Verteporfin and Intravitreal Triamcinolone Acetonide Combination Therapy for Occult Choroidal Neovascularization in Age-Related Macular Degeneration

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• PURPOSE: To evaluate the efficacy and safety of photodynamic therapy (PDT) with verteporfin combined with intravitreal triamcinolone (IVTA) in occult choroidal neovascularization (CNV) secondary to age-related macular degeneration (AMD).
• DESIGN: Single center, nonrandomized interventional case series.
• METHODS: A prospective, noncomparative, interventional case series of 41 eyes of 41 patients with a two-year follow-up period. Verteporfin PDT was performed using the recommended standard procedure for approved forms of AMD. A solution containing 25 mg of crystalline triamcinolone acetonide was injected intravitreally 16 hours post PDT. The procedure was repeated after three months in case of persistent CNV leakage.
• RESULTS: The mean number of treatments needed was 1.8. Thirty-four eyes (82.9%) required one retreatment at three months. No additional retreatments were necessary. Visual acuity improved gradually in most of the patients with mean values of 20/133 and 20/115 at baseline and three months; 20/101 and 20/84 at six and twelve months; and 20/83 and 20/81 at eighteen and twenty-four months. Eleven of 41 treated study eyes (26.8%) underwent cataract surgery between six and fifteen months after the first treatment. Nine patients required local or systemic glaucoma therapy because of a transient steroid induced intraocular pressure increase.
• CONCLUSIONS: Verteporfin PDT combined with intravitreal triamcinolone may improve the outcome of standard verteporfin PDT in the treatment of occult CNV secondary to AMD. An improvement in visual acuity was observed in most of the treated patients and was maintained during a two-year follow-up period. Retreatment numbers were lower than expected from monotherapy trials. (Am J Ophthalmol 2006;141:638–645. © 2006 by Elsevier Inc. All rights reserved.)

Photodynamic therapy (PDT) with verteporfin is an established therapy in patients with predominantly classic subfoveal choroidal neovascularization (CNV) secondary to age-related macular degeneration (AMD).1–3 PDT with verteporfin is also useful in the treatment of predominantly occult CNV secondary to AMD. The patients who benefited from photodynamic therapy in the Verteportin in Photodynamic Therapy (VIP) Trial were occult with no classic CNV measuring less than four Macular Photocoagulation Study (MPS) disk areas or with visual acuity worse than 20/50 at baseline.4 The treatment is well tolerated and visual loss can often be prevented.4 However, reactivation and persistence of CNV is not uncommon and frequent retreatments may be required.2 Particularly in the subpopulation of purely occult lesions, outcomes may vary. In the overall population of occult lesions in the VIP trial, a mean loss of five lines was observed in PDT-treated eyes compared with a loss of 4 lines in untreated eyes.4,5 Lesions larger than four MPS disk areas had an even worse outcome; severe adverse events with massive vision loss were seen more frequently in this subgroup.4,5

The persistence and recurrence of CNV, requiring frequent retreatments, can compromise the success of therapy. The pathogenesis of CNV is thought to involve not only photodynamic processes, but also oxidative and inflammatory mechanisms.6,7 Such mechanisms include cell mediated inflammation, leukocyte adhesion, leukocyte extravasation, and angiogenesis, features that are similar to but not

Accepted for publication Nov 26, 2005.

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Ursula Schmidt-Erfurth, MD, is an inventor on the patent on the use of verteporfin therapy in ocular neovascular disease under the guidelines of the Wellman Laboratories of Photomedicine, Harvard Medical School, Boston, Institutional Patent Policy and Procedures.

The authors gratefully acknowledge Piotr Szczesny for his scientific expertise and assistance with the statistical analysis.

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0002-9394/06/$32.00
necessarily identical to those of wound healing. Evidence is also increasing that upregulation of vascular endothelial growth factor (VEGF) can be responsible for vascular leakage and neovascularization. While demonstrating therapeutic benefit in controlled clinical trials, PDT itself, by triggering the generation of free radicals and lipid peroxides, may contribute to the oxidation-induced VEGF-expression that has been observed in PDT treated-areas. PDT-induced release of VEGF enhances the decrease in choroidal perfusion and resultant hypoxia associated with the promotion of CNV. Multiple PDT applications, with renewed choroidal alteration and angiogenic stimulation, may trigger more persistent and accelerated regrowth and lesion activity.

