Photodynamic therapy for inflammatory choroidal neovascularisation unresponsive to immunosuppression

T Leslie, N Lois, D Christopoulou, J A Olson, J V Forrester

Aim: To report on visual and angiographic outcomes of a consecutive series of patients with inflammatory choroidal neovascular membranes (CNV) unresponsive to systemic immunosuppression treated with photodynamic therapy (PDT).

Methods: The medical records of six consecutive patients with inflammatory CNVs that failed to respond to systemic immunosuppression and that later underwent PDT were retrospectively reviewed. Patient demographics, visual acuity, and fluorescein angiographic findings were evaluated.

Results: There were five females and one male with a mean age of 40.8 years (range 35–58 years). Four patients had clinical features consistent with punctate inner choroidopathy and two with presumed ocular histioplasmosis. In all cases clinical signs of CNV activity, including subretinal fluid, subretinal blood, hard exudates, and/or recent decrease in visual acuity were present prior to PDT. All patients had been treated with high dose systemic immunosuppressants, which failed to induce regression of the CNV and/or to improve vision. The CNVs were subfoveal in five patients and juxtafoveal in one; all were classified as predominantly classic. Following PDT an improvement in vision occurred in all cases (median improvement of 18 letters, range 3–42 letters). At last follow up, signs of decreased activity in the CNV were detected in all cases. Patients were followed for a median of 10 months (range 9–20 months).

Conclusion: PDT appears to be a useful option in the management of patients with inflammatory CNVs unresponsive to immunosuppressive therapies.

Punctate inner choroidopathy (PIC) is an idiopathic ocular inflammatory disease first described by Watzke and associates in 1984.1 It usually affects young, myopic women. Small yellow-white lesions at the level of the retinal pigment epithelium (RPE) choroid are seen in the posterior pole and mid peripheral retina, often bilaterally. Once inactive, these lesions leave variably pigmented punched out scars. The anterior segment and vitreous are typically inactive, these lesions leave variably pigmented punched pole and midperipheral retina, often bilaterally. Once pigment epithelium (RPE) choroid are seen in the posterior pole and posterior pole chorioretinal yellow-white lesions associated with choroidal neovascularisation (CNV) and peripapillary atrophy.2 The aqueous humour and vitreous remain free of inflammatory cells. Males and females are equally affected.

In both PIC and POHS, CNV is the major sight threatening complication.4–7 Previous case studies have reported good results in some patients with intensive high dose immunosuppression. However, not all patients respond well to this form of therapy. Furthermore, in some instances, even when an initial good response is observed following this treatment, recurrence of the CNV and visual loss can occur when the immunosuppression therapy is reduced.

Prospective randomised controlled clinical trials have demonstrated the value of photodynamic therapy (PDT) in the treatment of subfoveal CNV secondary to age related macular degeneration8 and degenerative myopia.9 The role of PDT in the management of other causes of subfoveal neovascularisation10–23 remains to be elucidated.

In this report, visual and angiographic outcomes of a consecutive series of patients with inflammatory subfoveal and juxtafoveal CNV secondary to POHS and PIC unresponsive to systemic immunosuppression that were treated with PDT are presented. All patients experienced an improvement in vision after this form of therapy, associated with a decreased activity in the CNV.

METHODS

The medical records of all consecutive patients with inflammatory CNVs treated with PDT at the Medical Retina Service, Ophthalmology Department, Aberdeen Royal Infirmary were retrospectively reviewed. Patient demographics, visual acuity (VA), and fluorescein angiographic findings were evaluated. VA was measured in all patients using Early Treatment Diabetic Retinopathy Study (ETDRS) VA charts and recorded as VA scores, as described in the Treatment for Age related macular degeneration with Photodynamic therapy (TAP) study.4 In all patients, PDT was performed according to TAP guidelines, with the exception that in two patients, the baseline visual acuity was worse than 20/200.8 Patients were reviewed at intervals every three months and retreated if the CNV remained active.

RESULTS

Six White patients—five females and one male—with CNV secondary to PIC (n = 4) or POHS (n = 2) were treated with PDT between December 2000 and September 2003 and were included in this study (table 1). The median age of the patients was 37 years (range 35–58 years).

In all cases, the CNV was classified as predominantly classic and appeared active on fluorescein angiography (early hyperfluorescence and late leakage obscuring the borders of the CNV). In addition, in all cases other clinical signs of CNV activity including recent decrease in visual acuity (n = 5), subretinal fluid (n = 3), subretinal blood (n = 1), and/or hard exudates were present. In all cases, the CNV was treated with high dose systemic immunosuppressants prior to PDT, which failed to induce regression of the CNV and/or to improve visual acuity. The CNVs were subfoveal in five patients and juxtafoveal in one; all were classified as predominantly classic.

