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# Cyclosporine-A plus steroids versus steroids alone in the 12-month treatment of systemic lupus erythematosus

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**Abstract** The positive results obtained with cyclosporine-A both in an experimental model and in selected patients with advanced systemic lupus erythematosus support the hypothesis that the drug could be used as a steroid sparer in the earliest stages of active disease. To determine the 12-month clinical efficacy (disease control and steroid sparing), safety, and tolerability of low-dose cyclosporine-A plus steroids versus steroids alone, we designed a multicenter, open, prospective, randomized, pilot study, controlled for parallel groups. The patients were then followed up to month 24. A total of 18 consenting patients with recently diagnosed systemic lupus erythematosus of moderate severity indicated for the use of steroids in acute boluses and subsequently per os were enrolled at two university hospital medical centers. The protocol was based on three 1-g boluses of 6-methylprednisolone followed by cyclosporine-A (<5 mg/kg per day) plus prednisone 0.5–1 mg/kg per day per os, reduced by 5 mg/day every 2 weeks following clinical remission, versus the same doses of oral prednisone alone. The efficacy evaluation was based on a four-point scale (from absent/none to severe) for signs and symptoms of systemic lupus erythematosus and immunoserological parameters. The disease activity index and cumulative prednisone dose per patient were analyzed. Any adverse events were reported. All patients showed a reduction in disease activity index within the 1st month. The results were significantly better in the group with cyclosporine-A plus prednisone throughout month 12 (baseline and 12-month disease activity indexes: 21.3±8.6 and 5.0±2.5 versus 20.4±7.1 and 8.8±6.0 in the prednisone group, $P<0.05$). The 12-month cumulative mean dose of prednisone was significantly lower in the group with both cyclosporine-A plus prednisone (179.4±40.1 versus 231.8±97.1 mg/kg, $P<0.005$). No unusual adverse events related to the study drugs have been reported. In particular, renal function and blood pressure monitoring revealed no significant changes from mean baseline values in either group. No disease flares were reported in the group treated with cyclosporine-A plus prednisone during the 12- to 24-month period. Thus cyclosporine-A represents a useful corticosteroid sparer in the maintenance of clinical remission in patients with an early-stage, active systemic lupus erythematosus.

**Key words** Cyclosporine-A · Steroids · Systemic lupus erythematosus

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## Introduction

Although the etiology of systemic lupus erythematosus (SLE) remains unknown, much has been learned about its pathogenic mechanisms, clinical patterns, and prognosis, as well as the role of various therapies in modifying the disease course [1]. In the vast majority of patients, SLE tends to be both benign and chronic, allowing management with anti-inflammatory drugs, antimalarials, and low-dose corticosteroids. Although these drugs are widely accepted as safe and without risks, there are substantial long-term complications associated with this "conservative" approach [2, 3].

Cyclosporine-A (CsA) is a cyclic, lypophilic undecapeptide that exerts immunosuppressive but not cytostatic effects by inhibiting lymphokine production, specifically interleukin-2 and interferon-γ [4]. Since 1978, CsA has been successfully used for the prevention of graft rejection in organ transplant recipients. In recent years, it has also been used with encouraging results in the treatment of various organ- and non-organ-specific autoimmune diseases [5, 6].

The positive results obtained with CsA in an experimental model of early as opposed to advanced stage SLE [7] support the hypothesis that the drug could also be used as a steroid sparer in the earliest stages of active disease. Indeed, a considerable number of uncontrolled clinical trials involving selected patients with advanced disease refractory to conventional treatments [8–12], and a few controlled trials in lupus nephritis [13–17], have been carried out using mean CsA doses of <5 mg/kg per day, combined with steroids and/or immunosuppressants, with periods of observation lasting for up to 4 years. Positive results have been reported, although these have not been lasting after drug discontinuation.

We here report the results of a multicenter, open, prospective, randomized, parallel-group, 12-month pilot study with a 24-month follow-up, which was designed to determine the clinical efficacy (disease controlling and steroid-sparing effects), safety, and tolerability of low-dose CsA when added to a maintenance dose of prednisone, versus prednisone alone.

