Verteporfin Therapy Combined with Intravitreal Triamcinolone in All Types of Choroidal Neovascularization due to Age-Related Macular Degeneration

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Objective: To evaluate the efficacy and safety of photodynamic therapy with verteporfin combined with intravitreal triamcinolone in choroidal neovascularization secondary to age-related macular degeneration (AMD).

Design: Prospective, noncomparative, interventional case series.

Participants: One hundred eighty-four patients undergoing treatment for neovascular AMD at one retinal referral center.

Methods: One hundred eighty-four eyes of 184 consecutive patients (63.6% female, 36.4% male) with a mean age of 76.5 years and a follow-up of a median of 38.8 weeks (range, 12–103) were included in a case series. One hundred forty-eight (80.4%) patients had subfoveal choroidal neovascularization, 19 patients (10.3%) had juxtafoveal choroidal neovascularization, and 17 patients (9.2%) had extrafoveal choroidal neovascularization. Verteporfin photodynamic therapy was performed using the recommended standard procedure. A solution containing 25 mg of triamcinolone was injected intravitreally 16 hours after photodynamic therapy in 184 patients. The combined therapy procedure was repeated at the 3-month follow-up visits whenever persistent choroidal neovascularization leakage was documented angiographically.

Main Outcome Measures: Mean change in best-refracted visual acuity (VA) between baseline and the last visit, and number of treatments necessary to achieve absence of leakage.

Results: Visual acuity improved in the majority of patients (baseline VA, mean 20/125) by a mean increase of 1.22 Snellen lines and 1.43 lines using laser interferometry \( (P<0.01) \). The mean number of required treatments was 1.21. Twenty-three eyes (12.5%) required 2 treatments, 6 eyes (3.26%) required 3 treatments, and 1 eye (0.5%) required 4 treatments. The combination treatment including laser and intravitreal steroid administration was well tolerated. Forty-six patients (25%) required glaucoma therapy due to a transient steroid-induced intraocular pressure (IOP) increase. Twelve patients (6.5%) were on topical medication for preexisting glaucoma. Two patients (1%) whose IOP increase could not be controlled with topical therapy required surgery.

Conclusions: Verteporfin photodynamic therapy combined with intravitreal triamcinolone may improve the outcome of standard verteporfin photodynamic therapy in the treatment of choroidal neovascularization secondary to AMD. A significant improvement in VA was observed in a majority of treated patients and was maintained during the maximum follow-up. In addition, retreatment rates were lower than anticipated. Ophthalmology 2006;113:14–22 © 2006 by the American Academy of Ophthalmology.

Photodynamic therapy with verteporfin was shown to be effective in 2 clinical trials in patients with classic subfoveal choroidal neovascularization secondary to age-related macular degeneration (AMD).1–3 In addition, the Verteporfin in Photodynamic Therapy Study showed that, after 2 years, photodynamic therapy with verteporfin significantly reduced the risk of moderate-to-severe vision loss in patients with occult and no classic choroidal neovascularization after AMD.4 The treatment is generally safe and well tolerated, and substantial vision loss can often be prevented.

The pathogenesis of choroidal neovascularization is multifactorial, involving oxidative and inflammatory events as well as photodynamic processes.5,6 The mechanisms include cell-mediated inflammation, leukocyte adhesion and extravasation, angiogenesis, and matrix deposition and remodeling. These features resemble those of wound healing, although they differ somewhat from the normal tissue repair response.6 There is also increasing evidence that enhanced expression of vascular endothelial growth factor (VEGF) may be responsible for vascular exudation and neovascularization in AMD.5 Photodynamic therapy itself, by triggering the generation of free radicals and lipid peroxides,
may also contribute to the phototoxicity-induced VEGF expression that has been observed in collateral choroids after each photodynamic therapy application.7 Steroids have a number of anti-angiogenic, antiinflammatory, and antipermeability properties that can contribute to the stabilization of the blood-retina barrier, resorption of exudation, and downregulation of inflammatory stimuli (Kaiser PK, unpublished data). Intravitreal administration of corticosteroidlike triamcinolone acetonide (TA) has been used in a host of eye diseases, including AMD, diabetic macular edema, retinal vein occlusion, and uveitis, for its antiinflammatory and anti-angiogenic effects.8 Intravitreal TA monotherapy has been found to increase visual acuity (VA) in patients with exudative AMD,8,9 although these beneficial effects were transient. In addition, intravitreal TA and photocoagulation were used successfully in the treatment of subfoveal recurrence of choroidal neovascularization.10 Other studies using intravitreal TA monotherapy did not show a similar effect.11,12