Intravitreal administration of a corticosteroid, such as triamcinolone acetonide (TA), has been used for a variety of eye diseases, for example, diabetic macular edema, retinal vein occlusion, uveitis, and AMD. Treatment with intravitreal TA (IVTA) alone was shown to improve visual acuity in patients with exudative AMD with optimal outcomes observed one to three months after treatment. IVTA was also combined with photocoagulation in the treatment of subfoveal recurrence of CNV. More recently, verteporfin PDT with adjunct IVTA was suggested in pilot studies. These studies evaluated the effects of 4 mg intravitreal TA as an adjunct to PDT with verteporfin in the treatment of patients with subfoveal or juxtafoveal CNV. All studies showed beneficial effects regarding visual acuity outcomes. The treatment was well tolerated and no patients experienced severe visual loss. However, patient numbers were small, follow-up was limited, and lesion types were ill defined.

The aim of the present study was to evaluate whether verteporfin PDT combined with IVTA can reduce the number of retreatments needed and improve visual outcomes in patients with purely occult CNV secondary to AMD.

METHODS

PATIENTS SUFFERING FROM OCCULT ONLY CNV SECONDARY TO AMD were included in this prospective interventional case series. Recruitment was consecutive for all patients presenting in a tertiary referral center. Inclusion criteria adhered to the recommendation of the VIP trial regarding angiographic criteria and symptoms of recent disease progression. The complete VIP criteria are: (1) patients with macular degeneration, with subfoveal choroidal neovascularization lesions measuring no greater than 5400 μm in greatest linear dimension with occult with no classic choroidal neovascular, (2) best-corrected visual score of at least 50 (Snellen equivalent of 20/100), and (3) evidence of hemorrhage or recent disease progression. At baseline all patients underwent a standardized ophthalmologic examination including best-corrected visual acuity measurement using Snellen charts, slit-lamp, and fundus examination, as well as intraocular pressure (IOP) measurement. Fluorescein angiography (FA) was performed to identify the lesion type and to assess CNV leakage, using the criteria described previously that included evidence of CNV caused by AMD that extended under the geometric center of the foveal avascular zone. All patients were reevaluated with fluorescein angiography every three months.

Following an oral informed consent, each participant signed a written informed form detailing the experimental character of the triamcinolone procedure. The protocol of the study adhered to the European Good Clinical Practice Guidelines and the Declaration of Helsinki.

PDT with verteporfin (Visudyne, Novartis Ophthalmics, Basel, Switzerland) was performed according to the recommended standard procedure for approved forms of AMD. Within a mean of 17 hours (16 to 18 hours) after PDT, the patients received retrobulbar anesthesia and the ocular surface was disinfected using polyvidone iodine solution. Retrobulbar anesthesia was performed to avoid lens or retinal damage attributable to fixation problems of the patients. According to pathophysiological findings, the induction of oxidative and inflammatory reactions following PDT is necessary for vessel closure. However, this finally leads to enhanced VEGF expression. When starting this case series, the rationale for designing the therapy was
to antagonize PDT side effects after the initiation of biochemical reactions necessary for vessel closure.

Subsequently, 25 mg of preservative-cleared crystalline triamcinolone acetonide (TA), prepared from Volon A, (Triamcinolon-Acetonide, Dermapharm AG, Grünwald, Germany), in a volume of 0.2 ml solution, was administered intravitreally through pars plana injection using a 27 gauge needle. Preservative-cleared TA was prepared by the institutional pharmacy using the method previously described by Jonas and coworkers. To prevent a potentially toxic effect of a vehicle to intraocular tissues, the pharmacy prepared the solu-
tion free of solvent agents or other vehicles. The amount of administered TA was determined by high-performance liquid chromatography measurement immediately following removal of the preservative. After injection of TA, patients were clinically controlled including measurement of IOP at day one, two, and six, and six weeks after injection of TA. These safety time points were not included in the standard observation. In case of CNV leakage, the patients were retreated at three-month intervals using the identical procedure.

The primary efficacy variable was defined as best-refracted visual acuity measured using Snellen charts. The primary efficacy time points were the follow up visits at twelve months and twenty-four months follow-

FIGURE 3. Occult choroidal neovascularization. (Top panel) Fluorescein angiography of a patient presenting with an occult choroidal neovascularization. Visual acuity at baseline was 20/2000. One single course of photodynamic therapy and intravitreal triamcinolone acetonide was performed at the baseline visit. (Bottom panel) Fluorescein angiography (FA) of this patient three months after combination treatment. The lesion appeared hypofluorescent in the early phase FA (Left image); leakage was absent during late phase FA (Right image) and had not recurred by the 24th month. Visual acuity improved to 20/200.
ing the initial treatment. The mean visual acuity data at these follow-up visits were compared with the mean visual acuity at the baseline visit using the paired t test to identify statistical significance.

