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CLINICAL STUDY

Photodynamic therapy combined with systemic corticosteroids for choroidal neovascularisation secondary to punctate inner choroidopathy

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Abstract

Aim **To report on visual acuity (VA) and angiographic outcomes in patients presenting with subfoveal choroidal neovascular membranes (CNV) secondary to punctate inner choroidopathy (PIC), treated with photodynamic therapy (PDT) with verteporfin combined with systemic corticosteroids.**

Methods **A prospective case series of patients with subfoveal CNV secondary to PIC was analysed. All patients were treated with PDT combined with oral prednisolone (1 mg/kg body weight/day) which was started 5 days before PDT. Fluorescein angiography was performed at baseline and every 3 months post-treatment to establish the size, position, and activity of the CNV. Visual acuity was measured using the ETDRS scale. Further PDT treatment was carried out at follow-up visits if there was angiographic evidence of ongoing CNV activity.**

Results **Five female patients with a mean age of 30.4 years (range 25–43 years) were treated over a 12-month period. The mean greatest linear diameter (GLD) of the CNV was 1.66 mm (range 0.46–3.28 mm). A mean improvement in vision of nine ETDRS letters (range −15–20 letters) after treatment was found, which was maintained at final follow-up. The mean follow-up time was 12 months (range 10–14 months). The mean number of PDT treatments was two (range 1–3).**

Conclusions**: The vaso-occlusive effect of PDT combined with the vasostatic and anti-inflammatory effect of systemic oral prednisolone appears to be a safe and effective option in the primary treatment of subfoveal CNV in patients with PIC.**

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Keywords: photodynamic therapy; systemic corticosteroids; choroidal neovascularisation; punctate inner choroidopathy

Introduction

Punctate inner choroidopathy (PIC) is an idiopathic ocular inflammatory disease that usually affects young, myopic women.[1] Small yellow-white lesions at the level of the retinal pigment epithelium (RPE) are seen in the posterior pole and midperipheral retina, often bilaterally. Once inactive, these lesions leave pigmented punched out scars. The anterior segment and vitreous are usually free of inflammation.

Choroidal neovascularisation (CNV) is the major sight-threatening complication in PIC and occurs in 33% of cases.[2] Patients with subfoveal CNV have the worst prognosis and in most cases, the visual acuity (VA) decreases to 6/60 or worse, even with treatment.[2,3] In inflammatory chorioretinal diseases like presumed ocular histoplasmosis syndrome (POHS) that behave and present like PIC, other therapeutic strategies like thermal laser[4] and surgical CNV extraction[5] have been used with limited benefit and a high recurrence rate,[6] for

example, up to 44% after surgical CNV removal.[7] Previous studies have reported some good results in patients treated with intensive high-dose immunosuppression but recurrence of the CNV and visual loss can occur when the immunosuppression therapy is reduced.[3]

Photodynamic therapy (PDT) was first shown to be of benefit in the treatment of subfoveal CNV secondary to age-related macular degeneration[8] Since then, several positive reports on its use in treatment of subfoveal CNV secondary to inflammatory chorioretinal diseases have been published.[9–13] However, all these studies were retrospective reviews of a variety of cases including PIC, POHS, multifocal choroiditis with panuveitis, and serpiginous choroiditis. Some of the cases had been previously treated with laser photocoagulation or systemic immunosuppression before PDT was performed.

In this paper, we present the visual and angiographic outcomes of a prospectively studied consecutive case series of patients with subfoveal CNV secondary to PIC that were treated with PDT combined with systemic oral predinisolone immunosuppression that was started 5 days before PDT.

Methods

In this prospective study carried out at the Kingston Hospital PDT service between March 2005 and March 2006, patients with subfoveal CNV owing to PIC were enrolled and underwent systemic immunosuppression with oral prednisolone (1 mg/kg body weight/day) 5 days before standard PDT treatment with verteporfin. The dose was then reduced by 10 mg every week and tapered altogether by 8 weeks. PDT was performed according to TAP study guidelines.[8] Informed consent was obtained from all patients before treatment.

