Photodynamic Therapy With Verteporfin in Subfoveal Choroidal Neovascularization Secondary to Central Serous Chorioretinopathy

Erdem Ergun, MD; Michael Tittl, MD; Michael Stur, MD

Objective: To examine the efficacy and safety of photodynamic therapy with verteporfin in the treatment of subfoveal choroidal neovascularization secondary to central serous chorioretinopathy (CSC).

Design: Prospective interventional, noncomparative case series.

Methods: After the diagnosis of a subfoveal choroidal neovascularization secondary to CSC, 26 eyes of 24 patients were treated with photodynamic therapy with verteporfin. Patients were then followed up every 2 to 3 months, with further treatments performed as deemed necessary through fluorescein angiography. The mean observation was 22.2 months (range, 6-36 months; median, 24 months).

Results: There was marked visual improvement, with patients gaining a mean of 1.6 lines after 1 year and a mean of 2.2 lines after 2 years. There was a statistically significant change in visual acuity from baseline to 12 and 24 months (mean difference, –0.16, P=.03; and mean difference, –0.22, P=.02; respectively; t test for both). There was no correlation between patients' age or greatest linear dimension of the lesions and the final outcome (P>.10 for all). No patient experienced any adverse effects.

Conclusion: Photodynamic therapy with verteporfin resulted in a beneficial outcome in the treatment of subfoveal choroidal neovascularization secondary to CSC, without serious adverse effects in this case series.


CENTRAL SEROUS CHORIORETINOPATHY (CSC) is a disease that typically affects middle-aged adults and involves the sensory retina, retinal pigment epithelium (RPE), and choroid. Patients usually have mild visual loss. This generally resolves without therapy, although the disease can become chronic, with ensuing RPE decompensation. Some patients, particularly older adults, can develop choroidal neovascularization (CNV), which leads to a severe loss in visual acuity.

Photodynamic therapy (PDT) with verteporfin is a new method for the treatment of subfoveal CNV in various diseases. Briefly, patients with a subfoveal CNV receive an infusion with verteporfin. Thereafter, the CNV is treated with a modified diode laser (689 nm). Besides conventional thermal laser therapy, this is the only method for the treatment of CNV that has a proven efficacy in large, multicenter, randomized clinical trials.

The fact that these clinical trials were efficacious and had few treatment-related adverse effects led us to examine the efficacy of PDT as a treatment for subfoveal CNV secondary to CSC, as there has hitherto been no proven treatment for this disorder. Because most patients are young and typically active in the workforce (so-called type A personalities), rehabilitation of these patients is particularly important.

METHODS

Twenty-six eyes of 24 patients were treated. The age range was 36 to 78 years (mean ± SD, 57.0 ± 13.0 years; median, 55 years). Nineteen eyes from men and 7 from women were treated.

All patients were examined for best-corrected Snellen visual acuity and underwent a dilated fundus examination and fluorescein and indocyanine green (ICG) angiography. Patients with subfoveal CNV defined on a fluorescein or ICG angiogram were treated according to treatment guidelines. Informed consent was received from each patient before treatment, and institutional review board approval was obtained.

All patients were seen at 2- to 3-month intervals, and Snellen visual acuity examination, dilated fundoscopy, and fluorescein or ICG angiography were repeated at each visit. The diagnosis of CSC was based on the patient’s history and typical fluorescein angiographic and ICG

From the Departments of Ophthalmology, University of Vienna Medical School (Drs Ergun and Stur) and Danube Hospital (Dr Tittl), Vienna, Austria. The authors have no relevant financial interest in this article.
After 2 years, 9 (47%) of 19 eyes had an improvement of 3 lines or more. Eight (42%) of 19 had stable visual acuity (within 2 lines), and 2 (11%) of 19 had lost 3 lines or more. The mean ± SD gain was 0.22 ± 0.37 logMAR units, or more than 2 lines. Figure 1 shows the changes in visual acuity throughout the treatment.

