

Cyclosporin A (CyA) in primary Sjögren's syndrome: a double blind study

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SUMMARY The efficacy and toxicity of cyclosporin A (CyA) were studied in a blind fashion in 20 patients with primary Sjögren's syndrome (pSS). The dose of CyA or placebo was 5 mg/kg of body weight daily. Among the 20 patients, 10 received CyA and 10 placebo. The two groups were matched for age, sex, and disease duration. Patients treated with CyA improved in subjective xerostomia in comparison with patients treated with placebo. Subjective xerophthalmia and recurrent parotid gland enlargement did not differ in the two groups. No change in Schirmer's test and stimulated parotid flow rate was observed in either group. In contrast, the histopathological lesion of patients treated with CyA remained unchanged in most of the patients, while in the placebo treated group the lesion deteriorated. Laboratory parameters did not change before or after treatment in either group. The only clinical side effect observed in the CyA treated group was hypertrichosis.

Key words: hypertrichosis (hirsutism).

Primary Sjögren's syndrome (pSS) is a chronic autoimmune disease expanding from a local exocrinopathy to systemic disease and finally to lymphoid neoplasia.¹ Recent studies have shown that the majority of the infiltrating cells in the affected minor salivary glands of pSS patients bear the T helper cell phenotype.² At present there is no therapy available to control this lymphoproliferation, except for the replacement of the exocrine gland secretions with artificial products. Corticosteroids do not affect this process, and cytotoxic agents may increase the risk of lymphoma development in these patients.³

Cyclosporin A (CyA) is a new immunomodulatory agent which acts by inhibiting the interleukin 2 production from T helper cells.⁴⁻⁷ CyA has been used in organ and bone marrow transplantation with good results.^{8,9}

Because the major immunoregulatory aberration in pSS seems to be an increased T helper cell function and CyA acts on T helper cells we considered that it might be a beneficial agent for the treatment of this disorder. Therefore the efficacy

and toxicity of CyA in pSS patients were studied in a double blind fashion.

Patients and methods

Twenty pSS patients entered this double blind study. All fulfilled two out of the three following diagnostic criteria for the disease: keratoconjunctivitis (as defined by a decreased Schirmer's test ≤ 5 mm/5 min and positive slit lamp examination after rose bengal staining), xerostomia (as defined by decreased stimulated parotid flow rate ≤ 1 ml/5 min/gland), and a history or the presence of recurrent parotid gland enlargement. The diagnosis was confirmed in all patients by a positive minor labial salivary gland biopsy showing focal lymphocytic infiltrates $\geq 2+$ (according to Tarpley's classification).¹⁰ None of these patients was receiving any other immunosuppressive therapy, had a history of malignancy, liver failure, chronic alcoholism, chronic infections, uncontrollable hypertension, or was receiving any other drugs known to interfere with CyA.

Before entry all patients underwent a complete clinical and laboratory evaluation, including full blood count, sedimentation rate, blood urea nitrogen, serum aspartate transaminase, serum

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alanine transaminase, creatine phosphokinase, alkaline phosphatase, bilirubin, electrolytes, uric acid, rheumatoid factor titres, and urine analysis. After the initial evaluation the patients were followed up in the outpatient rheumatology clinic every two weeks for the first two months and then every month for the next four months. At every visit the same clinical and laboratory evaluation was performed. At the end of the study, in addition to clinical and laboratory evaluation, Schirmer's test, stimulated parotid flow rate, and minor salivary gland biopsy were repeated. The labial minor salivary gland histopathology was read blindly by two pathologists (JSC and CSP) and graded according to Tarpley's classification.¹⁰ Briefly, class 0=normal salivary tissue; class I (1+)=one or two round cell aggregates consisting of approximately 50 lymphocytes per lobule present; class II (2+)=more than three aggregates of round cells per lobule present; class III (3+)=diffuse lobular round cell infiltrates without fibrosis; and finally, class IV (4+)=diffuse infiltrates accompanied by fibrosis. The patients were assigned blindly and randomly to receive orally either CyA 5 mg/kg body weight daily or identical placebo. The duration of the study was six months. Before entry into the study all patients gave informed consent after receiving complete information about the possible efficacy and toxicity of the drug. χ^2 and Wilcoxon tests were applied for statistical analysis where indicated.