All patients showed evidence of active exudative maculopathy with subfoveal localisation of the CNV and a recent decrease in VA or occurrence of metamorphopsia. Patients with signs of age-related macular degeneration (AMD), liver diseases, porphyria or other forms of light sensitivity or who were pregnant or breastfeeding were not included in the study.

Visual acuity at the time of first treatment had to be more than five letters on the Early Treatment of Diabetic Retinopathy Study scale (6/60). The greatest linear diameter (GLD) of the lesion had to be not greater than 5.40 mm, and the area of CNV had to be at least 50% of the size of the whole lesion including blocked hyperfluorescence, that is, predominantly classic CNV.

In all cases, fluorescein angiography, fundus photography, VA assessment with ETDRS charts, and binocular fundoscopy were performed before treatment and at each follow-up visit. Follow-up examinations were carried out regularly every 3 months after PDT treatment. Retreatment with PDT was carried out if the CNV remained active. All patients also had measurement of their blood pressure and serum glucose at each follow-up visit while they were on systemic corticosteroid treatment.

Results

Five eyes of five patients were treated in this study. All the patients were women with a mean age of 30.4 years (median 29 years; range 25–43 years). Table 1 summarises that demographics, CNV characteristics, and VA at presentation and at last follow-up, of the patients in the study.

In all cases, the CNV was classified as predominantly classic based on the fluorescein angiography appearance (early hyperfluorescence and late leakage obscuring the borders of the CNV). In addition, other clinical signs of CNV activity included recent decrease in VA ($n=5$), subretinal fluid ($n=4$), and subretinal blood ($n=1$). The mean GLD of the CNV was 1.66 mm (range 0.46–3.28 mm), and the mean area of the CNV was 1.14 mm^2 (range 0.21–2.80 mm^2).

The mean VA before treatment was 28.4 letters (median 25 letters; range 10–47 letters) whereas the mean VA at last follow-up was 38.8 letters (median 46; range

Table 1 Demographics, CNV characteristics, and visual acuity at presentation and at last follow-up

Patient number	*Age*	*Size CNV GLD (mm)*	*Size CNV area (mm^2)*	*Baseline VA. ETDRS letters (Snellen equivalent)*	*VA at last follow-up ETDRS letters (Snellen equivalent)*	*Number of PDT treatments*	*Follow-up (months)*
1	30	1.50	0.50	25 (6/24)	46 (6/9)	2	12
2	43	1.80	1.61	47 (6/9)	65 (6/5)	3	14
3	29	1.27	0.58	10 (6/48)	18 (6/30)	3	12
4	25	0.46	0.21	40 (6/12)	60 (6/6)	1	12
5	25	3.28	2.80	20 (6/30)	5 (6/60)	1	10

Abbreviations: CNV, choroidal neovascular membrane; GLD, greatest linear diameter; ETDRS, Early Treatment Diabetic Retinopathy Study; PDT, photodynamic therapy; VA, visual acuity.

5–65 letters). Patients improved a mean of 8.6 letters (median 11; range –15 to 20 letters). The mean follow-up was 12 months (median 12 months; range 10–14 months). The mean number of PDT treatments was two (median 2; range 1–3). No adverse events related to PDT were seen. At last follow-up, signs of decreased activity in the CNV were observed both clinically (disappearance of subretinal fluid and subretinal blood) and angiographically (decreased early hyperfluorescence and late leakage) in all cases (Figures 1 and 2).

Patient 5 was the only patient who showed a reduction in VA after treatment and had the largest area (2.80 mm^2) and GLD (3.28 mm) of CNV. No further treatment was performed at the 3-month follow-up as a neovascular scar had formed.