The greatest linear dimension (GLD) of the CNV was 2225 ± 4 μm before treatment. The GLD remained virtually unchanged during treatment; the mean GLD at the last treatment was 2410 μm. However, 11 patients required only 1 treatment. None of the patients showed any leakage on fluorescein angiography at their last follow-up.

There was a statistically significant difference in the change in mean logMAR values from baseline at 12 and 24 months (mean difference, −0.16, P = .03; and mean difference, −0.22, P = .02), that is, patients gained 1.6 and 2.2 lines, respectively, although there was no statistically relevant change at 6 months (mean difference, −0.10; P = .07). Interestingly, neither patient age nor GLD of the lesion correlated with the change (gain or loss) in visual acuity after 1, 12, and 24 months (P > .10 for all) (Table). However, baseline visual acuity correlated with the change in visual acuity at 12 and 24 months. These results were confirmed on regression analysis. Furthermore, there was a statistically significant correlation between the change at 6 months and the changes at 12 and 24 months (R² = 0.87, P < .001; and R² = 0.59, P = .04; respectively).

The mean number of treatments needed per patient was 2.6 (range, 1-7; median, 2). In the first year, a median of 2 treatments was necessary; in the second, the median number was 1. None of the patients experienced adverse effects. No photosensitivity reaction was seen.

Figure 2A-C shows images from a typical patient with CSC and CNV. Before PDT, the visual acuity was 20/200 OS. The red-free image and the fluorescein angiogram show an active CNV lesion. After 2 years, the visual acuity was 20/22 OS, and angiograms show an inactive CNV (Figure 2D-F). The patient had 3 treatments with PDT.

This study shows that PDT is a beneficial treatment for subfoveal CNV secondary to CSC. More than three quarters of all patients have stable or better visual acuity 2 years after beginning treatment. Because some patients were lost to follow-up, it is possible that there is a bias to the treatment benefit, with those losing visual acuity not coming back. However, the results indicated that most patients had at least stable visual acuity, which minimizes any possible bias, in our opinion.

Conventional laser therapy offers a proven benefit in the treatment of CNV, particularly in lesions that are outside the center of the foveal avascular zone (extrafoveal or juxtafoveal) and in small, well-demarcated classic CNV lesions that are located subfoveally. However, subfoveal treatment leads to an immediate, marked loss of visual acuity as the overlying neurosensory retina is damaged, and extrafoveal and juxtafoveal CNVs treated with laser can also have a subfoveal recurrence. Most patients treated with PDT experience a less dramatic loss of vision, and some describe a subjective improvement.
in visual acuity that cannot be seen on an objective vision examination. Furthermore, as seen in the Treatment of Age-Related Macular Degeneration With Photodynamic Therapy (TAP) study, contrast sensitivity is much better in patients treated with PDT. This makes it a viable alternative in routine clinical practice.

Central serous chorioretinopathy has a heterogeneous course. Most cases resolve spontaneously without any treatment. However, some persons, particularly older patients, develop chronic disease, leading to decompensation of the RPE and other complications. One study demonstrated in older patients that CNV, persistent pig-

<table>
<thead>
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<th>Variable</th>
<th>6 mo</th>
<th>12 mo</th>
<th>24 mo</th>
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<tbody>
<tr>
<td>Age</td>
<td>$R^2 = 0.03$, $P = .90$</td>
<td>$R^2 = 0.11$, $P = .61$</td>
<td>$R^2 = 0.003$, $P = .99$</td>
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<tr>
<td>Lesion size, µm</td>
<td>$R^2 = 0.11$, $P = .60$</td>
<td>$R^2 = 0.05$, $P = .83$</td>
<td>$R^2 = 0.11$, $P = .64$</td>
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<td>Baseline visual acuity</td>
<td>$R^2 = 0.38$, $P = .06$</td>
<td>$R^2 = 0.44$, $P = .03$</td>
<td>$R^2 = 0.49$, $P = .03$</td>
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Figure 2. A, Red-free image before photodynamic therapy (PDT), visual acuity 20/200. B, Early-phase fluorescein angiogram before PDT. C, Late-phase fluorescein angiogram before PDT. D, Red-free image 2 years after first PDT, visual acuity 20/22. E, Early-phase fluorescein angiogram 2 years after first PDT. F, Late-phase fluorescein angiogram 2 years after first PDT.
ment epithelial detachment, and the accumulation of subretinal fluid are primary causes of deteriorating visual acuity, aside from the frequent recurrences of CSC. For extrafoveal leaks, focal laser photocoagulation has been advocated, however, this procedure is known to induce CNV.32