A number of pilot studies have investigated the use of verteporfin photodynamic therapy in combination with intravitreal TA (Table 1).13,14 These studies have evaluated the effects of 4 mg of intravitreal TA after verteporfin photodynamic therapy in patients with subfoveal or juxtapfoveal choroidal neovascularization. All of these studies reported positive VA outcomes and were associated with a cessation of fluorescein leakage on angiography. The combination was well tolerated, with treatable adverse effects such as cataract progression and a transient increase in intraocular pressure (IOP). However, there were few patients in these studies, follow-up was limited, and lesion types were not well defined. Thus, this therapeutic approach, though promising, warrants further investigation. The aim of the present study is to provide preliminary efficacy and safety data to help determine whether verteporfin photodynamic therapy combined with intravitreal TA can improve VA and reduce the overall number of treatments in patients with choroidal neovascularization secondary to AMD.

### Materials and Methods

Patients with all types of choroidal neovascularization secondary to AMD were included in this prospective interventional case series. Recruitment was drawn from patients who presented at a tertiary referral center. At baseline, all patients underwent a standardized ophthalmological examination, including VA measurement using Snellen charts, slit-lamp and fundus examination, and assessment of IOP. Intraocular pressure was determined weekly until 4 weeks, then in 6-week intervals. Fluorescein angiography (FA) was performed to identify lesion type and location and to determine whether active choroidal neovascularization leakage was present. Laser interferometry was used successfully to determine retinal function before cataract surgery due to the ability to circumvent lens opacities.15 All patients were reevaluated every 12 weeks.

After oral informed consent was given, each participant signed a written consent form, which described the experimental nature of the triamcinolone procedure and potential risks. The study protocol adhered to the European Good Clinical Practice Guidelines and the Declaration of Helsinki.

Photodynamic therapy with verteporfin (Visudyne, Novartis Ophthalmics, Basel, Switzerland) was performed according to the recommended standard procedure.1,2 Within a mean of 16 hours after photodynamic therapy (±1.5 hours), patients received retrobulbar anesthesia, and the ocular surface was disinfected using polyvidone iodine solution. Retrobulbar anesthesia was used to exclude eye movements and to avoid lens or retinal damage due to fixation problems of the eye. Twenty-five milligrams of preservative-free crystalline TA (prepared from Volon A, Triaminolon-Acetonide, Dermapharm AG, Gruenwald, Germany) in a volume of 0.2-ml solution, was administered intravitreally through pars plana injection using a 27-gauge needle. Preservative-free TA was prepared by the institutional pharmacy using the method previously described by Jonas et al.8 The actual dose of administered TA was determined by high-performance

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**Table 1. Pilot Studies of Verteporfin Photodynamic Therapy–Intravitreal Triamcinolone Acetonide**

<table>
<thead>
<tr>
<th>Author</th>
<th>No. of Patients</th>
<th>Visual Acuity Change</th>
<th>Follow-up</th>
<th>Retreatment Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spaide et al*</td>
<td>12</td>
<td>2.4</td>
<td>6 mos</td>
<td>1.08</td>
</tr>
<tr>
<td>Spaide et al*</td>
<td>11</td>
<td>0.1</td>
<td>6 mos</td>
<td>0</td>
</tr>
<tr>
<td>Spaide et al†</td>
<td>13</td>
<td>2.5</td>
<td>12 mos</td>
<td>1.24</td>
</tr>
<tr>
<td>Spaide et al†</td>
<td>13</td>
<td>0.44</td>
<td>12 mos</td>
<td>1.2</td>
</tr>
<tr>
<td>Rechtman et al‡</td>
<td>14</td>
<td>7% gained ≥30 letters</td>
<td>18 mos</td>
<td>2.57</td>
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<tr>
<td></td>
<td></td>
<td>50% were stable</td>
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<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>14% lost 15–29 letters</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>29% lost ≥30 letters</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Roth et al§</td>
<td>73</td>
<td>74–87% stable or improvement of VA</td>
<td>Up to 6 mos</td>
<td>Up to 35% required one additional treatment</td>
</tr>
</tbody>
</table>