RESULTS

A TOTAL OF 41 CONSECUTIVE PATIENTS SUFFERING FROM occult CNV secondary to AMD was included into the study. Twenty-four individuals were female and 17 male, and the mean age of the patients was 76.2 ± 5.1 year (mean ± standard deviation, SD, range 66 to 87 years). VIP-criteria were met in all patients except that eyes presenting with a visual acuity lower than 20/200 were also included.4 Twenty-six (63.4%) of the study eyes were phakic and 15 (36.6%) were pseudophakic. The study eye of each of the 41 patients was treated primarily and documented as study eye, the fellow eye was treated in five patients, but data were excluded from the study documentation for the second eye.

Most of the study eyes, 34 of 41 eyes (82.9%) required one additional treatment at three months because of persistent leakage originating from the CNV lesion. Complete resolution of leakage was seen in all eyes by three to six months, and no patient required additional retreatments after the 6-month interval. Thus, the mean number of treatments was 1.83 for the study eye. The median size of lesions before first combination was 3600 μm (range 800 to 7100 μm); 34 of 41 eyes showed persistent leakage after three months. The median size of lesions of these 34 patients was 3200 μm (range 1200 to 4700 μm).

Figure 1 presents data on best-corrected visual acuity (mean, SD) for the study eyes during the two-year follow-up period after the first treatment. The mean visual acuity at baseline was 20/133 (SD 20/57) and significantly (P < .0001) improved to 20/84 at the twelve-month follow-up visit. The improvement in visual acuity was maintained throughout the twenty-four-month follow-up with a mean visual acuity of 20/81 (SD 20/38) at the final visit. Notably, the mean visual acuity at the twenty-four-month visit also represented a significant improvement in comparison with baseline values.

The mean visual acuity of the study eye before treatment was 20/133 (range 20/40 to 20/2000). Visual acuity improved gradually in all of the patients except for nine patients. Mean visual acuity was 20/115, 20/101, 20/89, 20/83, and 20/81 at three, six, twelve, eighteen, and twenty-four months, respectively.

At twelve months, 43% of the 18 patients remained stable (±1 line), after twenty-four months, 41.5% of the 17 patients remained stable. The percentage of patients who improved 3 or more lines was 29.3% (12 patients) at twelve months and 31.7% (13 patients) at twenty-four months. The percentage of patients who gained 6 or more lines at twelve and twenty-four months was 9.8% (4

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**TABLE.** Mean Visual Acuity (Snellen Chart) of Patients With Occult Choroidal Neovascularization Attributable to Age-Related Macular Degeneration Following Combined Therapy With Photodynamic Therapy and Intravitreal Triamcinolone for Each Visit During a Two-Year Follow-Up

<table>
<thead>
<tr>
<th>Visit Duration</th>
<th>Mean Visual Acuity (Snellen Chart)</th>
<th>Standard deviation</th>
<th>Median Visual Acuity (Snellen Chart)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>20/133</td>
<td></td>
<td>20/100</td>
<td>20/40–20/2000*</td>
</tr>
<tr>
<td>3 Months</td>
<td>20/101</td>
<td>20/100</td>
<td>20/80</td>
<td>20/40–20/2000*</td>
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<tr>
<td>6 Months</td>
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<td>20/80</td>
<td>20/80</td>
<td>20/40–20/2000*</td>
</tr>
<tr>
<td>9 Months</td>
<td>20/83</td>
<td>20/80</td>
<td>20/80</td>
<td>20/40–20/2000*</td>
</tr>
<tr>
<td>12 Months</td>
<td>20/81</td>
<td>20/80</td>
<td>20/80</td>
<td>20/40–20/2000*</td>
</tr>
<tr>
<td>15 Months</td>
<td>20/87</td>
<td>20/80</td>
<td>20/80</td>
<td>20/40–20/2000*</td>
</tr>
<tr>
<td>18 Months</td>
<td>20/83</td>
<td>20/80</td>
<td>20/80</td>
<td>20/40–20/2000*</td>
</tr>
<tr>
<td>21 Months</td>
<td>20/82</td>
<td>20/80</td>
<td>20/80</td>
<td>20/40–20/2000*</td>
</tr>
<tr>
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<td>20/83</td>
<td>20/80</td>
<td>20/80</td>
<td>20/40–20/2000*</td>
</tr>
</tbody>
</table>

*Patients who failed to read any letters (counting fingers or hand motion) are arbitrarily assigned to 20/2000.*
patients). No deterioration in visual acuity was observed in any of the patients during the two-year observation period. Figure 2 shows a characteristic finding in a patient suffering from occult CNV treated with IVTA. The patient required one combination treatment, and during twenty-four month follow-up, the lesion became inactive. Accordingly, vision increased from 20/63 to 20/32 and remained stable.

