Influence of Treatment Parameters on Selectivity of Verteporfin Therapy

Stephan Michels,1 Fabian Hansmann,2 Wolfgang Geitzenauer,1 and Ursula Schmidt-Erfurth1

Verteporfin therapy induces a nonthermal occlusion of the CNV lesion without affecting the overlying neurosensory retina, as shown experimentally.4 Only minor effects on the retinal pigment epithelium (RPE) were documented after a single treatment in animal models.4 However, definite dose-dependent choriocapillaris closure is seen histologically in human eyes 1 week after verteporfin treatment according to the standard treatment parameters.5,6 These morphologic findings correlate well with characteristic indocyanine green angiography (ICGA) features documented after standard verteporfin therapy.7 Choroidal hypofluorescence reaching its maximum at 1 week after treatment, comparable in size with the treatment spot used, is regularly documented by ICGA. At least partial reperfusion of the choriocapillary layer was seen at 3 months follow-up; however, repeated verteporfin therapy in patients treated in the Treatment of Age-Related Macular Degeneration with Photodynamic Therapy (TAP) trial led to persistent choriocapillary nonperfusion in most eyes.8 Associated with choriocapillary occlusion, an angiogenic response with upregulation of vascular endothelial growth factor (VEGF) was also documented in human eyes.9 The collateral impact of verteporfin therapy on the physiologic choroid strongly compromises the concept of selectivity and may be the reason for additional vision loss and the need for repeated intervention.

Ideally a selective approach should include maximum efficacy (i.e., complete closure of the CNV) and minimal damage to the physiologic choroid (i.e., absence of nonperfusion or vascular–retinal pigment epithelium [RPE] barrier breakdown). Based on the principles of photodynamic mechanisms, there are distinct strategies to enhance selectivity, including modification of the route of administration, the timing of laser exposure, and a reduction of fluence and/or irradiance. Previous clinical trials have provided solid information about the range of safe and effective dosages, such as the phase I/II trials and the verteporfin treatment of subfoveal minimally classic CNV in age-related macular degeneration (VIM) study.10–12 However, selectivity in terms of avoiding damage to the physiologic choroid was never evaluated. In a prospective case series, we chose a bolus infusion of verteporfin, which has been shown safe and effective in the treatment of choroidal hemangiomata.13 A bolus administration is generally used in PDT tumor therapy, to achieve an optimal and selective biodistribution of the sensitizer.14,15 Bolus injection was also used in the pilot work in experimental photothermolysis of ocular vasculature and was not associated with significant choroidal damage.4 A reduced light dose was selected based on the results of the phase I/II studies and the VIM study.12

The purpose of this study was to demonstrate proof of the principle that verteporfin therapy can achieve selectivity, defined as complete CNV closure, with reduced choroidal occlusion or barrier breakdown.

METHODS

The presented study is the result of a prospective interventional case series. The treatment protocol was approved by the local ethics committee. The study was conducted according to the tenets of the

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Verteporfin therapy (PDT) has been the standard of care for many patients with exudative age-related macular degeneration (AMD). Even though its effectiveness had been shown in several multicenter controlled clinical trials,1,2 patients treated with verteporfin therapy still lose a mean of 2.2 lines of visual acuity over 12 months.3 Seventy-five percent of vision treated with verteporfin therapy as well as in combination strategies. (Invest Ophthalmol Vis Sci. 2006;47:371–376) DOI:10.1167/iovs.05-0354

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Declaration of Helsinki and patients gave written informed consent before enrolling, after a detailed discussion of the study procedures, potential risks, and goals.

Patient Selection

Nineteen consecutive patients were enrolled in the study. All patients presented with a subfoveal, predominantly classic CNV due to AMD, without any prior treatment. Visual acuity ranged between 20/200 and 20/40. The total lesion size was measured to have a greatest linear diameter (GLD) of less than 540 μm, and the CNV component had to cover at least 50% of the total lesion size, according to the TAP study recommendations.\(^1\)

Treatment Parameters

All patients received a bolus infusion of 6 mg/m² body surface area over 1 minute. Patients were assigned to two treatment protocols, using a fluence of either 25 or 50 J/cm². In each group, one additional parameter was modified. In the 25-J/cm² group, patients received an irradiance of either 600 or 300 mW. Depending on the irradiance, the time of photosensitization was 42 or 83 seconds. In the 50-J/cm² group, the time of photosensitization was 5 or 15 minutes after verteporfin bolus infusion.