VA = visual acuity.


liquid chromatography measurement. The injection was performed using magnifying glasses and with dimmed room light; any direct light exposure of the treated eye was avoided. All injections were administered in the operating room. A paracentesis was not required for any of the procedures.

Patients were scheduled for follow-up visits in 3-month intervals and underwent identical examination procedures, including best-refracted VA measurement, IOP documentation, slit-lamp and ophthalmoscopic examination, and angiography. If patients showed active choroidal neovascularization leakage at the time of the regularly scheduled 3-month follow-up visits, they were treated using verteporfin and TA as described above.

The primary efficacy variable was defined as change in VA from baseline to the last visit (median follow-up, 38.8 weeks [range, 12–103]) as measured using Snellen VA charts. The mean VA at the final follow-up visit was compared with baseline measures using the paired t test to test for statistical significance.

**Results**

A reduction in leakage was documented angiographically for classic and occult components using Macular Photocoagulation Study and Treatment of Age-Related Macular Degeneration with Photodynamic Therapy criteria. Evaluation was done by an experienced retinologist. The greatest linear diameter was measured if the lesion was judged to be active. Optical coherence tomography measurements were not a requirement in any of the verteporfin studies and were not added to the standard of photodynamic therapy care in this trial. The response to treatment was independent of the location; subfoveal choroidal neovascularization (n = 148) increased in VA by 1.14 lines, and juxtafoveal and subfoveal lesions increased by 1.53 lines. There was no difference in the response regarding predominantly classic, minimally classic, or occult lesions.

One patient (0.5%) had a follow-up of 12 weeks, 3 patients (1.6%) had a follow-up of 16 weeks, and 9 patients (4.9%) were observed for a minimum of 3 months. All other patients were observed for 6 months and longer. The average change in vision in this group with extended follow-up was an increase of 1.2 Snellen lines.

**Visual Outcome and Treatment Rate**

A total of 184 patients with choroidal neovascularization secondary to AMD were included in the study. The study eye of each of the 184 patients was treated and documented as the study eye. There were 67 males and 117 females, with a mean age of 76.5 years. The mean lesion size was 3553 μm (range, 500–7700); in 21 patients, the lesion size was ≥5400 μm (range, 5500–7700).

The locations of the lesion as determined by FA were subfoveal in 148 eyes (80.4%), juxtafoveal in 19 eyes (10.3%), and extrafoveal in 17 eyes (9.2%). The mean VA at baseline was 20/125 (range, counting fingers–20/32).

Figure 1 presents data on the change in VA measured on Snellen charts from baseline to the time of the last follow-up visit and the change in VA as measured with laser interferometry. There were significant mean increases in VA at both temporal end points of 1.22 lines (P < 0.01) and 1.43 lines using the Snellen chart and laser interferometry (P < 0.01), respectively. The 148 patients with subfoveal choroidal neovascularization experienced a significant mean increase of 1.14 lines (P < 0.01), and the 36 eyes with either juxtafoveal or extrafoveal choroidal neovascularization reported an even greater significant mean gain of 1.53 lines (P < 0.05).

The majority of patients (n = 154 [83.69%]) required only 1 combination treatment. Twenty-three patients (12.5%) received 2 combination treatments, 6 (3.26%) received 3 treatments, and 1 patient (0.5%) received 4 treatments, due to persistent leakage from the choroidal neovascularization lesion. The mean number of combination treatments was 1.21 for the study eye.