Figure 3 shows a characteristic finding in a patient suffering from occult CNV treated with IVTA. The patient required one combination treatment, and during twenty-four month follow-up, the lesion became inactive. Accordingly, vision increased from 20/2000 to 20/200 and remained stable.

Generally, treatments were well tolerated. Eleven of 41 treated study eyes (26.8%) underwent cataract surgery between months 6 and 15 after the first treatment; 11 of the 26 phakic study eyes (42.3%) underwent cataract surgery. One of these patients was treated with Yttrium Aluminum Garnet (YAG) laser capsulotomy six months after the cataract surgery. Three untreated fellow eyes also had cataract surgery at eighteen to twenty-one months and one untreated fellow eye was treated with YAG laser capsulotomy.

A transient IOP-increase was observed in nine eyes, which was controlled by topical monotherapy in seven patients. Two patients required intermittent systemic therapy using carbonic anhydrase inhibitors. The median IOP was 15 at baseline visit (range 11 to 19 mm Hg), 16 at follow-up visit after three months (range 11 to 34 mm Hg), 15 at follow-up visit after 6 and 9 months (range 10 to 42 mm Hg and 10 to 19 mm Hg, respectively), 16 at follow-up visit after twelve months (range 11 to 20 mm Hg), and 15 at follow-up visits after twenty-four months (range 11 to 18 mm Hg). Complications attributable to the injection procedure such as pseudoendophthalmitis, retinal detachment, retinal tears, or vitreous hemorrhage were not observed.

**DISCUSSION**

**THE PRESENT STUDY ILLUSTRATES THE USEFULNESS OF VERTEPORFIN PDT COMBINED WITH IVTA IN THE TREATMENT OF OCCULT CNV SECONDARY TO AMD.** The treatment course with a mean number of 1.8 treatments needed during a two-year period is favorable. In addition, visual acuity improved in most of the patients, consistent with pilot results from small studies using verteporfin PDT combined with IVTA in other CNV subgroups.17,18 This study includes a well-defined population of eyes with purely occult lesions and clearly demonstrates that the improvement in visual acuity and absence of leakage was maintained throughout the twenty-four-month follow-up visit.

Verteporfin PDT alone is effective in the treatment of occult CNV secondary to AMD, but the number of retreatments necessary for CNV closure was found to be relatively high. For the subgroup of cases with occult with no classic CNV in the VIP trial, verteporfin-treated patients received an average of 3.1 treatments (of a possible total of four) before the follow-up at month twelve and an average of 1.8 in the second twelve months.4 In comparison, a recently published study reports a mean number of 5.6 retreatments in patients with classic subfoveal CNV during a period of two years.2

There are several hypothesis for the persistence of CNV and the need of retreatments after PDT monotherapy. One of the mechanisms of photodynamic action is the production of oxidative radicals, thus enhancing a major pathogenic process of CNV induction. Following PDT, the acute oxidative damage represents a much more powerful reaction than the chronic life-long photodynamic light-induced process that eventually leads to CNV.6 Each PDT retreatment may acutely enhance the long lasting disease process and increase the amount of photoreceptor loss. After the acute phase of the PDT reaction, oxidation- or ischemia-induced expression of VEGF, VEGF receptor 3, and pigment epithelium-derived factor was described in the PDT-treated areas.6 This effect may represent another subacute and longer lasting stimulus for neovascular growth and leakage and induce inflammatory reactions. In experimental studies, PDT was shown to induce a rapid inflammatory response including infiltration of leukocytes, increased expression of cytokines for example, intracellular adhesion molecule (ICAM)-1 and interleukin (IL)-6.19 Following application of PDT using standard parameters to the macula of human eyes, histologic studies have identified thrombotic occlusion of the choriocapillary layer; characteristic hypofluorescence seen in indocyanine green (ICG) angiography was clearly consistent with a thrombosis of choriocapillaries and individual larger vessels.20 Choroidal hypoperfusion and resulting tissue hypoxia may represent an angiogenic stimulus responsible for CNV progression and may be enhanced by PDT-induced release of VEGF.6 Corticosteroids have antiproliferative, anti-inflammatory and angiostatic effects and are known to decrease vascular permeability.21–23 The rationale for the present study was to combine verteporfin PDT with an antiinflammatory and/or antiangiogenic drug thus antagonizing VEGF-expression and inflammatory reactions in the subacute phase following PDT. IVTA alone has been used in a number of conditions, including AMD and macular edema of different origins.14,24 Several approaches have been employed to administer corticosteroids, for example, intravitreal injections, implants, periocular, or systemic administration. Although the mode of action is not fully clarified for IVTA, promising results have been obtained in the treatment of intraocular proliferative, edematous, and neovascular diseases.14–16,25,26 Most studies have reported beneficial effects on visual acuity from the use of either 4 mg or 25 mg IVTA.14–16,25,26 However, in the case of AMD associated with CNV, the effect was mostly anatomical and did not translate into functional improvement: IVTA...
inhibited neovascular growth in an experimental model of laser-induced CNV, a model of limited value for age-related CNV.\textsuperscript{23} In sub- and juxtafoveal CNV eyes, a single IVTA resulted in 55% stabilization, but 33% of eyes experienced vision loss.\textsuperscript{26} In predominantly occult lesions, CNV enlargement was reduced to 31% in the IVTA group compared with 70% growth in the control group with only minor effects on vision outcome.\textsuperscript{25} A single IVTA course in predominantly classic lesions reduced lesion growth, but showed no difference in vision outcome at twelve months.\textsuperscript{27} Following IVTA using a high dose of 25 mg, visual acuity increased after each injection, but the overall effect was transient during follow-up.\textsuperscript{28} Obviously, the effects of IVTA alone are not appropriate to achieve persistent absence of CNV leakage together with vision stabilization or even improvement.

