CNV persistence are the two major findings of this study.

There is intense controversy in the interpretation of hypofluorescence after PDT. By FA, hypofluorescence 1 week after PDT was intense, homogenous, and unstructured. No insight into the extent of choroidal nonperfusion or persistence of neovascular components was possible. Masking by serous fluid or hemoglobin was suspected. ICG-A is less susceptible to transmission deficits by masking fluids. Tomographic analysis of hypofluorescence demonstrates loss of the superficial choriocapillary layer in conjunction with maintenance of perfusion of larger choroidal vessels, which remain clearly visible without masking.

The ability of PDT to occlude physiological choroidal vasculature was shown in several experimental studies in a direct dose-response relationship. By confocal ICG-A a single PDT application produced an area of hypofluorescence which, at 1 week, was identical in size to the area of the treatment spot used, consistent with a direct occlusive effect. The similar size of hypofluorescence in early- and late-phase ICG-A suggests complete absence of ICG, caused by a substantial reduction of the perfusion without inflow of ICG from adjacent patent vessels. Experimentally, angiography using verteporfin as a fluorescent marker demonstrated selective accumulation of sensitizer within the CNV complex. In fact, substantial undetected amounts of sensitizer must also be localized within physiological vessels, which are usually less sensitive to phototoxic damage than proliferating neovascularulature. Occlusion of normal choriocapillaries is not restricted to PDT using verteporfin, but has also been described with mono-L-aspartyl chlorin e6, a hydrophilic sensitizer.

FA showed rapid disappearance of hypofluorescence after PDT, which contrasts considerably with ICG-A findings that demonstrated persistence of choroidal hypofluorescence over extended periods and, in one subgroup, even after many months. During early-phase ICG-A the rapid perfusion sequence of patent arterioles, capillary lobules, and venules is captured. Any vascular obstacle (e.g., endothelial swelling) can prevent the filling of the regular vascular pattern. A homogeneous loss of early perfusion occurred after PDT, consistent with a complete thrombosis of the capillary layer. Late-phase ICG-A documents the diffuse distribution of dye molecules throughout the fenestrations of the choroidal vascular sponge. Leakage from the intact borders or deep layers now leads to fluorescent filling of large parts, particularly in the periphery of the lesion, so that the area of hypofluorescence is typically

![Figure 3](http://iovs.arvojournals.org/pdfaccess.ashx?url=/data/journals/iovs/933592/)  
**FIGURE 3.** (Continued)

![Figure 4](http://iovs.arvojournals.org/pdfaccess.ashx?url=/data/journals/iovs/933592/)  
**FIGURE 4.** Regression of CNV size and leakage area during a multiple-treatment regimen. The decrease in CNV size and leakage area is significant for all post-PDT intervals up to 12 weeks (P < 0.01 and P < 0.015, respectively). There is no notable significant decrease between pre-PDT data and long-term follow-up data. Error bars, SEM.

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Figure 5. Area of collateral posttreatment hypofluorescence in early- and late-phase ICG-A in a single-treatment group. The area of hypofluorescence was significantly reduced compared with the initial size, seen first at 1 week after PDT, at 4 weeks after PDT for the late phase, and at 12 weeks after PDT and at the long-term follow-up for both early- and late-phase ICG-A ($P < 0.004$ and $P = 0.005$, respectively). Error bars, SEM.

Figure 6. Area of collateral choroidal hypofluorescence in early- and late-phase ICG-A in a multiple-treatment regimen. There was no significant difference in hypofluorescence area at 1 week after PDT1, PDT2, and PDT3. The decrease in the hypofluorescent area between the initial hypofluorescence at 1 week after PDT1 and the late phase at 12 weeks after PDT3 and both early and late phase at long-term observation was statistically significant ($P = 0.04$ and $P = 0.003$, respectively). Error bars, SEM.

Figure 7. Rate of CNV persistence in single- and multiple-treatment regimens (after the third application). Persistence was defined as the presence of a distinct neovascular structure within the area of CNV identified at baseline.
smaller in late-phase ICG-A, a sequence taken 15 minutes after injection. Obviously, multiple treatments do not enhance or prolong choroidal thrombosis, most likely because the next PDT application hits an area with persistent vascular occlusion, so that less sensitizer and less oxygen are available, and the PDT effect is less intense. Late-phase leakage and recanalization from the borders of the occluded area finally lead to a decrease in the size of the hypoﬂuorescent area. Regarding the regenerative potential of the choriocapillary in patients with AMD, age- or disease-related primary alteration of choriocapillary density and perfusion must be considered. Filling of the choriocapillaries with ICG was delayed in people more than 50 years of age, and areas of hypoﬂuorescence were observed in the macula of patients with AMD.17,18 Accordingly, irregular hypoﬂuorescence before PDT was substantiated in this study group. Whether choroidal nonperfusion facilitates CNV occlusion is speculative. A decrease in flow within the surrounding choroid would also secondarily reduce perfusion of the CNV, where blood flow is primarily more sluggish.19 It is noteworthy that repeated treatments did not prolong choriocapillary nonperfusion and that recovery occurred within the same time frame.

