Cyclosporin in the treatment of corticosteroid resistant autoimmune chronic active hepatitis

L D Jackson, E Song

Abstract
A 17 year old Asian patient with autoimmune chronic active hepatitis resistant to treatment with high dose corticosteroids and azathioprine was given cyclosporin at a dose of 5 mg/kg/day. Within two weeks of starting the cyclosporin treatment a favourable clinical and biochemical response was obtained and by one month serum aminotransferase activities were within normal limits. An attempted reduction in the daily dose of cyclosporin resulted in a relapse of the patient's disease. Remission was again attained by returning the dose of cyclosporin to 5 mg/kg/day. No significant side effects of the treatment have been shown. Cyclosporin seems to have a role in the treatment of corticosteroid resistant autoimmune chronic active hepatitis and its further evaluation is warranted.

Case report
The patient, a 17 year old Asian Indian man, was well until September 1991 when he presented with a two week history of jaundice, malaise, weight loss, and vague right hypochondrial pain. Examination showed deep jaundice and hepatosplenomegaly. There had been no exposure to drugs, blood transfusions or alcohol. There was no family history of hepatic illnesses. Laboratory studies gave these results: aspartate aminotransferase (AST) 1031 U/l, alanine aminotransferase (ALT) 820 U/l, total bilirubin 400 μg/l, antinuclear factor positive (titre 1/640), antismooth muscle antibody positive (titre 1/320). Hepatitis A, B, and C serological tests were negative. Protein electrophoresis showed a total protein of 102 g/l with a normal albumin concentration of 34 g/l and hypergammaglobulinaemia of 52 g/l (normal=9–18 g/l). An open wedge liver biopsy was performed under cover of fresh frozen plasma because of a prolonged bleeding time (INR=2). Histological examination showed bridging necrosis accompanied by a severe chronic inflammatory infiltrate of lymphocytes and plasma cells extending from the portal tracts into the lobules in keeping with the diagnosis of autoimmune chronic active hepatitis. There was no evidence of cirrhosis. Treatment was started with a daily oral dose of 30 mg prednisone.

During the ensuing two months the patient's aminotransferase activities decreased AST=221 U/l and ALT=188 U/l but he became profoundly cushingoid and developed a gastric ulcer, which was treated successfully with ranitidine 300 mg twice daily. An attempt was then made to reduce the patient's corticosteroid dose (October 1991), but his liver disease relapsed with a significant rise in his transaminase activities (AST=1400 U/l and ALT=1098 U/l) that required a hospital admission. Azathioprine at a dose of 1 mg/kg was introduced in combination with the prednisone but resulted in an attack of pancreatitis and had to be stopped.

Over the next six months the patient was maintained with prednisone 30 mg daily. Remission was never achieved with aminotransferase activities remaining in the 100–150 U/l range. The patient remained cushingoid and suffered a recurrence of his gastric ulcer. An attempt was made to reintroduce the azathioprine but the patient developed severe acute pancreatitis, which was accompanied by...
Aminotransferase activities as a result of treatment.

- Prednisone
- Cyclosporin A

Length of illness

<table>
<thead>
<tr>
<th>Year</th>
<th>Azathioprine</th>
<th>AZ1</th>
<th>AM1C</th>
<th>AM19</th>
<th>AM9</th>
<th>AM4N</th>
<th>AM1C</th>
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<td>5</td>
<td>30</td>
<td>30</td>
<td>30</td>
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<td>30</td>
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</tr>
</tbody>
</table>

AST activities
- 1000
- 1500

ALT activities
- 1000
- 1500

IU/ml
- 5
- 10
- 15
- 20
- 30
- 50

A considerable rise in transaminase activities (June 1992). At this stage (July 1992) a therapeutic trial of cyclosporin was begun after informed consent was obtained from the patient’s parents.