Conclusion: PDT appears to be a useful option in the management of patients with inflammatory CNVs unresponsive to immunosuppressive therapies.

Abbreviations: CNV, choroidal neovascularisation; PDT, photodynamic therapy; PIC, punctate inner choroidopathy; POHS, presumed ocular histioplasmosis syndrome; RPE, retinal pigment epithelium; ETDRS, Early Treatment Diabetic Retinopathy Study; VA, visual acuity.
exudates (n = 1) were present. The CNVs were subfoveal in five patients and juxtafoveal in one. The mean greatest linear diameter of the CNV was 1.96 mm (median 1.59 mm, range 1.16–4.08 mm), and the mean area of the CNV was 2.74 mm² (median 1.34 mm², range 0.72–9.35 mm²).

In all patients, the underlying uveitis seemed to be quiescent at the time the CNV developed and the immunosuppressive therapy was started to treat the CNV.

In all cases, the CNV had been treated previously with high dose systemic immunosuppressants, including oral steroids (n = 6), intravenous methyl prednisolone (n = 4), ciclosporin A (n = 3), and tacrolimus (n = 1), which failed to induce regression of the CNV and/or to improve vision (table 1). The following immunosuppressive doses were initially used and then tapered: oral prednisolone 80 mg/day and ciclosporin A 150 mg/twice a day (patients 1 and 3); intravenous methyl-prednisolone 1 g for three consecutive days followed by oral prednisolone 60 mg/day and tacrolimus 1 mg/twice a day (patient 2) or ciclosporin A 150 mg/twice a day (patient 4); and 60–80 mg of oral prednisolone (patients 5 and 6).

Patients 1 to 6 had a CNV for 9, 20, 24, 7, 7, and 3 months, respectively, prior to PDT, and they were immunosuppressed for approximately 9, 14, 2, 5, 1, and 3 months, respectively. In three patients (patients 2, 3, and 4) VA deteriorated despite immunosuppressive treatment; in two patients (patient 1 and 5) VA deteriorated when tapering or stopping immunosuppression.

In one other patient (patient 6) vision improved after immunosuppressive therapy, but it failed to return to normal values (6/6) and the CNV was still active when PDT was offered.

Patients 1, 3, and 4 were still receiving immunosuppressive therapy when PDT was started. In patients 2 and 5 immunosuppression had been stopped 5 months and 3 weeks prior to PDT, respectively. In patient 6, systemic immunosuppression was discontinued at the time of the first session of PDT.

The VA of all patients at baseline and last follow up is shown in table 1. The mean VA score prior to PDT was 27.2 letters (median 26 letters; range 5–61 letters). The mean VA score at last follow up was 46 letters (median 53 letters; range 18–66 letters). Patients improved a mean of 18.8 letters following PDT (median 18 letters; range 3–42 letters). The mean follow up was 12 months (median 10 months; range 9–20 months) (table 1). The mean number of PDT treatments required was 2.5 (median 2; range 2–4). Only patient 6 is still undergoing treatment. No adverse events related to PDT were observed. At last follow up, signs of decreased activity in the CNV clinically (disappearance of subretinal fluid, subretinal blood, and hard exudates) and angiographically (decreased early hyperfluorescence and late leakage) were observed in all cases (figs 1 and 2).

**DISCUSSION**

Treatment of CNV in PIC and POHS has included argon laser photocoagulation,72 42 5 local or systemic steroids and other immunosuppressants,362 62 7 and submacular surgery.3 28–32

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**Table 1** Demographics, previous treatments, CNV characteristics, and visual acuity at presentation and at last follow up in six patients with subfoveal CNV secondary to PIC and POHS treated with PDT

