

## Treatment of idiopathic retroperitoneal fibrosis using cyclosporin

A Marzano, A Trapani, N Leone, G C Actis, M Rizzetto

### Abstract

**The main goal of traditional treatment of idiopathic retroperitoneal fibrosis is limitation of morbidity, and surgery of already formed fibrous masses has been the main therapeutic approach. More recently, the knowledge that the disorder may be the result of an allergic reaction to atherosclerotic lipids has prompted the use of corticosteroids and cytotoxic drugs, which proved efficacious, but also toxic. On the basis of data indicating a T cell pathogenesis of idiopathic retroperitoneal fibrosis, cyclosporin, a non-cytotoxic pretranscriptional inhibitor of proinflammatory cytokines, was used to treat the case reported here. A 65 year old man with aggressive retroperitoneal fibrosis and obstructive renal failure initially received steroids, which eventually lost their efficacy and led to vertebral collapse. He responded to 5 mg/kg/day cyclosporin, with radiological reduction of tissue deposition, relief of ureter compression, and reduction in acute phase reactants in the blood. Chronic disease remission required stable drug concentrations. In conclusion, progress in research into the T cell pathogenesis of idiopathic retroperitoneal fibrosis may justify attempts with drugs such as cyclosporin to block the disease at its origin rather than treating the morbidity.**

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Surgical debulking of fibrous masses has been the traditional treatment of idiopathic retroperitoneal fibrosis (IRF), and the empirical use of steroids or, in a few cases, immune suppressors has only recently been encouraged by the evidence that IRF may be the result of an allergic reaction to lipid components of the aortic wall.<sup>1</sup> We recently treated a patient with full

blown IRF with cyclosporin, achieving a dramatically positive result.

### Case report

In July 1995, a 65 year old man was admitted because of anorexia and a 10 kg weight loss. His serum biochemistry included markers of inflammation (erythrocyte sedimentation rate, 80 in the hour; white blood cell count, 13 670; C reactive protein, 94 mg/l) and renal dysfunction (creatinine, 190 µmol/l), the cause of the latter being identified by a computed tomography (CT) scan as the deposition of dense material around the lumbar aorta and the ureters, leading to hydronephrosis. On the basis of histological examination of a guided biopsy specimen showing the material to be fibrous tissue, a diagnosis was made of IRF. The positioning of bilateral stents relieved the urological symptoms, but, by December 1995, fibrosis had worsened radiologically to involve the iliac vessels. In-hospital infusion of a maximum steroid dose, followed by a daily oral dose of prednisone of 50 mg to be tapered off did not prevent the development of oedema in the left leg. Eventually, unchecked disease activity and patient's intolerance to maintenance drugs led to a state of dependence on 25 mg steroids daily. In November 1996, the patient became bed bound because of multiple vertebral collapses. In May 1997, he was started on a daily dose of 5 mg/kg oral microemulsion cyclosporin (Novartis Pharma, Basel, Switzerland), with the aim of achieving a therapeutic concentration of 200 ng/ml. A biochemical response, indicated by normalisation of the inflammatory variables, was rapid (table 1). In October 1997, the patient was weaned from steroids, and a CT scan in December showed no progression of the retroperitoneal fibrous masses. The patient finally recovered from his lumbar fractures and had the stents removed. He is currently stable on cyclosporin without further need for steroids, and, at the concentrations cited above, is not showing any major cyclosporin related toxicity.

### Discussion

The laboratory demonstration of sensitisation to ceroid, the clinical evidence of an association with other immune mediated connective tissue diseases, and the common finding of coincidental fibrosis at sites other than the retroperitoneum<sup>1</sup> all indicate an allergic pathogenesis of IRF. On this basis, steroids first, and, more anecdotally, azathioprine and cyclophosphamide, have been used as treatment, with delayed action and toxicity being limitations.

