The use of cyclosporin in corticosteroid dependent asthma

M E Coren, M Rosenthal, A Bush

Abstract
Five children with severe asthma requiring at least 10 mg of prednisolone daily were treated with cyclosporin. Three were weaned from prednisolone, but one quickly relapsed. One girl had her steroid dose lowered but suffered unacceptable hirsutism and one child failed to respond. Cyclosporin may be useful in refractory childhood asthma. A prospective study is required to confirm this.

(Arch Dis Child 1997;77:522–523)

Keywords: asthma; cyclosporin

Asthma is increasingly recognised as a disease characterised by airway inflammation. Bronchial mucosal biopsy specimens taken from asthmatics show inflammatory infiltrates with prominence of T cells and eosinophils.1 This correlates with disease activity.2 Inhibition of T cell function is central to the mechanism of action of corticosteroids in asthma.3 Unfortunately, steroids—especially when they are used systemically—have many side effects, of which growth failure is probably the most important in childhood. Steroid sparing agents have been tried including methotrexate, intravenous immunoglobulin, gold, and cyclosporin.4 Cyclosporin acts primarily by inhibition of T helper lymphocyte function and has been shown to be effective in improving lung function and allowing weaning from long term steroids in adult sufferers of asthma.5 There is no published work on the use of cyclosporin in childhood asthma.

We present our experience with cyclosporin in five children with severe steroid dependent asthma.

Patients and methods
Five patients from the Royal Brompton’s paediatric asthma clinic were treated with cyclosporin over a period of 18 months. All were tertiary referrals with poorly controlled asthma despite long term systemic steroids—at least 10 mg of prednisolone daily. Table 1 presents the details.

Table 1 shows the results for each case and figs 1–5 show the steroid dose during the time that the patients were taking cyclosporin.

Discussion
We report our experience in five children who had a therapeutic trial of cyclosporin. All of the

Figure 1 Changes in total monthly dose of prednisolone in case 1.

Figure 2 Changes in total monthly dose of prednisolone in case 2.
The use of cyclosporin in corticosteroid dependent asthma

Table 1  Case details with results and side effects of period on cyclosporin

<table>
<thead>
<tr>
<th>Sex (age in years)</th>
<th>Duration of continuous prednisolone (years)</th>
<th>Other medication</th>
<th>Effect of cyclosporin</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Girl (8)</td>
<td>2</td>
<td>Budesonide 1 mg/12 hours, terbutaline 5 mg when necessary</td>
<td>No benefit, abandoned after six months</td>
<td>Nil</td>
</tr>
<tr>
<td>2 Girl (15)</td>
<td>0.8</td>
<td>Fluticasone 1 mg/12 hours, terbutaline 5 mg when necessary, salmeterol 100 µg/12 hours</td>
<td>Successful reduction in steroid dose, stopped due to side effect</td>
<td>Severe hirsutism</td>
</tr>
<tr>
<td>3 Girl (8)</td>
<td>3</td>
<td>Budesonide 1 mg/12 hours, salbutamol 5 mg when necessary, salmeterol 50 µg/12 hours, theophylline 200 mg at night</td>
<td>Initial successful reduction in prednisolone dose but relapsed within six months</td>
<td>Mild hirsutism</td>
</tr>
<tr>
<td>4 Boy (9)</td>
<td>5</td>
<td>Budesonide 1.5 mg/12 hours, terbutaline 1 mg when necessary, salmeterol 100 µg/12 hours</td>
<td>Weaned off prednisolone over 10 months, major improvement in height and weight centiles, back at school full time</td>
<td>28% decline in glomerular filtration rate, no change in creatinine or blood pressure over baseline</td>
</tr>
<tr>
<td>5 Girl (10)</td>
<td>5</td>
<td>Budesonide 1.5 mg/12 hours, salbutamol 5 mg when necessary, salmeterol 100 µg/12 hours, theophylline 125 mg/12 hours</td>
<td>Weaned from prednisolone completely, major improvement in height/weight centiles</td>
<td>Transient lymphadenopathy, mild hirsutism</td>
</tr>
</tbody>
</table>

patients described had severe asthma and so were unable to stop taking systemic steroids. These represent the most refractory cases in our asthma clinic: about 1% of patients over that period of time. They were all steroid responsive, but needed unacceptably high doses to control their symptoms. None was clinically steroid resistant, although in vitro T cell function was not determined.

We undertook a thorough review of all aspects of management before considering cyclosporin. This is an essential first step because in many patients who are initially referred for a steroid sparing agent there are major issues such as poor compliance. The finding that almost all trials of steroid sparing agents in asthma show significant benefit with placebo, as well as the active drug, is important in this respect. This implies that some patients may be over treated with corticosteroids. In addition, some cases improve spontaneously over time, for example during puberty.

In the cases described, there was clear benefit in three patients, one had temporary, but unsustained benefit, and one did not respond. Three patients complained of hirsutism and this caused one, a teenage girl, to decide to stop taking the drug despite success in lowering her steroid dose and subjective improvement. None of the patients had any rise in creatinine, potassium, or blood pressure over baseline. One patient (case 4) had a 28% decline in isotope glomerular filtration rate, although no change in creatinine. One patient (case 5) had an episode of tender lymphadenopathy which was resolved when cyclosporin was temporarily stopped.

The experience of cyclosporin in adult asthmatics showed most side effects to be minor and tolerable (hirsutism, paraesthesia, tremor, headaches, mild hypertension). The main concern with cyclosporin is renal toxicity. Irreversible damage can occur, but was not reported in any of the trial patients.

Unfortunately, the benefit of cyclosporin was shown to be lost once treatment is stopped. It is possible that a very low dose over the long term or even an inhaled/nebulised preparation might be beneficial.

In conclusion, we have treated five children, with good responses in three. An open study cannot, however, determine the place of cyclosporin in the management of these most difficult patients. A controlled multicentre trial is needed to generate suitable cases.