Detailed treatment parameters and the treatment groups are shown in Table 1.

Documentation

Patients were seen for regular follow-up visits within 1 week before and at day 1, week 1, week 4, and month 3 after treatment. A standardized evaluation was performed at each visit including best corrected visual acuity according to the guidelines of the Early Treatment Diabetic Retinopathy Study (ETDRS), confocal scanning laser fluorescence angiography (FA), ICGA (Heidelberg Engineering, Dossenheim, Germany), fundus photography, and a complete eye examination. Selected patients were imaged with optical coherence tomography (OCT).

The main outcome measures were choroidal perfusion changes, as documented by early and late ICGA. A PDT-induced increase in collateral leakage area seen by late FA 1 day after PDT was defined as a secondary outcome, as was primary CNV closure documented by early ICGA.

Data were statistically analyzed with the Wilcoxon signed-rank and Wilcoxon rank sum tests. Statistical significance was defined as \(P < 0.05\).

Procedures for Evaluation

The Heidelberg Eye Explorer (software 1.0; Heidelberg Engineering), an imaging software developed for analysis and visualization of images obtained with the Heidelberg Retina Angiograph (HRA), was used for planimetric evaluation of the area of hypo/hyperperfusion detected by ICGA and the area of PDT-induced leakage seen on FA. Choriocapillaries were graded according to a scale (Table 2). Primary CNV closure was evaluated with FA 1 day after PDT. Angiographies were evaluated by two masked readers, and planimetric and grading results of both readers were averaged. There was 100% agreement on CNV closure at day 1.

RESULTS

PDT-Induced Choroidal Perfusion Changes

The effect of treatment parameters on choroidal perfusion was evaluated based on angiographic loss of perfused choriocapillary patterns during early ICGA (Table 2) and hypo/hyperfluorescence in late ICGA.

At day 1, a significant loss of early choriocapillary perfusion patterns was seen in early ICGA in the 50-J/cm² light dose regimen (Table 3, Fig. 1D). Two of three patients with photosensitization 5 minutes after the end of the verteporfin infusion showed nonperfusion of some larger choroidal vessels (grade IV). None of the protocols showed any effect at the level of the retinal circulation. An occlusive effect on the choriocapillary layer was much less evident in the 25-J/cm² treatment group (Table 3, Fig. 2D). On average, patients treated in this protocol showed only minor grades of malperfusion of the choriocapillaris (≥grade II). At day 1 high grades of malperfusion (≥grade III) were significantly more common in the 50 J/cm² group compared with the 25-J/cm² group (\(P = 0.0048\)). At the 1-week follow-up no patient showed more than grade II choroidal perfusion changes in the 25-J/cm² treatment group (Table 3). However, a significant nonperfusion effect (≥grade III) was evident in 66.6% of patients treated with 50 J/cm² at 1 week (Table 3, Fig. 1E). Perfusion changes of at least grade III were significantly more frequent in the 50-J/cm² group than in the 25-J/cm² group (\(P = 0.0027\)). During further follow-up, all groups showed progressive recovery of the choriocapillaris.

The 3-month follow-up examination did not document any moderate perfusion changes (grade II) in the 25-J/cm² protocol. However, especially in patients with early photosensitization in the 50-J/cm² group, at least moderate perfusion changes were present at 3 months (60% of patients; Table 3).

Late hypo/hyperfluorescence on ICGA provides information about the completeness of choroidal and choriocapillary perfusion. Figure 3 summarizes the follow-up data on the area of late hypo/hyperfluorescence. At baseline, focal perfusion changes were visible due to the underlying disease and were restricted to the lesion site. Verteporfin therapy induced an increase in the hypo/hyperfluorescent area in late ICGA in all regimens at 1 day and 1 week; however, most pronounced changes were documented in the 50-J/cm² protocol (Fig. 1F). The 25-J/cm² protocol showed recovery to pretreatment levels at 4 weeks and 3 months, whereas in the 50-J/cm² protocol, large areas with persistent hypo/hyperfluorescence were detectable during follow-up (Fig. 3). At month 3, the treatment-induced hypo/hyperfluorescent area was significantly smaller in the 25-J/cm² group than in the 50-J/cm² group (\(P = 0.0033\)).