Discussion

Treatment of CNV in PIC, to date, has included argon laser photocoagulation,[14] local or systemic corticosteroids or other immunosuppressants,[2,3] and submacular surgery.[15] Both argon laser photocoagulation and submacular surgery have been largely discounted as treatment options for subfoveal CNV in PIC owing to the high rate of CNV recurrence in the surgical group[15] and poor results in the argon laser group.[14]

The use of PDT in the management of subfoveal CNV in PIC has been reported by several authors.[9–13] A literature review reveals a total of 56 cases of CNV caused by inflammatory chorioretinal disease treated with PDT. Of these, 37 cases (66%) had PIC. Table 2 summarises the VA results from some of these reports and compares them with our findings in our series.

The literature contains several retrospective case series of patients with sub- or juxta-foveal CNV owing to inflammatory chorioretinal disease, like PIC, POHS, multifocal choroiditis, treated with PDT. Some cases had been treated with systemic immunosuppression or with laser photocoagulation before treatment with PDT.

Flaxel *et al*[3] reported a series of 10 eyes (eight patients) with CNV owing to PIC who were treated with high-dose oral corticosteroids alone. Eight eyes showed improvement or stabilisation of vision, although in two eyes VA was 6/60 or less. Leslie *et al*[11] reported a series of four eyes from four patients with CNV owing to PIC that were treated with PDT. All four patients were treated with immunosuppression that was started between 3 and 9 months before receiving PDT. Two patients were still receiving immunosuppression when PDT was started. All four eyes showed a mean improvement in VA of 20 letters after a mean follow-up of 10.8 months. In this study, after a mean follow-up of 12 months, the majority of patients (80%) with CNV owing to PIC showed a mean

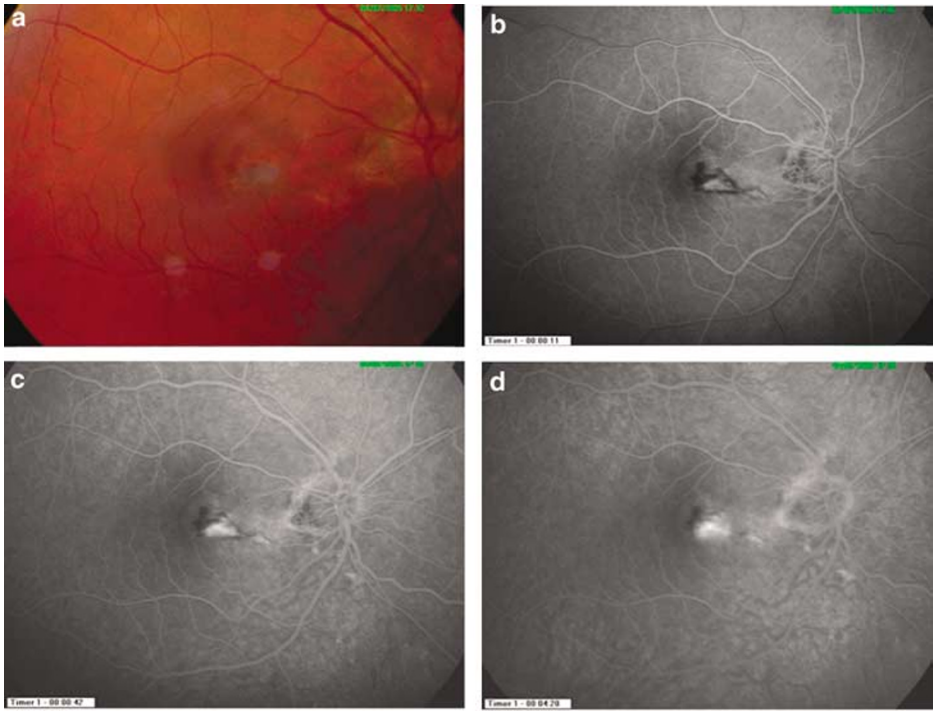

Figure 1 Colour photograph (a) and fluorescein angiogram (b–d) of the right eye of patient 1 before treatment. This shows a well-defined subfoveal predominant classic CNV with early hyperflourescence (b) and late leakage (d).