Preliminary experience with combination of PDT and IVTA seems to promise improved visual outcome and lower retreatment rates. Spaide and associates\textsuperscript{18} found that in patients not pretreated with PDT alone, an increase of at least 3 lines was seen in 33% at six months, the mean change in VA was 2.4 lines.

After a mean follow-up of eighteen months, combination therapy resulted in vision gain in 7%, stabilization in 50%, and vision loss in 43% of all patients.\textsuperscript{17} Numbers or retreatment needed to achieve absence of leakage using combination therapy ranged from 1.2 to 2.7, significantly lower than with PDT monotherapy.

In our study population, verteporfin PDT combined with IVTA was well tolerated. However, at the current state it must be highlighted that the use of IVTA in any condition still is experimental and that the experience from its use in various conditions is based on small uncontrolled studies.\textsuperscript{29} Potential complications of IVTA include cataract progression and increased intraocular pressure.\textsuperscript{14,17,25,27,29} Rare cases of endophthalmitis have also been reported after IVTA.\textsuperscript{29,33} This side-effect might be related to the content of alcohol in the original formulation. In a study of commercially available depot corticosteroids, Hida and associates\textsuperscript{34} found that the development of proliferative vitreoretinopathy in some cases could be the result of retinal necrosis and repair processes caused by these vehicles. Concentrations of benzyl alcohol, the preservative in intravitreal triamcinolone, higher than 1 mmol/l have been found to reduced the b-wave in electroretinography.\textsuperscript{35} When alcohol was extracted before intravitreal administration in our study, endophthalmitis or even mild inflammation did not occur at all. In the present study, 26.8% of the study eyes underwent cataract surgery between six and fifteen months after the first combined treatment. In the pilot study by Rechtman and coworkers using 4 mg intravitreal TA , three out of six phakic eyes developed cataract.\textsuperscript{17} In another study with 4 mg IVTA and laser treatment, no significant effect on cataract progression was observed.\textsuperscript{16} In our series, nine patients suffered from a transient increased IOP due to the intravitreal corticosteroid. This increase could be controlled by topical monotherapy or short-term systemic therapy. Published studies have reported elevation in intraocular pressure in 30% to 50% of patients treated with IVTA during the first three months after the injection.\textsuperscript{31,32} The corticosteroid-induced elevation in intraocular pressure can usually be controlled with topical medication.\textsuperscript{31} In comparison, the incidence of cataracts in the Treatment of AMD in Photodynamic Therapy (TAP) investigation, was 14.9% for verteporfin-treated patients compared with 15.0% for patients receiving placebo (P = 1.00); in the VIP AMD trial, the incidence of cataracts was 13.3% and 8.8% in verteporfin- and placebo-treated patients, respectively (P = .285).\textsuperscript{36}

This interventional case series had several limitations, including lack of standardized protocol refractions/visual acuity testing, lack of randomization, and absence of a control group. Without a control group, the number of patients who may have improved or remained stable without treatment can not be determined.

In conclusion, there is a need for more effective new treatments of occult CNV secondary to AMD. If verteporfin monotherapy is being used, the need for multiple retreatments is a significant concern. Future treatments are likely to include combinations of PDT with corticosteroids, angiostatic corticosteroids, or antiangiogenic/anti permeability drugs. Prospective, randomized, and controlled studies are needed to further evaluate the benefit of combination strategies (Table).

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Biosketch

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