## Materials and methods

### Patient selection

Patients were eligible for the study if they were aged between 18 and 70 years, and had SLE, as determined by the revised criteria of the American Rheumatism Association [18], of moderate severity indicating the use of steroids in acute boluses and subsequently per os, including those who had occasionally taken steroids (0.2–0.3 mg/kg per day) during the previous 6 months.

Patients with very severe SLE or at first diagnosis and indicated for treatment with chloroquine alone were excluded, as were pregnant women, patients with contraindications to the use of CsA (renal function impairment, liver disease, uncontrolled infections, neoplasm, concomitant nephrotoxic drug therapies), and cases of malabsorption or alcohol abuse.

All of the eligible patients gave their informed consent to the study, approval for which was obtained from the ethics committee of each center.

### Trial treatments

During the 3 days before randomization, the selected patients received three 1-g boluses of 6-methylprednisolone. The initial CsA dose was <5 mg/kg per day per os divided into two administrations, subsequently adjusted by means of dose reductions of 25%–50%, and temporary or permanent discontinuation in the case of an increase in: (1) serum creatinine levels >30% above the mean of two baseline measurements; (2) serum transaminases, alkaline phosphatase, or total bilirubin levels of more than twice the upper reference value for the laboratory used by the center; (3) serum potassium levels >5.0 mmol/l; (4) CsA trough levels >200 ng/ml, measured in whole blood by the specific monoclonal antibody radioimmunoassay; and/or (5) systolic/diastolic blood pressure >160/95 mmHg on two consecutive visits [19].

After month 12, the CsA dose was gradually reduced (by 0.5 mg/kg every 15–30 days) until complete withdrawal, or the individual minimum maintenance dose was determined, which was then continued up to month 24. Prednisone (PDN) was given with low-dose CsA or alone, at doses of 0.5–1 mg/kg per os, reduced by 5 mg/day every 2 weeks following clinical remission.

### Monitoring

Control examinations were planned at baseline, on day 15, and at months 1, 2, 3, 4, 5, 6, 9, 12, 18, and 24. *Efficacy* monitoring was based on the following criteria: (1) a four-point scale (from absent/none to severe) that was used to evaluate the presence of SLE signs and symptoms (asthenia, arthralgia/arthritis, cutaneous vasculitis, malar rash, alopecia, Raynaud's phenomenon, purpura, sicca syndrome, mucosal ulcers, lymph node enlargement, splenomegaly, hepatomegaly, pleuritis, pericarditis, abdominal pains, myalgia/myositis, psychosis, convulsions, peripheral neuropathy) [20]; (2) the behavior of immunoserological parameters, namely antinuclear antibodies (ANA) using indirect immunofluorescence on Hep-2 cells; anti-double-stranded DNA antibodies (anti-dsDNA) using the *Crithidia luciliae* test; serum levels of C3 and C4 complement components, IgG, IgA, and IgM, by means of radial immunodiffusion; and (3) routine laboratory parameters, such as the erythrocyte sedimentation rate (ESR), blood cell counts, liver and kidney function tests, total serum protein and electrophoresis, 24-h urinary protein excretion, and urine sediment.

The SLE disease activity index (SLE-DAI) score [21] and cumulative dose of PDN per patient were calculated. Clinical remission was defined as the resolution of any systemic signs and symptoms that were present at the time of diagnosis, immunological remission as the normalization of altered immunoserological parameters, and complete or partial clinical remission as the occurrence of both clinical and immunoserological remission, simultaneously or not. A relapse was defined as the appearance or reappearance of signs and symptoms after clinical remission.

In addition to the physical examinations, *safety* monitoring was based on the evaluation of blood pressure and hemoglobin, differential leukocyte counts, platelets, transaminases, total bilirubin, alkaline phophatase, serum creatinine, blood urea nitrogen, electrolytes, uric acid, and urinalysis. In addition, creatinine clearance was calculated using the Cockroft formula [22]. The assessment of *tolerability* was based on the occurrence of any adverse events.