One hundred twenty-seven eyes met the eligibility criteria for the Treatment of Age-Related Macular Degeneration with Photodynamic Therapy study. The mean baseline VA of this specific group was 20/160. The mean increase in VA was 1.16 lines (P < 0.01), and the mean increase in VA using laser interferometry was 1.35 lines (P < 0.01). A mean number of treatments of 1.26 was necessary. For lesions larger than 5400 μm, the entire lesion plus a safety margin of 1000 μm was covered by the treatment spot.

**Response in Different Lesion Types**

Lesions responded in a uniform pattern to the combination treatment. Independent of lesion composition and lesion size, leakage resolved most intensively after the first administration; residual exudation disappeared with additional treatments. In predominantly classic lesions, leakage subsided after a single treatment (Fig 2). In minimally classic lesion types, both the classic and the occult component responded (Fig 3). In lesions with retinal angiomatous proliferation, the retinal angiomatous proliferation complex became dry, and exudation into the surrounding tissue resolved completely (Fig 4).

Serous detachments of the retinal pigment epithelium (RPE) disappeared over the course of several weeks (Fig 5). In combined
lesions of retinal angiomatous proliferation and a vascularized RPE detachment (Fig 6), a granular pattern of window defects without any leakage was seen after a single photodynamic therapy. Juxtafoveal lesions became inactive, without further growth towards the center of the fovea.

Ophthalmoscopically, there was no difference seen compared with features known from verteporfin monotherapy. The retinal transparency improved with resolving subretinal and intraretinal fluid; no hemorrhage occurred in any of the treated eyes. Angiographically, the classic component of the choroidal neovascularization lesion became more mature in appearance, with larger vessel diameters and less capillary leakage. The occult component stopped leaking, and a slight granular RPE pattern associated with chronic occult lesions was noted by FA. The fibrotic neovascular branches were well perfused, but did not leak fluid during follow-up. Once absence of leakage was achieved, no recurrence was noted. The RPE remained unchanged; no signs of increasing atrophy were seen clinically. Choriocapillary perfusion was unremarkable by standard FA, and retinal perfusion was not impaired.

When treatment effects were related to lesion size, the mean improvement in VA was statistically significant in lesions smaller

Figure 2. At baseline, a small subfoveal lesion with predominantly classic composition is delineated in early fluorescein angiography (FA) (A) and demonstrates intensive exudation in late FA (B). After one combination treatment, the lesion is inactive, without neovascular features, in early (C) and late (D) FA. Visual acuity increased from 20/40 to 20/25 over 12 months.
than 4000 μm, whereas larger lesions maintained stable vision, but the improvement was not statistically significant.

Safety

The treatment was generally well tolerated. Overall, 46 patients (25%) who did not have an increase in IOP (>25 mmHg without medication) at baseline required the use of topical antiglaucoma- tous therapy due to a transient steroid-induced increase in IOP. Twelve of those 46 patients had received IOP-lowering medication already before their AMD treatment due to preexisting glaucoma.

Two patients whose IOP could not be controlled by topical treatment underwent a successful cyclodestructive procedure and now have their IOP controlled without additional treatment. Cyclodestruction was considered a reliable and riskless procedure in the elderly population; a single topical medication was used in all patients. Prostaglandin agents were avoided because of the potential proinflammatory activity. All 12 patients (6.5%) who had preexisting glaucoma continued their usual medication. Intraocular pressure was controlled and documented below 25 mmHg. No glaucoma patient experienced a decompensation of IOP.

Figure 3. In a minimally classic lesion, the area of the classic component identified early during fluorescein angiography (FA) (A) demonstrates more intensive leakage than the occult portion in late FA (B). At 18 months and after a single treatment, the lesion appears inactive in early FA (C) and with staining in late FA (D). Vision was 20/100 at baseline and returned to 20/40 during the entire follow-up.
In the present study, 31.5% (48.73% of the phakic eyes) of the treated eyes experienced cataract progression or underwent cataract surgery during the mean follow-up period of 43 weeks. No patient experienced inflammation or endophthalmitis.