Results

Ten patients received CyA and 10 placebo. As shown in Table 1 all patients except one were female. The mean age and disease duration were similar in both groups. All the patients completed the study. In Table 2 the subjective changes in the oral and ocular symptoms in the two groups are shown. Most of the patients receiving CyA (eight out of 10) experienced definite improvement of xerostomia, while xerophthalmia and parotid gland enlargement remained the same in the two groups.

Table 1 Anthropometric data in patients with primary Sjögren's syndrome

	CyA	Placebo
Number of patients	10	10
Male/female	1/9	0/10
Age (years) (\bar{x} (SD))	47.3 (8.4)	54.0 (11.2)
Disease duration (years) (\bar{x} (SD))	8.6 (5.0)	9.2 (8.0)

Table 2 Subjective improvement of patients with primary Sjögren's syndrome after treatment (numbers of patients)

	CyA (n=10)	Placebo (n=10)
Xerophthalmia	2	0
Xerostomia	8	2*
Parotid gland enlargement	3	1

* $\chi^2=7.1$, $p<0.01$.

Schirmer's test and parotid flow rate (Table 3) did not show any significant difference after treatment with either CyA or placebo.

The histopathological lesion of the labial minor salivary glands remained unchanged in half of the patients treated with CyA, improved in two, and worsened in one. In two patients we were unable to obtain adequate tissue at the end of the study for re-evaluation. In contrast, in the placebo treated group two biopsies showed the same histopathological lesion as before treatment, in six the lesion deteriorated, and in two patients we were unable to obtain tissue for re-evaluation (Table 4).

During follow up all the laboratory parameters remained unchanged (data not shown). Six out of 10 patients treated with CyA developed hirsutism, which did not occur in any of the placebo treated group. Other clinical side effects were similar in both groups (Table 5).

Table 3 Schirmer's test and parotid flow

	Schirmer's test (mm/5 min)				Parotid flow (ml/5 min)			
	CyA		Placebo		CyA		Placebo	
	\bar{x}	SD	\bar{x}	SD	\bar{x}	SD	\bar{x}	SD
Before treatment	4.8	6.2	7.4	5.3	0.62	0.67	0.62	0.66
After treatment	5.2	10.6	5.0	5.1	1.14	1.28	1.06	1.08

Table 4 Lymphocytic infiltration in the labial minor salivary glands in patients with primary Sjögren's syndrome

Treatment	No of patients		
	Unchanged	Improved	Worsened
CyA (n=10)	5	2	1
Placebo (n=10)	2	—	6

Table 5 Clinical side effects of patients with primary Sjögren's syndrome

	CyA (n=10)	Placebo (n=10)
Hirsutism	6	0
Infections	4	5
Hypertension	1	0
Gingival hypertrophy	1	0
Nausea, vomiting	1	1

Discussion

Autoimmune diseases reported to respond to CyA range from Grave's disease to ichthyosis.¹¹ CyA has been found to improve a majority of patients with inflammatory uveitis unresponsive to corticosteroids or cytotoxic agents, or both.¹²⁻¹³ In Grave's ophthalmopathy CyA has been reported to be effective by some investigators and ineffective by others.¹⁴⁻¹⁶ In an uncontrolled study of five patients with active systemic lupus erythematosus no improvement was noted in the seven weeks' treatment period.¹⁷ Treatment with CyA in rheumatoid arthritis has been reported both to be useful¹⁸⁻¹⁹ and ineffective.²⁰

In this double blind study small doses of CyA improved subjective xerostomia and seemed to retard the histopathological lesion of pSS patients. No changes of the objective indices of lacrimal and parotid flow were observed, however. This subjective-objective discrepancy could be explained on two grounds. There is a tremendous variability of parotid flow in normal people. Menstrual cycle, time of the day, food, emotions, and other factors interfere with the flow.²¹ Thus the lack of change in parotid flow might be explained by the unreliability of this factor. Alternatively, the unchanged parotid flow rate might relate to the short duration of treatment. The latter explanation will be answered in the one year follow up study of CyA.

The clinical side effects observed in CyA treated patients were minimal. Hirsutism, of course, distressed the patients. Infections, hypertension, deterioration of renal function, and lymphoma were not observed. This can be attributed to the small dose of CyA used. Although no clinical and/or laboratory renal toxicity was observed, renal biopsy done in these patients showed early CyA toxicity (Siamopoulos *et al*, unpublished information). Thus the minimal clinical improvement observed in these patients, coupled with the potentially serious side effects (nephrotoxicity), makes the use of this agent questionable in this disease.

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