### Statistical analysis

To establish the statistical significance of the observed differences, analysis of variance, Student's *t*-test for paired data, and Wilcoxon's signed rank test were used as appropriate. *P* values of less than 0.05 were considered significant.

## Results

### Patients

The baseline clinical characteristics and previous corticosteroid therapy of the study patients are summarized in Table 1. Eighteen consenting patients aged 18–43 years, whose SLE had been diagnosed a median of 4 months before, were enrolled. Ten (6 women/4 men) were given CsA plus PDN and 8 (all women) PDN alone. Nine patients on CsA plus PDN and 3 on PDN alone completed the 12-month treatment, as scheduled in the study protocol. One patient per group prematurely withdrew due to worsening of disease, and 3 of the PDN-treated patients who worsened after remission were given immunosuppressant rescue therapy. One of the patients in the PDN group died of acute pulmonary edema at month 7. Twelve patients completed the 24-month follow-up.

**Table 1** Patient characteristics (*SLE* systemic lupus erythematosus, *CsA* cyclosporine-A, *PDN* prednisone, *ARA* American Rheumatism Association, *DAI* disease activity index)

| | CsA + PDN ($n$=10) | PDN ($n$=8) |
|---|---|---|
| Age (median, years) | 30 | 29 |
| Sex (F/M) | 6/4 | 8/0 |
| Disease duration (median, years) | 0.3 | 0.1 |
| SLE ARA criteria (No. of patients) | | |
| Malar rash | 7 | 2 |
| Discoid erythema | 7 | 1 |
| Photosensitivity | 7 | 4 |
| Oral/nasopharyngeal ulcers | 0 | 1 |
| Arthritis/arthralgia | 8 | 6 |
| Serositis | 5 | 6 |
| Nephropathy (proteinuria) | 6 | 4 |
| Neurological disorders (headaches, seizures) | 1 | 1 |
| Hematological disorders (anemia, leukopenia, lymphopenia, thrombocytopenia) | 3 | 4 |
| Immunological disorders (anti-dsDNA antibodies) | 8 | 8 |
| Antinuclear antibodies | 8 | 8 |
| SLE-DAI (median, points) | 21 | 20 |
| Previous treatments | | |
| Cumulative prednisone dose (mean ± SD, mg/kg) | 25±14.4 | 20.9±16.1 |
| Cumulative 6-methylprednisolone (mean ± SD, mg prednisone equivalent/kg) | 64.1±10.5 | 61.3±11.8 |

### Clinical manifestations

Good disease control was obtained in both groups, with 8 patients treated with CsA and PDN and 7 PDN-treated patients entering partial remission, and 1 of the CsA plus PDN group achieving complete remission. These results were maintained throughout the study in all the patients treated with CsA plus PDN, whereas 3 of the PDN-treated patients worsened after remission and were treated with immunosuppressant rescue therapy (Fig. 1).

With regard to clinical conditions and symptoms, when present at study entry, asthenia disappeared within 1month in 6 of 7 patients in the CsA plus PDN group and in 5 of 7 in the PDN group. Erythematous manifestations completely resolved in all the 7 CsA plus PDN patients (1 by month 3). Joint pain and tenderness, which were present at entry in 80% of the patients in both groups, disappeared within 2 months in all but 1 of the patients in the CsA plus PDN group, but persisted up to month 12 in 2 patients in the control group. Cutaneous vasculitis, purpura, myositis, and hepatomegaly were significantly reduced by CsA treatment. Pericarditis and/or pleuritis, which were present in 5 and 6 patients of the CsA plus PDN and PDN groups respectively, were promptly responsive to corticosteroid pulses.

All of the patients showed a reduction in SLE-DAI scores within the 1st month, although the results were significantly better in the CsA plus PDN group up to month 12 (mean values±SD at baseline and after 1 and 12 months ranging from 21.3±8.6 to 11.1±6.4 and 5.0±2.5 in the CsA plus PDN group, and from 20.4±7.1 to 9.3±4.8 and 8.8±6.0 in the PDN group, $P<0.05$).

