

# Role of cyclophosphamide and high dose steroid in ocular cicatricial pemphigoid

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## Abstract

**Aims/background**—Ocular cicatricial pemphigoid (OCP) can present with severe conjunctival inflammation that requires systemic immunosuppression to avoid serious ocular morbidity. This study aimed to assess the clinical response to cyclophosphamide and short term, high dose prednisolone in this group of patients.

**Methods**—A prospective, unmasked study assessed patients presenting with either 'severe' ocular inflammation (n=4) or 'marked' or 'severe' ocular inflammation that had failed to respond to other systemic immunosuppression (n=6). Nineteen inflamed eyes of 10 consecutive patients were enrolled.

**Results**—The ocular inflammation resolved in 15 eyes in a mean time of 2.4 months. Two eyes perforated despite treatment and one patient was unable to tolerate the medication. Progressive cicatrization occurred in 21%.

**Conclusion**—Cyclophosphamide and short term, high dose prednisolone are effective in severe inflammation caused by OCP but may not completely prevent cicatrization. (*Br J Ophthalmol* 1995; 79: 264–266)

immunosuppressives.<sup>1-7</sup> These patients are usually elderly and therefore the clinician must balance the potential harm of powerful immunosuppressive drugs with those of the ocular disease.

This study aimed to assess patients with severe conjunctival inflammation caused by OCP who were treated with cyclophosphamide and short term high dose oral prednisolone.

## Materials and methods

Patients were selected from the Corneal and External Disease Clinics at Moorfields Eye Hospital over the 18 month period from September 1992. All patients with OCP were categorised from 0–4+ by the amount of conjunctival inflammation. These were defined as: mild (+), conjunctival hyperaemia only; moderate (++) , hyperaemia with conjunctival oedema; marked (+++) , significant conjunctival stromal and epithelial oedema; severe (++++), very oedematous conjunctival stroma and epithelium in four quadrants.<sup>1-9</sup> The inclusion criteria for this study were all patients with OCP who had 'severe' ocular inflammation (n=4) or whom had 'marked' or 'severe' ocular inflammation that had failed to respond to systemic immunosuppression (n=6, dapsone – three, sulphapyridine – three). All patients were consecutive and there were no exclusions. All patients had bilateral inflammation of a moderate degree or worse, except for one (patient no 1, Table 1). Other causes of conjunctival inflammation such as lid margin disease and trichiasis were resolved before entry into the study. Conjunctival biopsy was performed on all but one patient and was defined as diagnostic if

Ocular cicatricial pemphigoid (OCP) is an inflammatory and cicatricial disease characterised by the systemic production and subsequent binding of antibodies to basement membrane. This is thought to activate complement and initiate a type II hypersensitivity reaction.<sup>1-3</sup> A small number of patients develop severe conjunctival inflammation that is not responsive to topical or mild oral

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Table 1 Outcome of patients treated with cyclophosphamide and prednisolone

Patient	Biopsy	Stage*	Inflammation†	Limbitis	Initial VA	Final VA	Time for inflammation to resolve	Duration of cyclophosphamide	Follow up (months)
1 OS	+	M4F3	+	–	CF	CF	–	6 Months	6
OD		M4F3	++++	+	6/9	6/12	4 Months		
2 OS	+	M4F3	++++	+	6/9	6/6	1½ months	14 Months	14
OD		M2F2	+++	–	6/9	6/6	1½ months		
3 OS	+	M4F3	++++	+	6/24	6/18	4 Months, cicatrization progressed	12 Months	12
OD		M4F3	++++	+	6/18	6/12	4 Months, cicatrization progressed		
4 OS	–	M4F3	++++	+	6/24	6/9	2 Months, switched to dapsone after 4 months	4 Months	25
OD		M4F3	++++	+	6/9	6/6	2 Months, switched to dapsone after 4 months		
5 OS	+	M4F3	+++	+	6/9	6/9	1 Month	18 Months	18
OD		M4F3	++	–	6/24	6/18	4 Months		
6 OS	Not done	M4F3	++++	+	CF	CF	1 Month	6 Months, then deceased	6
OD		M4F3	++++	+	HM	HM	1 Month		
7 OS	+	M4F3	+++	–	6/9	6/12	Unable to tolerate the medication	1½ months	4
OD		M4F3	+++	–	6/12	6/18	Unable to tolerate the medication		
8 OS	+	M4F3	++++	+	6/9	6/12	2 Months, cicatrization progressed	18 Months	18
OD		M4F3	+++	–	6/12	6/24	2 Months, cicatrization progressed		
9 OS	+	M4F3	++++	+	PL	NPL	Perforated after 2/12 with microbial keratitis	3 Months	19
OD		M4F3	++++	–	PL	PL	3 Months, previous severe glaucoma		
10 OS	+	M4F3	++	–	6/24	6/36	3 Months	4 Months	18
OD		M4F3	+++	+	6/18	CF	Perforated after 1 month		