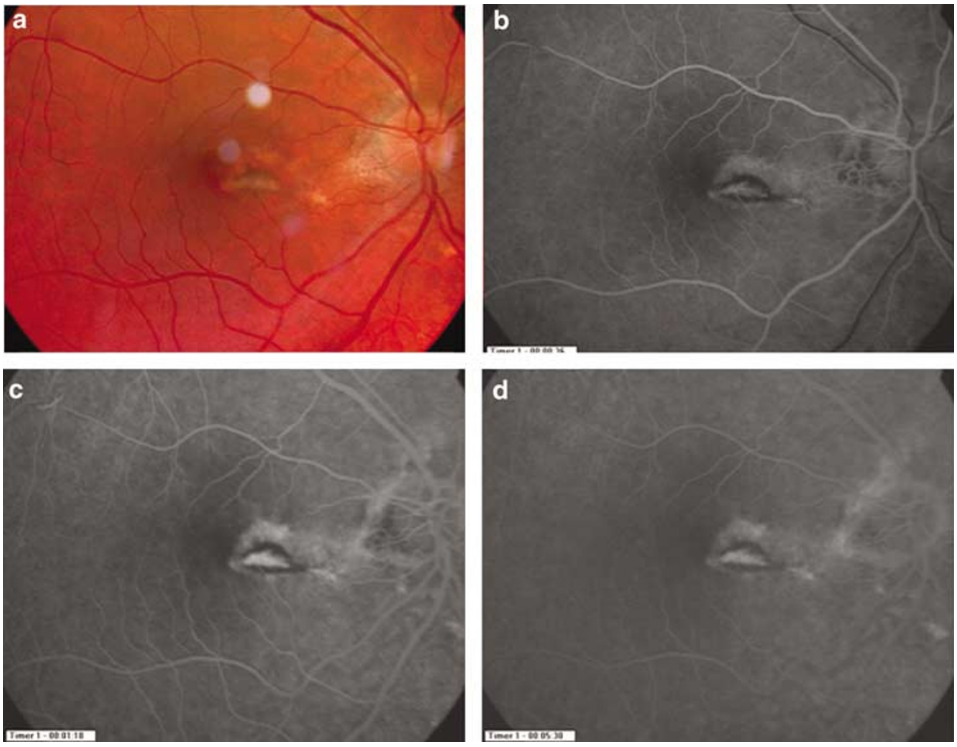

Figure 2 Colour photograph (a) and fluorescein angiogram (b–d) of the right eye of patient 16 months after two sessions of PDT. This shows staining of the treated area of CNV with no late leakage seen.

Table 2 Comparison of studies on PDT for subfoveal CNV secondary to PIC

	Rogers et al[27]	*Leslie et al*[11]	*Postelmans et al*[12]	*Lim et al*[13]	*This study*
No. of eyes	6	4	16	2	5
Mean VA before PDT (ETDRS letters)	8	29	35	3	28.4
Mean final VA (ETDRS letters)	15	50	45	23	38.8
Mean follow-up (months)	12.8	10.8	21	18	12
No. of patients with improved or stable VA	5/6 (83%)	4/4 (100%)	13/16 (81%)	1/2 (50%)	4/5 (80%)

Abbreviations: CNV, choroidal neovascular membrane; GLD, greatest linear diameter; ETDRS, Early Treatment Diabetic Retinopathy Study; PDT, photodynamic therapy; VA, visual acuity.

improvement in VA of nine letters after treatment with systemic corticosteroids started 5 days before PDT.

The CNV lesion size was relatively small in our series, apart from patient 5 who did not improve with treatment. This may explain the good VA results seen. In AMD, smaller lesion size has been found to increase the likelihood of better visual outcome, regardless of lesion composition.[16] The CNV associated with inflammation are generally smaller than those in AMD, which may make them more amenable to treatment. Patient 5, who showed reduction in VA after treatment, had the largest GLD and mean area of CNV among all the five patients in our series. This suggests that a larger CNV lesion size, particularly CNV with GLD greater than 2.00 mm may have a poorer prognosis with treatment by this modality. If patient 5 was excluded from the analysis, the mean improvement in VA after treatment was 14.5 letters (median 15 letters, range 8–20 letters).