CNV Closure and Collateral Vascular–RPE Barrier Breakdown

The change in size of the total leakage area, including leakage from the CNV and new leakage arising from the entire PDT-exposed area, was used as a measure of increased permeability and breakdown of vascular barriers and was evaluated by FA.

At baseline, the leakage area during late FA correlated well with CNV size, ranging from 5.05 to 8.25 mm². At day 1 after treatment, the higher light dose protocol (50 J/cm²) showed a more intensive increase in leakage area of 2.9 mm². The reduced-light protocol induced only a moderate increase in leakage area of 1.16 mm². This difference between both treatment protocols was not statistically significant (\(P = 0.2570\)). OCT, performed in selected cases, showed characteristic changes in the 50-J/cm² group an increase in mostly subretinal fluid at day 1, which resolved by week 1 (Fig. 4).

CNV size at baseline was well balanced between the 25- and 50-J/cm² group (2.72 mm² vs. 3.12 mm²). Complete closure of

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**Table 1. Treatment Parameters and Distribution of Patients**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>50 J/cm²</th>
<th>25 J/cm²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Timing (min)</td>
<td>5</td>
<td>15</td>
</tr>
<tr>
<td>Patients (n)</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Fluence (mW)</td>
<td>600</td>
<td>600</td>
</tr>
<tr>
<td>Duration (sec)</td>
<td>85</td>
<td>42</td>
</tr>
<tr>
<td>Drug dose (mg/m²)</td>
<td>6</td>
<td>6</td>
</tr>
</tbody>
</table>
the CNV, a parameter for early-treatment efficacy, was achieved in all eyes of both treatment groups. Figures 1 and 2 demonstrate complete CNV closure in FA in eyes treated with 50 and 25 J/cm². Further follow-up showed recurrent CNV in all patients at month 3, indicating requirement for retreatment. There was an increase in CNV lesion size in the 25- and 50-J/cm² groups to 6.37 mm² and 4.63 mm², respectively.

**Table 2. Grading of Verteporfin Therapy’s Effect on the Choriocapillaris as Documented by ICGA**

<table>
<thead>
<tr>
<th>GRADE</th>
<th>ICGA-Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No effect on choriocapillaris in early and late ICGA</td>
</tr>
<tr>
<td>I</td>
<td>No significant choriocapillary non-perfusion in early ICGA, discrete hypofluorescence in late ICGA</td>
</tr>
<tr>
<td>II</td>
<td>Moderate non-perfusion of choriocapillaris in early ICGA</td>
</tr>
<tr>
<td>III</td>
<td>Significant non-perfusion of choriocapillaris in early ICGA</td>
</tr>
<tr>
<td>IV</td>
<td>Non-perfusion of larger choroidal vessels in early ICGA</td>
</tr>
</tbody>
</table>

**Table 3. Patients with Choriocapillary Perfusion Changes of at Least Grade II or III in ICGA According to Table 2**

<table>
<thead>
<tr>
<th></th>
<th>Day 1</th>
<th>Week 1</th>
<th>Week 4</th>
<th>Month 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 J</td>
<td>83.3</td>
<td>66.6</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td>50 J</td>
<td>61.5</td>
<td>45.5</td>
<td>16.6</td>
<td>0</td>
</tr>
<tr>
<td>25 J</td>
<td>15.4</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Data are expressed as percentages of the total sample.

