CYCLOSPORIN A IN THE TREATMENT OF SEVERE BEHÇET'S UVEITIS

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SUMMARY

Twelve patients with active Behçet's uveitis with marked deterioration of visual acuity in at least one eye were treated with cyclosporin A (CyA). An initial improvement in the severity of ocular inflammation and systemic features occurred in all cases and persisted until the dose was reduced or the drug withdrawn when a rapid recurrence of symptoms was noted. The visual acuity also initially improved in ten patients and this was maintained in seven cases until the dose of CyA was reduced. At this time, acuity was unchanged in two patients and was worse in three others—two of the latter as a result of vitreous haemorrhage in the absence of active inflammation. Seven of the 12 patients had therapy stopped because of complications; severe malaise and nausea (three cases), decreased renal function (three cases), and blindness (one case).

Cyclosporin A is of value in the control of Behçet's uveitis but toxicity limits its use and the benefits only last while the patient is on this therapy.

Key words: Behçets, Uveitis, Cyclosporin A.

BEHÇET'S syndrome often produces severe uveitis which may progress to early blindness [1-3]. Cytotoxic drugs, notably chlorambucil, cyclophosphamide and azathioprine have been used to treat the uveitis in an attempt to reduce dependence on high-dose corticosteroid therapy. There have been many uncontrolled reports of success, but few controlled studies. Moreover, the disease may progress despite recourse to these drugs [4, 5] and there are severe short-term risks of alkylating agents, such as sterility [6], and long-term concern about their oncogenic properties [7].

Cyclosporin A (CyA) has been used to treat Behçet's uveitis with encouraging preliminary results [8]. Such treatment has been based on the principle that experimental autoallergic uveitis can be induced by immunization with a retinal antigen (retinal S antigen) and that autoimmune reactions to this antigen have been detected in inflammatory eye disease [9, 10]. CyA abrogates this reaction in animal models [11] and might be expected to abrogate the analogous autoimmune reaction in man.

PATIENTS AND METHODS

Twelve patients (eight male, four female) with Behçet's disease were studied. They all fulfilled the Mason and Barnes clinical criteria for this diagnosis [12] and all had inflammatory eye disease with severely impaired vision in at least one eye and active uveitis at the time of entry into the study. The clinical details of each patient, including previous treatment, are shown in Table I. Their ages ranged from 16-47 years; all except patient 7 had previously been treated with high-dose systemic steroids and eight of the twelve had received cytotoxic agents. The treatment had failed either because it was ineffective or because of intolerable side-effects. CyA was started at a daily dose of 10 mg/kg body weight, taken either as divided (eight cases) or a single early morning (four cases) dose. After a year the CyA was tailed off by 50 mg/day at monthly intervals. Cytotoxic agents were stopped on entry to the trial and systemic steroids reduced as rapidly as possible.

A full clinical and ophthalmological assessment was carried out before treatment and at 1, 3, 6, 9 and 12 months. Ophthalmological assessment included visual acuity and slit lamp examination. The pupils were dilated and the vitreous and the fundus were examined by indirect ophthalmoscopy, contact lens and hruby lens. The activity of the inflammation in both anterior and posterior segments was scored according to published criteria [13]. Fluorescein angiography was performed before CyA was begun and repeated at 6 and 12 months, or earlier if necessary. Trough CyA levels in whole blood were...
TABLE I
CLINICAL DETAILS OF PATIENTS AT INCLUSION IN STUDY