OS=left eye, OD=right eye. CF=counting fingers, HM=hand movements, PL=perception of light.

\*M4F3=Mondino's stage 4 and Foster's stage 3. †Inflammation was divided into four stages; + (mild), ++ (moderate), +++ (marked), ++++ (severe).

there was basement membrane deposition of IgG, IgA, complement, or fibrinogen. Patients that were basement membrane antibody negative had characteristic subepithelial fibrosis and progressive conjunctival cicatrization.

Each eye was staged according to the two systems of Mondino and Foster.<sup>2,8-10</sup> Foster's stages are based on specific clinical signs; stage 2 – fornix shortening, stage 3 – symblepharon, stage 4 – ankyloblepharon. Mondino's stages are based on the lower fornix depth – for example, stage 3 is a loss of depth of 50–75%. This depth was measured optically with a normal depth being defined as 11 mm.<sup>11</sup> Limbitis was defined as a raised, inflamed region involving the limbal tissues extending for one quadrant or more. The visual acuity data were that assessed at the initiation of cyclophosphamide and after the resolution of inflammation.

All patients were treated with oral cyclophosphamide at an initial dose of 1.5–2.0 mg/kg/day and oral prednisolone, 60 mg/day (n=9) or 80 mg/day (n=1). Other oral immunosuppressive agents were stopped. Success was defined as an objective improvement in the conjunctival inflammation to 'mild' (+) or less. Patients were assessed at monthly intervals for 6 months and 2–3 monthly thereafter. Full blood counts and differential white blood counts were obtained at each visit. A proforma was used to record the data prospectively with the same observer (MJE) for all patients over the 18 months.

## Results

Ten consecutive patients were enrolled. The mean age was 74.3 (SD 6.0) years and ranged from 62–82 years. Nine patients were male and eight had a positive biopsy. At the onset of therapy, seven patients had severe ocular inflammation (unilateral or bilateral) and three patients had marked inflammation. Limbitis was present in 12 eyes of nine patients. All eyes were categorised as Mondino's stage 4 and Foster's stage 3 except for one which was stage 2 and 2 respectively (Table 1). Systemic manifestations of OCP were found in 7/10 patients; mouth or pharyngeal ulceration (n=5), oesophageal ulceration (n=4), bullous skin lesions (n=1).

All patients remained on cyclophosphamide for more than 6 months except one (no 7). He developed marked feelings of being distant from the world, 'like being on [recreational] drugs'. These were so unpleasant that the cyclophosphamide was discontinued after 6 weeks. The symptoms abated within 3 days despite no change in the prednisolone dose. The ocular inflammation had reduced to 'moderate' bilaterally and ultimately became quiescent on dapson. This patient is excluded from the following data.

The dose of cyclophosphamide was altered to achieve a lymphocyte count of  $0.5\text{--}1.0 \times 10^9/\text{l}$ . This was achieved in all patients on a maintenance dose of 50–150 mg/day, typically 100 mg/day (n=7). No patient had reduced haemoglobin to less than 10 g/dl. The prednisolone was reduced rapidly

to a small maintenance dose after a clinical response was observed. When the ocular and systemic features were judged to be clinically stable, the prednisolone was stopped and the cyclophosphamide was continued alone. The mean total duration of prednisolone was 5.9 months and ranged from 4–8 months.

Of the nine patients, 17/18 eyes were inflamed. The ocular inflammation resolved in 15 eyes in a mean time of 2.4 months. During treatment, two eyes perforated, one of which was due to acute microbial keratitis (no 9). This patient had a poor ocular surface and a white blood count of  $2.0 \times 10^9/\text{l}$  at the time of the keratitis. The other perforation was the result of gradual corneal thinning that was not arrested with 1 month of medication (no 10). Progression of conjunctival cicatrization occurred in four eyes of two patients (nos 3 and 8) and represents 21% of inflamed eyes (4/19).