In PIC, CNV appears to develop in response to chronic low-grade intraocular inflammation, in the absence of degenerative changes in the RPE. Angiogenic growth factors and cytokines released during chronic inflammation may induce neovascular vessel growth. In a clinicopathological correlation, perivascular choroidal infiltrates and the presence of early CNV was found over areas of most intense inflammation.[17] Therefore, immunosuppressive treatment like systemic corticosteroids have a key role in reducing or eradicating the stimulus that leads to CNV formation.

Spaide[18] proposed a two-component model for CNV consisting of a (a) vascular component comprising vascular endothelial cells, endothelial cell precursors,

and pericytes, and (b) an extravascular component comprising inflammatory, glial, and retinal pigment epithelial cells, and fibroblasts. PDT plays a key role in treating the vascular component of the CNV by stimulating choroidal vascular closure in the area of CNV. There are no published reports of pure inhibitors of the extravascular component of CNV at present. Corticosteroids may potentially inhibit many aspects of the extravascular component because their mechanism of action includes, decreasing vascular permeability, inhibiting cytokine expression,[19] reducing vascular endothelial growth factor (VEGF) secretion,[20] and inhibiting VEGF production by macrophages[21] Corticosteroids also target the vascular component of CNV by its antiangiogenic effect (downregulation of matrix metalloproteinases).[19] Combination therapy with systemic corticosteroids and PDT is therefore a logical choice in treating CNV owing to PIC.

Our rationale for starting patients on systemic corticosteroids 5 days before PDT is to ensure that they are immunosuppressed before they have PDT. There is evidence of increased inflammation following PDT, both *in vitro* and *in vivo*. An optical coherence tomography study showed accumulation of intraretinal fluid and increased retinal thickness, seen 1 h after treatment, that resolved within 1 week.[22] This is compatible with the increased leakage at this stage noted on fluorescein angiography. PDT damages both the CNV and normal choroidal vessels through generation of singlet oxygen and free radicals. Local release of VEGF occurs after PDT as well.[23] This could have a detrimental effect on the CNV process when inflammation is the main mechanism.

Systemic corticosteroids are well tolerated in healthy young adults when used for short periods of time. In our series, the patients were on oral corticosteroids for no longer than 2 months with no reported side effects. Another alternative combination could be intravitreal triamcinolone acetonide injection after PDT. This combination has shown promising results in AMD-related CNV.[24] However, we have to take into account the potential sight-threatening side effects of intravitreal injections that include cataract, retinal detachment, raised intraocular pressure, and endophthalmitis.[25] Other possible periocular steroid treatment modalities include posterior juxtascleral (subtenons) injection,[26] subconjunctival injection, and retrobulbar injection.

PDT may be most effective in achieving closure of already formed blood vessels, whereas immunosuppressive therapies may work best during the early stages of endothelial cell migration and proliferation.[11] The selection of each treatment would depend on the stage of development of the CNV. Early lesions should respond well to immunosuppression, whereas formed CNV will require PDT. Most cases should do well with a combination of both forms of treatment.

Although the number of patients in our study is small, our findings are supported by previously published series on using PDT to treat CNV in PIC. As PIC is a rare disease, it is unlikely that large number of patients would be found for large randomised controlled studies. As such, we may have to rely on small nonrandomised case series to establish the best way of treating subfoveal CNV caused by inflammatory chorioretinal diseases like PIC.

In conclusion, our study suggests that combined treatment with systemic corticosteroids and PDT for subfoveal CNV in PIC is a safe, effective and logical option for these young and professionally active patients. After follow-up for 12 months, the mean VA was maintained at 39 letters, which is far better than the natural history of the condition if untreated.[1,2]

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