<table>
<thead>
<tr>
<th>No.</th>
<th>Age at entry (years)</th>
<th>Sex</th>
<th>Race or national origin</th>
<th>Age at onset</th>
<th>Other systemic features</th>
<th>Previous therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HDS</td>
</tr>
<tr>
<td>1</td>
<td>24</td>
<td>M</td>
<td>Caucasian</td>
<td>Lifelong</td>
<td>Arthritis Pustules</td>
<td>+</td>
</tr>
<tr>
<td>2</td>
<td>31</td>
<td>M</td>
<td>Greek</td>
<td>20</td>
<td>Arthritis Pustules</td>
<td>+</td>
</tr>
<tr>
<td>3</td>
<td>28</td>
<td>F</td>
<td>Egyptian</td>
<td>18</td>
<td>Arthritis Erythema nodosum</td>
<td>+</td>
</tr>
<tr>
<td>4</td>
<td>30</td>
<td>M</td>
<td>Chinese</td>
<td>28</td>
<td>Arthritis Erythema nodosum</td>
<td>+</td>
</tr>
<tr>
<td>5</td>
<td>35</td>
<td>F</td>
<td>Caucasian</td>
<td>33</td>
<td>Arthritis Thrombophlebitis Erythema nodosum</td>
<td>+</td>
</tr>
<tr>
<td>6</td>
<td>40</td>
<td>M</td>
<td>Kuwaiti</td>
<td>11</td>
<td>Arthritis Pustules</td>
<td>+</td>
</tr>
<tr>
<td>7</td>
<td>16</td>
<td>M</td>
<td>Caucasian</td>
<td>15</td>
<td>Erythema nodosum Pustules</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>34</td>
<td>M</td>
<td>Caucasian</td>
<td>Lifelong</td>
<td>Arthritis</td>
<td>+</td>
</tr>
<tr>
<td>9</td>
<td>47</td>
<td>F</td>
<td>Caucasian</td>
<td>Lifelong</td>
<td>Arthritis Thrombophlebitis</td>
<td>+</td>
</tr>
<tr>
<td>10</td>
<td>36</td>
<td>M</td>
<td>Caucasian</td>
<td>26</td>
<td>Erythema nodosum</td>
<td>+</td>
</tr>
<tr>
<td>11</td>
<td>24</td>
<td>M</td>
<td>Bangladeshi</td>
<td>21</td>
<td>Arthritis Pustules</td>
<td>+</td>
</tr>
<tr>
<td>12</td>
<td>28</td>
<td>F</td>
<td>Caucasian</td>
<td>10</td>
<td>Erythema nodosum</td>
<td>+</td>
</tr>
</tbody>
</table>

HDS = high dose steroids; Chlora. = chlorambucil; Aza. = azathioprine; Cyclo. = cyclophosphamide; IIS = intensive immunosuppression (HDS + aza. + antilymphocytic globulin).
measured using the Sandoz radioimmunoassay 1 week and 2 weeks after starting treatment, and thereafter at monthly intervals. Ethical committee approval for the study was obtained from the relevant hospital bodies.

RESULTS

Clinical response

Ten of the 12 patients showed an initial improvement in the visual acuity and this benefit was maintained in seven cases while full dosage CyA was continued (Table II). In the other two patients the ocular damage in both eyes was so severe that no improvement in visual acuity resulted from the reduction in ocular inflammation. In two other patients a deterioration in vision occurred while on full dosage CyA as a result of vitreous haemorrhage in the absence of active inflammation. Patient 10, developed hypopyon uveitis immediately prior to his first dose of CyA and as this did not settle over the first 48 h on CyA, high-dosage prednisolone had to be added to the regimen. However, it was possible to reduce the steroid dosage rapidly without recurrence of the hypopyon uveitis. The ocular inflammation improved so much in patient 9 that it was possible to perform a left cataract extraction with consequent improvement in visual acuity from counting fingers to 6/9. All the patients showed a reduction in the systemic features of Behçet’s such as orogenital ulceration, thrombophlebitis, erythema nodosum and skin pustules while full-dosage CyA was maintained.

Twenty eyes were amenable to serial study of the ocular inflammation, the others being excluded due to vitreous haemorrhage. There was a significant reduction in the ocular inflammation (p<0.01) when comparing the score at each follow-up visit while on CyA with the initial visit (Time 0), using Wilcoxon rank sum tests. Furthermore, a significant increase in the inflammatory score (p<0.01) was found when comparing the patients 6 weeks after stopping the CyA with the initial visit (Fig. 1).