**Visual Acuity**

Visual acuity monitoring served as a safety precaution for the different protocols. Best-corrected visual acuity using the ETDRS protocol was balanced between the groups at baseline. None of the patients experienced an early severe vision decrease or lost more than 2 lines in 3 months of follow-up.
This study was designed to provide proof of principle that CNV closure may be achieved while avoiding damage to the surrounding physiologic choroid. The data show that an occlusion of the surrounding choriocapillaris is not necessary to achieve closure of the CNV lesion, but that these effects can be separated by choosing an appropriate dosimetry. Achievement of complete CNV closure together with an intact choroidal perfusion is a qualitative observation, a quantitative analysis of different dosages was not intended and further patient enrollment in the 50-J/cm² group was stopped after evidence of a significant photodynamic effect on the choroidal circulation. So far, the only parameters used for the treatment of CNV in AMD are those recommended by the TAP guidelines. The fact that the TAP regimen regularly leads to damage to the physiologic choroid has been demonstrated by ICGA showing early and often persistent nonperfusion of the surrounding choroid, by histology showing a dose-dependent thrombosis of the choriocapillaris, and by immunostaining demonstrating a reactive upregulation of VEGF. However, the present study clearly demonstrates that such consequences are the result of the parameter selection and that such overtreatment effects may be avoided. Selecting optimal parameters allows differentiation between intended effects on the pathologic neovascularu- lature and unwanted effects on the physiologic choroid. Patients treated with a light dose of 25 J/cm² demonstrated, similar to patients treated with a light dose of 50 J/cm², a complete closure of CNV at the 1-day follow-up. However, the choriocapillaris was substantially less affected by treatment with the lower light dose, as seen in early and late ICGA at day 1 and during further follow-up (Figs. 1, 2). No overall difference was seen in the 300- and 600-mW subgroups in the 25-J/cm² regimen. Patients in the 50-J/cm² group, receiving photosensitization 5 minutes after verteporfin infusion tended to have earlier, more, and longer-lasting choroidal changes. A detailed study was performed earlier quantifying the early effects of standard verteporfin therapy by using the same FA and ICGA measurements. Comparing results of the 50-J/cm² protocol with the previous standard regimen study demonstrates that the qualitative sequence of angiographic events is identical with regard to standard infusion therapy or bolus administration.
However, choroidal damage appeared to be inseparable from CNV effects with the standard therapy. Modification of treatment parameters with bolus administration and reduced fluence allowed selective closure of the CNV and less effect on the physiologic choroidal vasculature. Changing treatment parameters appeared not to have a relevant effect on short-term safety. None of the patients in any group lost more than 2 lines of vision over a 3-month follow-up and no closure of retinal vessels was observed.

A selective approach may be particularly useful if earlier retreatment is considered or when other lesion types that are primarily less sensitive to PDT are treated as shown in the VIM study. Combining verteporfin therapy with antiangiogenic and anti-inflammatory therapies is currently in debate. The postulated benefits are a lower CNV recurrence rate after verteporfin PDT, improved durability, inhibition of the verteporfin PDT–induced angiogenic response, and eventually better functional outcomes. In experimental studies, PDT was shown to induce a rapid inflammatory response including infiltration of leukocytes, increased expression of cytokines (e.g., intracellular adhesion molecules [ICAM]-1 and interleukin [IL]-6). This inflammatory response correlates with increased retinal edema detected especially by OCT. Selective verteporfin therapy primarily induces less angiogenic and inflammatory side effects on the level of the choroid and should respond even better to combination therapy. The additional benefit of adjunct therapy provides further evidence to support the hypothesis that outcomes are improved when the collateral side effects are reduced or, ideally, primarily avoided.

Anti-VEGF therapy by intravitreal injection or systemic therapy has shown promising initial results. Adding selective verteporfin therapy may improve angiographic and functional outcomes. However, VEGF is not only a potent angiogenic and permeability inducing factor but is also essential in maintaining normal vascular structures. Inhibiting a physiologic angiogenic response secondary to choriocapillary hypoxia after standard PDT will most likely prevent choriocapillary recanalization and lead to more extensive and persistent choriocapillary closure.

Bolus infusion and reduced light dose in verteporfin therapy have demonstrated an improved selectivity with complete angiographic closure of the CNV and absence of a significant effect on the choroid. Modified parameters in verteporfin ther-
apy should be of particular interest for evaluating the potential of combination therapy of PDT and antiangiogenic drugs.

References