The patient was admitted to hospital and cyclosporin was begun at 5 mg/kg/day orally in two divided doses. The patient was carefully monitored for the development of hypertension, electrolyte abnormalities, fall in white cell count, and decrease in creatinine clearance. Cyclosporin trough concentrations were maintained at 50–300 ng/ml. The cyclosporin assay used is the TDX system (Abbott Labs, Illinois, USA) in which cyclosporin and its metabolites (AM1, AM19, AM9, AM4N, and AM1C) are measured using fluorescence polarisation immunoassay technology. Within two weeks there was a favourable symptomatic and biochemical response with aminotransferase activities falling to normal (within one month) for the first time since the onset of the illness. The patient was weaned from prednisone and the noticeable cushingoid features resolved.

The patient remained in remission until March 1993 when an attempt was made to halve the dose of cyclosporin given. Within a period of two weeks the aminotransferase activities had risen dramatically (AST=1103 IU/ml and ALT=1212 IU/ml). Cyclosporin was once again introduced at a dose of 5 mg/kg/day. Again the response was dramatic with aminotransferase activities returning to normal values (AST=41 IU/ml, ALT=40 IU/ml) within six weeks of increasing the dose of cyclosporin. Currently the patient is in remission receiving cyclosporin alone.

**Discussion**

The treatment of AICAH is immunosuppression and the drugs used to achieve remission in most cases are corticosteroids alone or in combination with azathioprine. Side effects of the corticosteroids are dose dependent and include changes such as cushingoid appearance, weight gain, acne, osteoporosis, myopathy, cataract formation, irritability, and psychosis. Severe corticosteroid side effects such as gastric ulceration, diabetes, and compression fractures occur in 16% of patients with AICAH. Azathioprine is an analogue of 6 mercaptopurine and it is this last metabolite that is responsible for most of the side effects. Mercaptopurine interferes with the synthesis of adenine and guanine nucleotides but its exact mechanism of action in AICAH is unknown. The drug increases the efficacy of the corticosteroids per dose given, thus permitting the patient to be treated with lower doses of corticosteroids. The major side effects are leucopenia and thrombocytopenia. Nausea, vomiting, anorexia, and diarrhoea tend to only occur with high doses. Alopecia, rashes, fever, arthralgias, retinopathy, Raynaud’s disease, pulmonary oedema, and pancreatitis have been described.

The reported use of cyclosporin A in AICAH unresponsive to corticosteroids and azathioprine is limited to two case reports. One was a 51 year old man who developed a hypersensitivity reaction to the azathioprine, the other was a 14 year old boy whose parents refused the use of azathioprine. Both cases were resistant to the use of high dose corticosteroids. Both had dramatic responses to the cyclosporin with minimal side effects.

Cyclosporin is a potent immunosuppressant drug. It acts by inhibiting the early events in T helper cell activation that would normally lead to recruitment and expansion of the cytotoxic T cells as well as to the activation of B cell clones eventually secreting specific immunoglobulins. Cyclosporin also interferes with the synthesis of interleukin 2 by activated T cells. The generation of other cytokines such as B cell activating factor and interferon gamma are also inhibited. Cyclosporin does not, however, affect the development of suppressor T cells, which decrease specific immune responses. The final result is a reduced expression of both the cell mediated and antibody mediated immune responses.

Cyclosporin does unfortunately have a number of side effects, the most important of which is nephrotoxicity, which may take a number of forms: a tubulopathy and peritubular congestion associated with acute toxicity, diffuse interstitial fibrosis, and arteriolopathy associated with longterm use. A recent study found histopathological evidence of nephropathy in 21% of the renal biopsy specimens of patients receiving cyclosporin for autoimmune diseases. The commonest finding
was that of stripes of interstitial fibrosis with tubular atrophy. A less common finding was that of arteriolar changes—a finding thought to be reversible on withdrawal of the drug. Other side effects associated with cyclosporin use include hypertension, hyperkalaemia, hyperuricaemia, anaemia, tremor, hypertrichosis, gingival hyperplasia, paraesthesiae, and gastrointestinal intolerance.30 Our patient has to date shown none of these side effects. In summary we present a case of AICAH refractory to high dose corticosteroids and azathioprine responding dramatically to cyclosporin. It seems to have a role in the treatment of corticosteroid resistant AICAH and thus merits further investigation.

24 Reed JC, Prystowsky CB, Nowell PC. Regulation of gene expression in leucin stimulated or lymphokine stimulated T lymphocytes. Transplantation 1986; 46: 85–90.