CyA was stopped in four patients because of severe malaise and nausea (cases 1, 4, 9) or gingivitis (case 3) and uveitis, orogenital ulceration and thrombophlebitis immediately recurred. Case 1 could not tolerate further CyA and in case 4 the uveitis could not be controlled after restarting therapy, and visual loss due to retinal vein occlusion ensued (Fig. 2). The uveitis relapsed with consequent drop in visual acuity in three further patients (cases 7, 8 and 10) when

<table>
<thead>
<tr>
<th>Table II</th>
<th>Effect of Cyclosporin A on Visual Acuity and Symptoms of Behçet's Syndrome</th>
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<tbody>
<tr>
<td>Duration of CyA therapy (months)</td>
<td>Visual acuity at inclusion</td>
</tr>
<tr>
<td>Right</td>
<td>Left</td>
</tr>
<tr>
<td>No.</td>
<td>2</td>
</tr>
<tr>
<td>CF = counting fingers; PL = perception of light; HM = hand movements; NPL = no perception of light; BE = both eyes.</td>
<td>285</td>
</tr>
<tr>
<td>CF = counting fingers; PL = perception of light; HM = hand movements; NPL = no perception of light; BE = both eyes.</td>
<td>285</td>
</tr>
</tbody>
</table>
the dose of CyA was reduced because of impaired renal function. Unfortunately, the lower maintenance dose of CyA was not sufficient to suppress the ocular inflammation and conventional therapy was re-established, but with only limited success. The drug was stopped in patient 11 because he had to return to Bangladesh.

When the daily dose of CyA was reduced after 12 months' treatment in the remaining four patients (50 mg each month), symptoms reurred in all cases when the dose was approximately 7 mg/kg/day. All of these patients elected to remain on CyA at a dose of 8 mg/kg/day as the uveitis had been better controlled with this treatment than any previous drug regimen. Eleven of the 12 patients had taken regular steroid therapy before the study and a reduction in the daily dose was achieved in eight cases with median daily dose decreasing from 25 (5–60) mg to 7.5 (5–12.5) mg from the start to end of CyA therapy. The relapse rate was halved in all patients (taking at least 8 mg/kg CyA) when compared to similar periods before treatment with CyA. There was no correlation between whole-blood levels of CyA and efficacy or toxicity of the drug.

Side-effects

All patients complained of minor discomforts: a burning sensation in the throat after swallowing the medicine, bloating, paraesthesiae and feeling cold. Eight patients developed gingivitis despite special attention to dental hygiene, but all these patients took the medicine in divided doses.

Renal toxicity was the most important side-effect: all patients showed some rise in serum creatinine and a fall in creatinine clearance. Serum creatinine levels rose significantly after 6 weeks of therapy compared to pretreatment levels (Fig. 3). However, only three patients (cases 7, 8 and 10) had therapy stopped for this

![Fig. 2.—Fluorescein angiogram of left eye of patient 4 showing occlusion of the capillaries supplying the macula and leakage of dye from the surrounding vessels and all the retinal capillaries.](https://academic.oup.com/rheumatology/article-abstract/26/4/285/1776005)
reason. Renal function returned to normal in all patients within 12 weeks of stopping or reducing the drug (Fig. 3). Five patients became hypertensive and one developed Candida oesophagitis. Malaise, nausea and anorexia occurred in seven patients and resulted in withdrawal of therapy in three of these cases (1, 4 and 9). Uveitis recurred but therapy could not be re-established in these patients. Minor abnormalities in liver function occurred in four patients.