### Laboratory parameters

There was a parallel reduction in the 12-month mean ESR values (from 80±51 to 34±22 mm/h in the CsA plus PDN group, and from 53±18 to 25±14 mm/h in the PDN group), and an increase in serum complement levels (C3 from 49±19 to 75±15 mg/dl and C4 from 15±12 to 22±13 mg/dl in the CsA plus PDN group, C3 from 52±23 to 78±28 mg/dl and C4 from 14±6 to 19±11 mg/dl in the PDN group). No changes were observed in peripheral blood cell counts or serum immunoglobulin levels. ANA titers decreased in half of the patients of both groups; anti-DNA titers became negative in 6 of 10 patients in the CsA plus PDN group, but in only 2 of the 8 PDN-treated patients. When present, proteinuria responded to the CsA plus PDN treatment within 6 months, but there was no response in 3 PDN-treated patients; proteinuria appeared during the course of treatment in 1 patient in the PDN group.

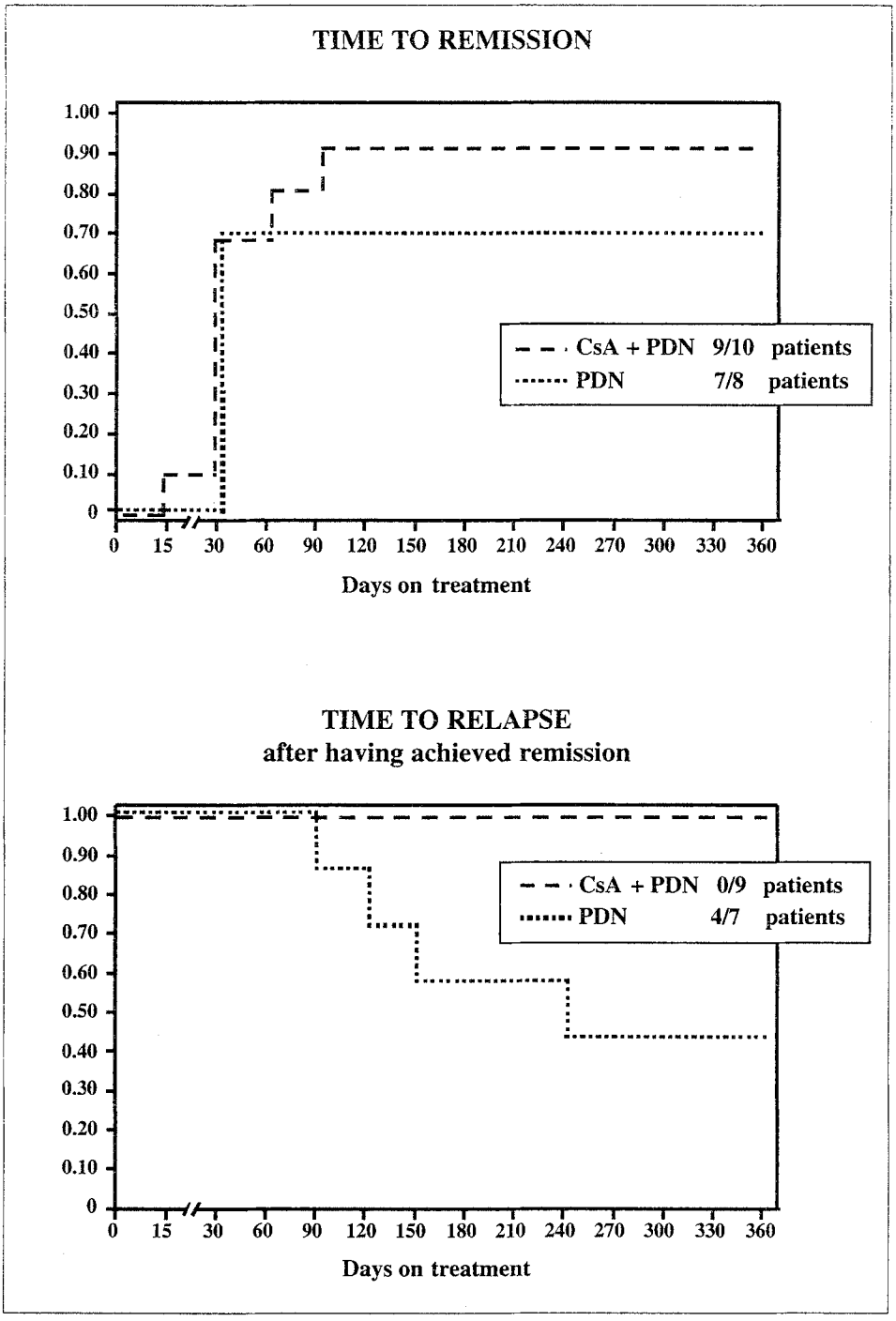


**Fig. 1** Time to remission and time to relapse after having achieved remission over 12 months in 10 cyclosporine-A (*CsA*) plus prednisone (*PDN*) and 8 PDN-treated patients

## Trial treatments

The mean CsA dose at baseline was 4.2±0.9 mg/kg per day, adjusted to 3.8±0.9 from month 6 and 3.1±1.3 at month 12. From month 6 to month 12, the initial PDN mean dose of 0.5 mg/kg per day per os was significantly reduced to 0.2±0.1 in the CsA plus PDN group, but only to 0.4±0.2 in the PDN group. The 12-month cumulative mean dose of PDN was significantly lower in the CsA plus PDN group (179.4±40.1 versus 231.8±97.1 mg/kg, $P<0.005$).

## Adverse events

The adverse events recorded during the study are summarized in Table 2. Most did not require specific treatment or the withdrawal of patients from the study, with the exception of 1 case of acute pulmonary edema that led to the death of 1 PDN-treated patient at month 7, and 1 case of renal insufficiency in 1 patient treated with CsA plus PDN on day 7 that was considered unlikely to be related to the trial treatments.