The exact cycle of events leading to CSC is still unknown. It is generally accepted that CSC develops primarily as a result of choroidal vascular hyperpermeability, which can be seen on ICG angiography.33,34 This leads to an increase in choroidal tissue hydrostatic pressure, which supersedes that of the retina, thus reducing or stopping solute flow across the RPE. As a result, a serous detachment can occur, as well as a change in the RPE layer that Carvalho-Recchia et al35 have described as a “blowout” of the RPE. It is not clear under what conditions CNV can develop. Our demographic results are, however, similar to those of Spaide et al in that 16 of 24 patients were older than 50 years.

Psychopharmacologic medications, corticosteroid use, and hypertension are risk factors for CSC. Investigations in cultured pigment epithelial cells show that epinephrine can induce apoptosis of RPE cells, although dexamethasone had no effect.39 Stress also plays a major role in this disease, particularly in highly motivated, eager individuals with a type A personality.23 Also, an increased activity of the sympathetic autonomic nervous system has been seen in patients with CSC, which would corroborate these findings.

Why is treatment with PDT in patients with CNV secondary to CSC successful? On the one hand, lesion size might play a role. Although no statistical significance was found in this study, the number of patients is relatively small, which does not rule out an effect in a larger cohort. All patients had a lesion size less than 4000 µm. The effect of lesion size has been shown to be an important factor in the success of PDT, with smaller lesions in age-related macular degeneration receiving more therapeutic benefit.

Age might be an important factor. Investigations in patients with pathologic myopia, which albeit has a different pathophysiology, have shown that younger patients benefit significantly more from therapy than older patients (E.E., unpublished data, 2003). There was no statistical correlation in the present study, but it stands to reason that the occlusive effect of PDT on CNV has a better and more long-standing effect in younger individuals. Similarly, in idiopathic CNV, favorable results have been shown with PDT with verteporfin.10,42

Another reason for the success of PDT in patients with CNV secondary to CSC might be because PDT may also treat the long-standing CSC. Yannuzzi et al and others (F. C. Piccolino, MD, written communication, May 2002) have shown that PDT can improve visual acuity in long-standing CSC. Therefore, our patients might have had a 2-fold advantage: treatment of the disease and the CNV. This might give the method an advantage over other procedures, such as surgery, particularly because it is less invasive.43

Our study also shows that the results after 6 months seem to set the course for further success or failure: ie, patients who experience an improvement after 6 months tend to stay improved and vice versa. This mimics results from the TAP trials for age-related macular degeneration, which have shown that the change in the first 6 months is the decisive period for the final outcome. In conclusion, PDT with verteporfin is a safe and efficacious method for the treatment of subfoveal CNV in CSC. A main issue is the differentiation from other diseases, particularly CNV secondary to age-related macular degeneration and secondary to polypoidal CNV.45 The use of ICG angiography is essential in making the diagnosis.46,47

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Dr Stur was principal investigator in 2 studies of verteporfin (TAP and Verteporfin in Photodynamic Therapy [VIP] trials) and is principal investigator and vice-chair in an ongoing verteporfin study (Verteporfin in Early Retreatment [VER] trial), as well as a permanent member of the Verte-

porfin Studies Advisory Group. Dr Ergun is a coinvestigator in the VER trial.

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Corresponding author: Erdem Ergun, MD, Department of Ophthalmology, University of Vienna Medical School, Allgemeines Krankenhaus, Wachinger Guertel 18-20, A-1090 Vienna, Austria (e-mail: erdem.ergun@akh-wien.ac.at).

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