**Other laboratory investigations**

The haemoglobin (Hb) concentration decreased by more than 1.0 g/dl in 9 of the 12 patients during the course of CyA treatment. The median Hb was 15.3 g/dl at the start and 12.8 g/dl at the end of therapy. The erythrocyte sedimentation rate (ESR) was more than 20 mm/h (Westergren) in three patients before and in 10 patients at the end of therapy. The median ESR also rose from 13.0 to 31.5 mm/h during this time. There was no change in the white cell count or lymphocyte count and the immunoglobulin levels and complement levels were also unaffected by therapy. Circulating immune complexes (Clq binding) were raised in three patients prior to therapy, but in two different patients during treatment. Antiretinal antibodies were found in three patients and the titres did not alter during the study.

**DISCUSSION**

This uncontrolled trial has suggested that CyA reduces the severity of both the ocular and systemic features of Behçet's syndrome. At the entry to the trial, all but one of our patients had active disease despite high-dose steroids, often in combination with cytotoxics. CyA produced a noticeable improvement in all the patients and four elected to remain on the drug after completing the year of the study, despite minor side-effects. Most patients preferred CyA to any previously used medication.

However, there are major difficulties in assessing results of this kind. For ethical reasons, we elected to treat patients with advanced disease who therefore already had severe damage to their eyes. Behçet's syndrome characteristically produces severe uveitis with a predilection for catastrophic retinal vascular occlusions. Consequently, irreversible fundal changes such as optic atrophy, ischaemia of the macula, new vessel formation, vitreous haemorrhage and retinal detachment are particularly common. These factors lead to a further problem which is the technical difficulty in quantitating the severity of the inflammatory uveitis and hence the effects of treatment. Deterioration of visual acuity can be due either to active inflammation or progression of the secondary complications such as glaucoma, cataract or vitreous...
haemorrhage. The latter two complications prevent accurate assessment of the vitreous and fundus and unfortunately vitreous haemorrhage often occurs when the inflammation is quiescent. We have tried to overcome these difficulties by adopting more objective criteria of ocular inflammatory activity (13).

The minor side-effects often encountered were gingival hyperplasia, hirsutism, depression, feeling of bloating and paraesthesiae. However, the effects of CyA on renal function were more worrying. There is continuing controversy about the extent to which renal dysfunction is reversible [14-16]. Most data have been obtained from patients receiving organ transplants and there are many complicating factors which might not be relevant to Behçet's syndrome [17]. Renal function returned to normal in all our patients after stopping the drug.

There are further doubts about the long-term effects of CyA. Azoospermia has not been reported in contrast to the effects of alkylating agents [6]. Lymphoproliferative changes and lymphomas have been reported, although in many cases the former are reversible [18,19] and previous immunosuppressive therapy may have caused these effects. It will be necessary to observe these patients for long periods to obtain evidence of oncogenic damage of the kind seen in patients treated with alkylating agents [7].

An additional worrying aspect was the inevitability of relapse when the dose was reduced below a certain critical level (7 mg/kg). This affected both systemic and ocular features and was often worse than at entry to the study. There are several possible explanations for this phenomenon. Behçet's has an unpredictable natural history and the drug may have had little effect on the normal relapses and remissions of the disease. This seems unlikely because the relapse rate was halved whilst patients were taking full dose CyA. The average daily steroid requirement was also halved during this time and with- out any increase in the relapse rate. Another explanation may be that CyA has similar effects to corticosteroids and that the rebound of symptoms is similar with both drugs. However, a rise in ESR and a fall in Hb are not usually noted in patients responding to steroids. This was evident in many of the patients on CyA, suggesting the drugs have different modes of action. These changes in haematological indices were most profound in patients who showed severe rebound symptoms when the drug was stopped.

Several early studies [1-3] showed that over 50% patients with Behçet's uveitis become blind within five years of diagnosis, and the visual prognosis may not have been substantially improved with recent changes in therapy [8]. These studies also suggested that the disease becomes quiescent after a variable period of time. CyA would be a valuable agent if it could be shown to suppress additional inflammation during the early phase of the disease when most severe retinal complications tend to occur. However, if CyA merely defers the inevitable outcome for the duration of therapy its use would be unjustified in view of the known risks and potential hazards.

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