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Age</th>
<th>Sex</th>
<th>Eye</th>
<th>Diagnosis</th>
<th>Previous immunosuppression</th>
<th>CNV location</th>
<th>Size CNV GLD (mm)</th>
<th>Size CNV area (mm²)</th>
<th>Baseline VA</th>
<th>VA at last follow up</th>
<th>Number of PDT treatments</th>
<th>Follow up (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>38</td>
<td>M</td>
<td>R</td>
<td>PIC</td>
<td>Prednisolone; ciclosporin A</td>
<td>Subfoveal</td>
<td>1.54</td>
<td>1.20</td>
<td>20/500 (5)</td>
<td>20/250 (18)</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>36</td>
<td>F</td>
<td>R</td>
<td>PIC</td>
<td>Prednisolone; ciclosporin A</td>
<td>Subfoveal</td>
<td>1.22</td>
<td>0.72</td>
<td>20/160 (28)</td>
<td>20/40 (52)</td>
<td>3</td>
<td>12</td>
</tr>
<tr>
<td>3</td>
<td>41</td>
<td>F</td>
<td>R</td>
<td>POHS</td>
<td>Prednisolone; ciclosporin A</td>
<td>Subfoveal</td>
<td>2.15</td>
<td>2.99</td>
<td>20/126 (32)</td>
<td>20/40 (55)</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>4</td>
<td>35</td>
<td>F</td>
<td>R</td>
<td>POHS</td>
<td>Prednisolone; ciclosporin A</td>
<td>Subfoveal</td>
<td>4.08</td>
<td>9.35</td>
<td>20/250 (13)</td>
<td>20/160 (21)</td>
<td>2</td>
<td>20</td>
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<tr>
<td>5</td>
<td>37</td>
<td>F</td>
<td>L</td>
<td>PIC</td>
<td>Prednisolone; ciclosporin A</td>
<td>Subfoveal</td>
<td>1.16</td>
<td>0.73</td>
<td>20/160 (24)</td>
<td>20/32 (66)</td>
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<td>10</td>
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<tr>
<td>6</td>
<td>58</td>
<td>F</td>
<td>R</td>
<td>PIC</td>
<td>Prednisolone; ciclosporin A</td>
<td>Subfoveal</td>
<td>1.64</td>
<td>1.48</td>
<td>20/32 (61)</td>
<td>20/26 (64)</td>
<td>4</td>
<td>11</td>
</tr>
</tbody>
</table>

VA*, visual acuity: Snellen equivalent (ETDRS VA score); CNV, choroidal neovascular membrane; GLD, greatest linear diameter; ETDRS, Early Treatment Diabetic Retinopathy Study; PDT, photodynamic therapy; POHS, presumed ocular histoplasmosis syndrome; PIC, punctate inner choroidopathy.

**Figure 1** Patient 1. (A) A largely elevated neurosensory retinal detachment associated with marked hard exudation and retinal striae was observed, on slit lamp biomicroscopy, at presentation. (B and C) Fluorescein angiography disclosed early hyperfluorescence and late leakage from a subfoveal choroidal neovascular membrane (CNV). (D) Following photodynamic therapy (PDT) resolution of subretinal fluid and hard exudation associated with the subfoveal CNV was evident clinically, and regression of the CNV was detected on fluorescein angiography (E and F).
A few studies have reported on the outcome of patients with PIC and subfoveal CNV managed with the above treatments. Thus, Flaxel and colleagues\(^\text{32}\) presented a series of 10 eyes (eight patients) treated with high dose oral steroids. In eight eyes improvement or stabilisation of vision occurred, although in two of these VA was 6/60 or less. Olsen and associates\(^\text{33}\) performed submacular surgery in five patients (six eyes), four of whom received systemic or periocular steroids concomitantly. Visual improvement was observed in all cases, with postoperative visual acuities ranging from 20/20 to 20/200. Recurrences were common. Brown and colleagues\(^\text{34}\) reported on three patients treated with subfoveal surgery; two of them had been treated previously with systemic steroids. In all patients final VA was 20/50 or better, but no information regarding follow up and recurrence of CNV was given.

Several studies have reported on the outcome of patients with subfoveal CNV secondary to POHS. In a small (n = 25) pilot randomised controlled trial no statistically significant difference in visual outcome was found between eyes treated with argon laser photocoagulation and untreated eyes.\(^\text{26}\) At one year follow up the VA of patients in both groups had dropped from an average of 20/125 to 20/200. Martidis and colleagues retrospectively reviewed a series of 18 patients treated with either oral prednisolone or sub-Tenons triamcinolone.\(^\text{26}\) Seven patients in the prednisolone group and five in the triamcinolone group showed improvement or stabilisation in vision. Thirteen patients (72%) however, had a final VA of 20/100 or less despite treatment. Thomas et al\(^\text{35}\) presented the clinical outcome of 67 consecutive patients treated with submacular surgery. Twenty six eyes (39%) had received previous laser treatment. VA improved in 34% and stabilised in 49% after a mean follow up of 10.5 months. In 24 patients (36%) VA was < 20/200. CNV recurred in 37% of cases. Other studies have found higher CNV recurrence rates after submacular surgery.\(^\text{36,37}\) The Submacular Surgery Trial is currently underway to clarify the role of this form of therapy in the management of subfoveal CNV in patients with POHS.\(^\text{38}\)