We chose to switch the patient described in this report to the non-cytotoxic drug cyclosporin, a molecule known to control the effects

Department of  
Gastroenterology,  
Ospedale Molinette,  
Torino 10126, Italy

A Marzano  
A Trapani  
N Leone  
G C Actis  
M Rizzetto

Correspondence to:  
Dr Actis  
actis\_g@libero.it

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**Table 1** Levels of erythrocyte sedimentation rate (ESR; normal range 0-10 mm/1st h), C reactive protein (CRP; normal range 0-5 mg/l), haemoglobin (Hb; normal range 140-180 g/l), cyclosporin (CsA; trough blood range 100-240 ng/ml, according to Actis et al<sup>2</sup>), and creatinine (Creat; normal range 50-110 µmol/l) before and during cyclosporin treatment (indicated in months)

Variable	-4	-1	+1	+2	+7	+10	+11	+16	+19	+20
ESR (mm/1st h)	53	74	67	33	65	36	50	26	52	21
CRP (mg/l)	38	122	49	7	87	4	17	5	11	10
Hb (g/l)	140	139	130	—	—	153	153	—	150	—
CsA (ng/ml)	—	—	163	207	77	180	170	266	180	174
Creat (µmol/l)	90	100	100	110	100	100	100	120	130	110

\*Disease activity (expressed by ESR and CRP) fluctuates around high levels four and one month before the beginning of CsA treatment. A >50% reduction in ESR and CRP is achieved after two months of CsA treatment. A recrudescence occurs at seven months concurrently with a CsA concentration <100; disease activity fluctuates thereafter, but is substantially controlled at 20 months. The mild inflammation associated anaemia disappears as the patient gains up to 2 g Hb. The creatinine concentrations tended to increase over time, reached a peak of >33% of baseline at 19 months, but normalised spontaneously on the following determination. An initial daily prednisone dose of 25 mg was tapered off before seven months.

of several proinflammatory cytokines at a pretranscriptional level.<sup>2</sup> The strategy underlying this choice was threefold. Firstly, we considered that prevention of the IRF associated morbidity largely equates to halting or delaying the progression of the inflammatory periaortic plaques towards mature fibrotic masses, and this needs a quick acting drug. Secondly, the immune cells responsible for this progression may be T cells, as shown by immunohistochemical studies on both IRF and the associated fibrosing diseases.<sup>3</sup> Thirdly, the soluble effectors used by these cells may well be both inflammatory and fibrosing cytokines falling under the control of cyclosporin, a molecule with a broad sphere of action. Also, data from the literature supported this choice, showing that cyclosporin is efficacious for the treatment of other "autoimmune" diseases presumably mediated by T cells—for example, psoriasis,<sup>4</sup> rheumatoid arthritis,<sup>5</sup> and uveitis.<sup>6</sup>

There was a biochemical as well as a radiological response to this strategy. The biochemical response (fall of acute phase reactants) was early, required constant drug levels in the blood to be maintained, and tended to fluctuate with time (table 1); this was followed by the radiographic demonstration of a stable scar deposition later on. Interestingly, rapid control of the acute phase response, a relative loss of activity over time, and a late local (endoscopic) response are findings noted by us<sup>7</sup> and others when using cyclosporin to treat ulcerative colitis, another disease in which the role of dysregulated T cells is currently being emphasised.<sup>8</sup>

Thus this paper provides some theoretical grounds for the use of cyclosporin to treat IRF, together with the anecdotal evidence of its efficacy.

The success of this initial trial should not overshadow the difficulties in understanding the fine mechanisms of action of cyclosporin. A

specific point that needs attention is how to reconcile a therapeutic action on IRF with the known ability of cyclosporin to enhance fibrosis through the upregulation of transforming growth factor  $\beta$  (TGF $\beta$ ),<sup>9</sup> a healing cytokine. For the moment, a reasonable answer is that TGF $\beta$  is not only fibrogenic but also suppressive for several inflammatory mediators,<sup>10</sup> and its *in vivo* effects can only be the algebraic sum of its distinct capacities.

Further clinical trials are needed to assess whether IRF should be added to the list of the immune disturbances that benefit from the action of cyclosporin.

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