**Discussion**

Our results suggest that verteporfin photodynamic therapy combined with intravitreal TA is beneficial in the treatment of all choroidal neovascularization subtypes secondary to AMD in our patient population regarding VA outcomes and the need for retreatment.

Visual acuity improved in the majority of patients, consistent with the results of small studies using verteporfin photodynamic therapy combined with intravitreal TA in various choroidal neovascularization subgroups. Intravitreal triamcinolone combined with photodynamic therapy for choroid neovascularization associated with age-related macular degeneration. Paper presented at: Association for Research in Vision and Ophthalmology Annual Meeting, April 27, 2004; Fort Lauderdale, Florida. Additionally, the mean number of treatments needed during a mean follow-up period of 43 weeks was a low 1.21. This study includes a population of eyes with all types of choroidal neovascularization and clearly demonstrates the improvement in mean VA through the follow-up period of up to 103 weeks. There was no significant change in mean VA beyond the 6-month interval, as lesions were generally inactive after a mean of 1.21 treatments. The VA increase observed was achieved during early follow-up and demonstrated a plateau during extended follow-up. Therefore, the length of follow-up is not considered to have an important influence on outcome. Limitations of this study are clearly its interventional character, noncomparative nature, and variability in follow-up. However, because this is the largest case series available so far, the information provided may be used to design subsequent comparative prospective studies.

To study the mechanism of combination therapy in more detail, further studies may address issues such as quantification of leakage by angiography or optical coherence tomography measurements of lesion growth and other anatomical features.
Verteporfin photodynamic therapy alone is effective in the treatment of choroidal neovascularization secondary to AMD. However, the number of retreatments necessary for persistent choroidal neovascularization closure was found to be as high as 5.6 over 2 years in a recent study of classic subfoveal choroidal neovascularization. There are several hypotheses for the persistence of choroidal neovascularization and the need for additional treatments after photody-

Figure 5. A. Baseline fluorescein angiography images demonstrate a small occult component centrally associated with a large serous pigment epithelial detachment (PED) in the upper portion of the lesion. B. Exposure of the central component to one standard photodynamic therapy and intravitreal triamcinolone leads to resolution of leakage and disappearance of the PED within 3 months. C. Resolution of leakage and a stable angiographic appearance are maintained throughout 18 months’ follow-up. Visual acuity has recovered from 20/125 to 20/50.

Figure 6. A deep retinal angiomatous complex (A) is embedded within a fibrovascular pigment epithelial detachment (PED) (B); vision is reduced to 20/100. C. After one treatment, the retinal angiomatous proliferation (RAP) component has disappeared, as seen on the 3-month angiogram. The lesion remains inactive throughout follow-up, and visual acuity of 20/63 is documented at the 12-month visit. D, The RAP component is absent in early fluorescein angiography (FA). E, No leakage is seen during late FA.
namic monotherapy. One of the mechanisms of photodynamic action with verteporfin is the production of free radicals, which are themselves part of a major pathogenic process of choroidal neovascularization induction. Further, after the initial stages of the photodynamic therapy reaction and oxidation- or ischemia-induced (and oxidation-induced) expression of VEGF, VEGF receptor 3 and pigment epithelium–derived factor can occur in the photodynamic therapy–treated areas. This effect may result in another, longer lasting stimulus for neovascular growth and leakage. In experimental studies, photodynamic therapy was shown to induce a rapid inflammatory response, including infiltration of leukocytes and increased expression of cytokines (e.g., intracellular adhesion molecule 1, interleukin 6). An interval of 18 hours between verteporfin photodynamic therapy and application of intravitreal TA was selected because a complete establishment of the inflammation cascade requires about 16 hours.

Corticosteroids have antiproliferative, antiinflammatory, and angiostatic effects and the ability to reduce vascular exudation. The rationale for the present study was to combine verteporfin photodynamic therapy with an appropriate antiinflammatory and anti-angiogenetic drug to antagonize VEGF expression and inflammatory reactions in the subacute phase after photodynamic therapy. Although the mode of action of TA is not known with certainty, promising results have been obtained with intravitreal TA alone in the treatment of various intraocular proliferative, edematous, and neovascular diseases.