The issue of persistence and/or recurrence has important implications for the clinical application of PDT. FA failed to detect persistence of the feeder vessel and the CNV, per se. The sensitive tomographic analysis of ICG-A features revealed angiographic persistence, defined as a residual neovascular net seen in early-phase ICG-A as early as during the first examina-
tion at 1 week after PDT. In addition to an absence of complete occlusion, persistent CNV activity was documented with the residual membrane leaking actively in late phase ICG-A, with an increase in late hyperfluorescence area over time. In contrast with FA, ICG-A was able to demonstrate persistence in nearly half of the treated neovascular lesions. A patent feeder vessel was identified as a potential source of lesion regrowth. CNV membranes were shown to possess one or several choroidal feeder vessels as they originated from physiological choroidal vasculature. Feeder vessel closure alone, using thermal photocoagulation, has been shown to shut down the perfusion of the entire neovascular complex with subsequent resolution of leakage and regression of CNV. Flower and Snyder have hypothesized that a reduction of choroidal perfusion in the surrounding choroid in CNV influences the perfusion dynamics with a decrease in the afferent and efferent flow of the feeder vessel. In an experimental model of CNV feeder vessels, ICG-A was used to visualize the feeder vessels originating from medium-diameter choroidal channels and to facilitate a selective dye-enhanced photothrombosis. Feeder vessel occlusion was achieved with minimum concomitant damage to overlying retinal tissue—proof of the principal of a method that has not demonstrated its efficacy.

The evolution of recurrent CNV lesions seems to require specific interpretation. Although recurrences were noted in 87% and 92% of eyes in the single- and multiple-treatment regimens, respectively, after 4 weeks only 50% and 58% demonstrated recurrent lesions at the final visit. In the TAP experience, CNV was re-treated until leakage subsided, and therefore there was no chance to monitor the spontaneous behavior of a lesion in which biological changes were induced by a single or a short-term cascade of treatments with a subsequently undisturbed process of involution. It is well known from the spontaneous course that the neovascular leakage activity subsides with time and that even large lesions become fibrotic, arrested in growth, and dry. Additional treatments with renewed choroidal alteration and angiogenic stimulation may trigger more persistent and accelerated regrowth and activity of these lesions and may interfere with the maturation process of the neovascular complex. The TAP data, furthermore, focus, on FA findings with active CNV identified by leakage, whereas leakage was not a prominent feature in ICG-A.

Whether regrowth or recanalization is the reason for subsequent CNV enlargement remains to be determined. The phenomenon of chronically recurrent CNV after PDT may be closely related to choroidal hypofluorescence. Regrowth may be stimulated by relative ischemia of RPE and photoreceptors within the PDT-affected choriocapillary region, with an increase in vascular endothelial growth factor (VEGF) secretion. Because choroidal malperfusion may promote recurrence of CNV by reactive angiogenic stimulation, combination therapy of PDT followed by suppression of angiogenesis appears most promising.

Investigators have learned that, compared with other treatment modalities such as laser photocoagulation, CNV never completely disappears after treatment. With treatment, membranes become smaller and exhibit less leakage than if left to their natural course, but they can still be seen on angiography, even after multiple treatments. Experimentally, an enveloping by proliferating RPE cells promotes the spontaneous involution of persistent CNV. In younger patients with idiopathic or myopia-related CNV, neovascular nets remain smaller and regress more often than in AMD, because of the higher regenerative potential of young RPE. If large parts of a choroidal neovascular lesion remain unperfused for several weeks after PDT, further destructive growth of the membrane can be transiently halted. Adjacent RPE cells may benefit from the interval required for the restoration of the CNV and may migrate and proliferate around the neovascular net. CNV engulged by RPE is still persistent, but inactive without further growth and late-phase hyperfluorescence as observed with ICG-A. Choroidal vascular nets that are abnormal in their distribution and location may no longer be in an active stage and may be arrested in growth and leakage activity, either by a maturation process alone or by an engulfing RPE barrier.

RPE proliferation was documented in experimental models histologically. Histology of human eyes exposed to PDT has meanwhile shown that RPE damage is significantly less intense in a human eye than in an animal’s (Schmidt-Erfurth et al., manuscript submitted). The hyperplastic RPE rim seen clinically in treated eyes, with good regression of the membrane, also highlights the regenerative potential of the RPE in a human eye, particularly at younger age. Immunohistology of human specimens has furthermore shown that after PDT, VEGF was
produced by choriocapillary endothelial cells and not by RPE cells (Schmidt-Erfurth et al., manuscript submitted).

Clinical investigations should include a search for more selective targeting systems or sensitive angiographic monitoring to select a time interval of optimal sensitizer accumulation to increase the selectivity for CNV. In fact, retreatments reduced the size of the CNV further (Fig. 4). However, even in the complete absence of the primary lesion, recurrence occurred at the same rate and speed as after a single treatment. At long-term follow-up, the outcome appeared to be even worse in the retreatment group. Therefore, multiple treatments at short intervals did not resolve the problem of chronic progressive disease.

The severity of hypoﬂuorescence intensity was measured separately and was most intense 1 week after PDT, with subsequent recovery to background levels beyond 12 weeks in most cases. There was a high interindividually variability between the absolute levels of hypoﬂuorescence which, in a most interesting finding, was independent of the drug or light dose applied. There was no correlation between the hypoﬂuorescence size or intensity and the degree of CNV persistence or rate of recurrence. There was a tight correlation between persistent and intense hypoﬂuorescence and retinal sensitivity, with a larger scotoma size and increased intensity associated with more intense hypoﬂuorescence. 26

Obviously, the occlusive effects on CNV and choroid are independent features. Choroidal nonperfusion within the entire light-exposed area is regularly present after PDT, but the degree of CNV and choroidal occlusive effects varies considerably within the same eye. Subsequent studies have shown that even the time course of thrombosis is different. Whereas the CNV size reaches its minimum as early as 1 day after PDT,
intensity and size of choroidal hypofluorescence peak at 1 week.27 Retreatment intervals must be long enough to guarantee complete recovery of choroidal perfusion. Measurements of retinal sensitivity using scanning laser ophthalmoscope micropachymetry have revealed that photoreceptor function improves at week 4, when choroidal perfusion seems to recover.26

References