During the study, one patient died, but this was unrelated to the medication. One man developed significant alopecia which reversed with a dose reduction of cyclophosphamide. No patient developed a systemic infection that required antibiotics.

Four patients have so far remained on cyclophosphamide for 1 year or more. This was because of ongoing systemic features (n=2), relapse after stopping the medication (n=1), and mild, persistent ocular inflammation (n=1).

## Discussion

The aims of treating OCP are to alleviate patients' ocular symptoms, reduce conjunctival inflammation, preserve corneal clarity, and to prevent further cicatrization. Unfortunately, a small group of patients do not respond adequately to topical treatment or other comparatively safe systemic immunosuppression such as dapson or sulphapyridine.<sup>1,4-7</sup> This study examined these severe cases.

The first objective of management of these cases is to resolve the conjunctival inflammation. This current study illustrates that combined cyclophosphamide and prednisolone is effective at resolving severe conjunctival inflammation in the majority of patients. It has been particularly useful when other immunosuppressive agents such as dapson and sulphapyridine have failed. Further, the visual acuity was preserved through these episodes of severe inflammation (Table 1).

The second objective of management is to prevent further cicatrization. This happens most commonly during inflammatory episodes.<sup>10,12,13</sup> In this study, 21% had progressive cicatrization despite adequate therapeutic reductions of the lymphocyte count and this is consistent with Mondino's experience.<sup>3</sup>

The rationale for this current combined treatment regimen is based on laboratory and clinical evidence. Histologically, these acutely inflamed eyes are infiltrated with neutrophils, macrophages, and T lymphocytes and the majority have antibodies, complement, and

fibrinogen bound to the conjunctival basement membrane.<sup>14 15</sup> Therefore, medical treatment should reduce acute inflammation and impair delayed hypersensitivity and the cell mediated immune system. This can be achieved with prednisolone and cyclophosphamide.

Clinically, high dose prednisolone on its own has been shown to be comparatively ineffective at reducing conjunctival inflammation.<sup>1 10 16</sup> Only 42% of patients with OCP had resolution of their inflammation. This required initial doses of 60–80 mg/day and a mean maintenance dose of 40 mg/day.<sup>16</sup> Side effects included peptic ulceration (33%), hypertension (25%), diabetes (25%), myopathy (25%), osteoporosis (25%), and psychosis (25%). One third of these patients became 'blind' using the legal definition.<sup>16</sup>

Foster reported that cyclophosphamide (2 mg/kg/day) and a 3 month course of high dose prednisolone resolved the conjunctival inflammation in 100% of stage 3 patients and prevented recurrence and cicatrization over 1 year.<sup>16</sup> However, 100% developed some degree of anaemia, 83% developed alopecia, 8% developed haematuria, and 8% developed leucopenia. A later retrospective study suggested that cyclophosphamide was the most successful treatment in severe inflammation.<sup>6</sup>

Mondino *et al* assessed conjunctival cicatrization over 24 months in a trial of cyclophosphamide, cyclophosphamide and prednisone, and placebo.<sup>23</sup> Progression of conjunctival cicatrization occurred in stage 1 in 25%, 17%, and 40% of eyes respectively; in stage 2 in 10%, 21%, and 62%; and in stage 3 in 75%, 25%, and 73%. This study suggests that combined cyclophosphamide and prednisone was the most effective treatment for prevention of cicatrization but no regimen to date has completely prevented it.

Cyclophosphamide is a nitrogen mustard derived alkylating agent that affects DNA replication and RNA transcription.<sup>17</sup> Side effects include alopecia, anovulation, azoospermia, haemorrhagic cystitis, bone marrow suppression, infection, and malignancy – especially bladder carcinoma.<sup>18–20</sup> The risks of infection are highest in the first month and may be bacterial or viral.

These side effects are very important. The increased risk of infection may have contributed to the very poor outcome in the patient with microbial keratitis. The effects on

fertility and the potential for malignancy are strong contraindications for young patients and the bone marrow suppression and risks of infection are significant problems for the elderly. In this series, the problems have been few but these patients have demanded much time of physicians, general practitioners, and laboratory services.

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