The role of PDT in the management of inflammatory CNV is, to date, unclear. Few case reports and small series have been reported in the literature.\(^\text{14–16, 31–37}\) Thus, Chatterjee and associates described the use of PDT in a patient with PIC and subfoveal CNV.\(^\text{39}\) After five sessions of PDT over a 15 month period, VA remained unchanged at 6/18 with clinical and angiographic evidence of stabilisation of the lesion. Rogers et al\(^\text{34}\) reported on a series of five patients (six eyes) with subfoveal inflammatory CNV managed with PDT. Five eyes had been treated previously with oral prednisolone and three with laser photocoagulation. VA improved in four (67%), remained stable in one (17%), and decreased in one (17%) after a mean follow up of 13.5 months (range 4–33). Sickenberg et al\(^\text{37}\) reported on the use of PDT in one patient with a subfoveal CNV secondary to POHS. After a single session of PDT, vision improved from 20/200 to 20/64, and remained stable for over 5 months follow up. The Verteporfin in Ocular Histoplasmosis study more recently reported the results of a non-comparative, non-randomised study of 26 patients with subfoveal CNV treated with PDT.\(^\text{40}\) VA improved in 14 patients (56%), remained stable in seven (28%), and deteriorated in four (16%). Busquets et al\(^\text{41}\) presented their results in 31 patients (32 eyes) with subfoveal (n = 30) or juxtapfoveal (n = 2) CNV secondary to POHS treated with PDT.\(^\text{42}\) On average, VA improved 0.88 lines after a mean follow up of 28 weeks (range 12–56 weeks).

In the current series, VA improved in all patients following PDT (median of 18 ETDRS letters if improvement). Similarly, in all cases, signs of decreased activity of the CNV were observed. All patients had failed to fully respond to medical treatment with a high dose of steroids and/or other immunosuppressants, suggesting a more aggressive nature of the CNV in these cases. These results appear to compare favourably with previous studies using other treatment modalities.

In two patients in this series VA at baseline was worse than 20/200 (20/250 and 20/500, see table 1). In these patients, and in one other patient with good vision at baseline (20/32), a less marked improvement in vision was achieved following PDT. It is possible that the limited response regarding visual recovery in these patients with poorer vision may be related to more severe damage to photoreceptor cells/RPE present at the time of the first session of PDT.

In patients with PIC and POHS, CNV seems to develop in response to a low grade chronic intraocular inflammation. Thus, one of the mechanisms by which immunosuppressive therapies work in these patients seems to be by reducing or eradicating the stimulus that leads to CNV formation. Although the mechanism of action of PDT is not completely understood, it appears that the excited photosensitiser, which accumulates predominantly in the CNV, generates singlet oxygen and free radicals that cause cellular damage, leading to CNV closure. It could be then hypothesised that in some patients, reducing the stimulus for CNV formation by reducing or abolishing the inflammatory response may not be sufficient to induce CNV regression once the CNV has formed. By acting through a different mechanism, PDT may be successful in these cases. However it is possible that, at least in some patients, the immunosuppressive therapy may
have improved the outcome of PDT by removing the stimulus for CNV growth.

To date, it is unclear which is the best way of treating patients with inflammatory CNVs. It is possible, however, that PDT may be most effective in achieving closure of already formed blood vessels, whereas immunosuppressive therapies may be most efficient during the early stages of endothelial cell migration and proliferation. Therefore, the selection of one or other treatment would be dependant on the stage of development of the CNV, which will vary greatly from patient to patient. In principle, early lesions should respond well to immunosuppression, while formed CNV will require PDT. It would be also expected that most cases should do well with a combination of both forms of therapy.

With one exception, the size of the CNV in the patients included in this series was relatively small. This may have affected favourably the outcome achieved following PDT.

Although the results of this study should be treated cautiously because of its retrospective nature, the lack of a control group, and the small number of patients treated, PDT appears to be a useful option in the management of patients with inflammatory CNVs unresponsive to immunosuppressive therapies.

Authors’ affiliations
T Leslie, N Lois, D Christopoulos, J A Olson, J V Forrester, The Ophthalmology Department, Aberdeen Royal Infirmary, Aberdeen, UK

Correspondence to: Dr N Lois, Retina Service, Ophthalmology Department, Aberdeen Royal Infirmary, Aberdeen, UK AB25 2ZN, UK; noemilois@aol.com

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