The majority of studies have reported beneficial effects on VA from the use of either 4 mg of intravitreal TA or 25 mg of intravitreal TA. However, in the case of AMD associated with choroidal neovascularization, the effect was mostly anatomical and did not translate into functional improvement. Intravitreal TA inhibited neovascular growth in an experimental model of laser-induced choroidal neovascularization, a model of limited value for age-related choroidal neovascularization. In patients with subfoveal and juxtapfoveal choroidal neovascularization, a single administration of intravitreal TA resulted in 55% stabilization, but 33% of eyes experienced vision loss. In predominantly occult lesions, 69% in the intravitreal TA group had stable or improved lesions on fundus FA, compared with 29% in the control group, with only minor effects on vision outcome. A single 4-mg intravitreal TA injection in classic choroidal neovascularization lesions reduced lesion growth at 3 months but showed no significant difference in lesion growth or vision outcome at 12 months. After using a high dose of 25 mg of intravitreal TA in a single patient with occult choroidal neovascularization, VA improved after each injection but tended to reduce to the baseline VA with time. It thus seems that intravitreal TA alone is not effective in achieving persistent absence of choroidal neovascularization leakage or even vision stabilization.

Early results of using a combination of photodynamic therapy and intravitreal TA suggest the potential to improve visual outcomes while reducing treatment rates. Spaide et al reported that, in 13 patients with various choroidal neovascularization subtypes and not pretreated with photodynamic therapy, the mean change in VA was an improvement of 2.4 lines, with only 1 patient requiring additional treatment. In addition, Rechtman et al showed that, after a median follow-up of 18 months in 14 patients with various choroidal neovascularization subtypes, combination therapy resulted in vision gain in 7%, stabilization in 50%, and vision loss in 43% of all patients, with a treatment rate of 2.6 during the first year. Another obvious benefit is the lower number of retreatments necessary, 1.2, versus 5.6 in the Treatment of Age-Related Macular Degeneration with Photodynamic Therapy trial. However, these differences should be evaluated in a randomized trial.

We observed that verteporfin photodynamic therapy combined with intravitreal TA was well tolerated. However, it must be emphasized that the use of intravitreal TA is still experimental and that the experience from its use in various conditions is based on small uncontrolled studies. Potential complications of intravitreal TA include cataract progression, increased IOP, and, rarely, endophthalmitis.

Rechtman et al, using 4-mg intravitreal TA, observed that 3 of 6 phakic eyes developed cataract. In another study with 4-mg intravitreal TA and laser treatment, no significant effect on cataract progression was observed. The expected rate of cataract development in this elderly patient population should also be kept in mind when evaluating the risk of cataract progression with intravitreal TA. Transient increase in IOP was observed de novo in 34 patients (18.4%) in our study, whereas 12 patients (6.5%) were already undergoing treatment for raised IOP. The transient increase in IOP was controlled by topical antiglaucoma medications, although 2 patients required surgery for persistent increased IOP. Our results are consistent with previous studies, which have observed elevated IOP in 25% to 50% of patients treated with intravitreal TA and were usually controlled with topical medication alone.

The rarely reported adverse effect of noninfectious endophthalmitis has been attributed to the content of benzyl alcohol in the original formulation of TA. We did not observe any form of endophthalmitis or even mild inflammation in our study, probably because we removed the alcohol before intravitreal TA administration.

In conclusion, there is a need for more effective therapeutic options for choroidal neovascularization secondary to AMD. With monotherapy, using either verteporfin photodynamic therapy or one of the anti-VEGF therapies currently approaching regulatory approval, the need for multiple retreatments and the lack of significant improvement in vision are major concerns. Therefore, future treatments are likely to include combinations of verteporfin photodynamic therapy with corticosteroids, angiostatic steroids, or anti-angiogenic/antipermeability drugs. Our results, which showed improved VA for the majority of patients and a reduced need for additional treatments, are consistent with those reported in previous publications. We recommend that prospective, randomized, controlled studies be conducted to confirm our observations.
References


