Long-term treatment of patients affected by systemic sclerosis with cyclosporin A

Sir, Systemic sclerosis (SSc) is a connective tissue disease characterized by vascular lesions and widespread fibrosis [1]. The therapy of SSc is still a matter of discussion [2]. Since 1993 we have treated SSc patients with low oral doses of cyclosporin A (CyA) associated or not with vasodilator drugs [3]. The rationale for the use of CyA in SSc lies in the fact that CyA blocks the activation of nuclear factors, such as NFAT and OAP, that are involved in the induction of mRNA transcription for several immune-activating and proinflammatory cytokines [4]. We have already described the results obtained after 1 yr of therapy with CyA and Iloprost infusion [5]. To verify whether therapeutic results can be maintained with long-term treatment without side-effects, we treated nine patients (seven females and two males, mean age 37.5 yr) affected by diffuse SSc (according to the major criteria of the American College of Rheumatology [6]) with CyA at 2.5 mg/kg/day for a period ranging from 3 to 5 yr. No patient used corticosteroids before and during the course of CyA therapy. The clinical analysis was performed by plicometry, oesophageal manometry and 24-h measurement of pH, spirometry, intrarenal duplex Doppler sonography, echocardiography and nailfold videocapillaroscopy, as described [5]. The results were expressed as scores according to a method of standardization described previously [5, 7]. The t-test for non-parametric data was used to detect statistically significant differences between means of scores.

CyA treatment was well tolerated by all the patients. In particular, blood pressure did not increase above the normal range and no abnormalities of renal function (studied by measuring serum creatinine and urea nitrogen concentrations and creatinine clearance) were observed. Only one patient had to stop CyA therapy temporarily, for 6 months, because of pneumonitis caused by a mycoplasma. Three patients showed hypertrichosis. Immunological variables (the number of CD4+ T lymphocytes and the serum concentration of immunoglobulins) did not change significantly as a result of the therapy. Indexes of inflammation (erythrocyte sedimentation rate and C-reactive protein concentration) were slightly elevated or in the normal range before treatment and did not change significantly upon CyA treatment.

Skin involvement declined progressively in seven of the nine patients and stabilized in the remaining two patients after 3 yr of treatment (Fig. 1a).

Five patients consented to pH and/or manometry studies. Progressive improvement in oesophageal parameters was observed in four of them (Fig. 1b). One patient improved initially, but then relapsed concomitantly with an infection with Helicobacter pylori, as demonstrated by examination of a biopsy of gastric mucosa.

A progressive improvement in lung score was observed during the course of therapy in the seven patients whose baseline values were abnormal (Fig. 1c). Consistently normal spirometric values were detected in the remaining two patients.

In four of the five patients who had a high basal intrarenal resistive (IR) index (determined by duplex Doppler sonography), there was progressive improvement until a normal value was reached during the first 3 yr of therapy (Fig. 1d). The remaining patients had a normal IR index at all times.

No cardiac alterations were noted at any time in any of the patients.

**FIG. 1.** Changes in skin (a), oesophageal (b), lung (c), renal (d) and nailfold videocapillaroscopy (NVC) (e) scores during 3 yr of CyA treatment. T0, T1, T2 and T3 indicate evaluations at baseline and after 1, 2 and 3 yr of treatment respectively. Statistically significant differences are indicated.
All patients had small vessel alterations at baseline and capillary lesions improved progressively during the first 2 yr of CyA therapy (Fig. 1e). Only one patient clearly worsened during the third year of treatment. The disease stabilized in patients who were treated for more than 3 yr.

Three patients stopped CyA treatment for almost 1 yr. This was because of pneumonitis in one patient; in the other two cases treatment was stopped because we wished to find out whether the disease had stabilized independently of CyA treatment. All three patients showed signs of relapse while CyA treatment was withheld, but improved when CyA treatment was restarted.

These results indicate that long-term CyA treatment is well tolerated, and that a dose of 2.5 mg/kg/day is immunosuppressive but has moderate side-effects. Disease improved or stabilized in all patients. However, the fact that in some cases the scores improved after more than 2 yr of CyA therapy suggests that the response to CyA may be slow and that a sound judgement of the efficacy of CyA cannot be formulated after a short period of clinical observation. The patients who relapsed after the interruption of CyA treatment were still responsive to CyA when the treatment was restarted. This suggests that CyA treatment in SSc should be thought of as a chronic therapy and warns against its sudden or unmotivated suspension. Larger, controlled clinical trials are needed to validate these preliminary results.


Division of Internal Medicine and 1Division of Rheumatology, Department of Internal Medicine, University of Genoa, 2Institute of Radiology, University of Genoa, 3Second Division of Pneumology, San Martino Hospital, Genoa and 4Division of Gastroenterology, Department of Internal Medicine, University of Genoa, Italy

Accepted 4 June 2001

Correspondence to: F. Indiveri, Dipartimento di Medicina Interna, Università di Genova, viale Benedetto XV n.6, 16132 Genova, Italy.