No unusual adverse events related to the study drugs were

**Table 2** Adverse events

| No. of patients with adverse events | CsA + PDN 6/10 | PDN 5/8 |
|---|---|---|
| Mucocutaneous alterations (hypertrichosis, striae rubrae) | – | 4 |
| Gastrointestinal disturbances (nausea) | – | 1 |
| Neurological disturbances (headache, insomnia, depression) | – | 3 |
| Hypertension (episodes) | 4 | 3 |
| Infections | | |
| bacterial | 1 | – |
| viral | – | – |
| mycotic | 1 | – |
| Increased liver enzyme levels | 2 | – |
| Thrombocytopenia | 1 | – |
| Renal impairment | | |
| increased serum creatinine | 1 | – |
| increased blood urea nitrogen | 1 | 1 |
| renal failure | 1 | 1 |
| Pulmonary edema | 1 | 1 (death) |
| Metabolic disorders (Cushing-like, thyroid goiter) | 1 | 2 |
| Weight increase ≥10% of body weight | 3 | 3 |

reported. In particular, renal function and blood pressure monitoring revealed no significant changes from the mean baseline values in either group. Episodes of hypertension occurred in 4 CsA plus PDN and 3 PDN-treated patients, and were resolved by the administration of calcium antagonists. The signs of kidney dysfunction present in 1 patient in each group were resolved by reducing the CsA dosage in 1, and by giving immunosuppressant rescue therapy to the other. Signs of hypercortisolism and neurological disturbances were present in 6 CsA plus PDN- and 3 PDN-treated patients. Intercurrent infections and a mild increase in liver enzyme levels respectively occurred in 2 CsA plus PDN-treated patients, none of whom required any treatment modification. Thrombocytopenia (platelets<150,000/mm$^3$) was resolved by modulating the CsA dosage up to 5 mg/kg per day for 1 month.

### Follow-up period

Of the 9 patients on CsA plus PDN completing the 12-month treatment as scheduled in the study protocol, 4 maintained remission at month 24 at a mean CsA dose of 2 mg/kg per day plus a mean PDN dose of 0.12 mg/kg per day, and 3 patients were able to discontinue steroids completely at maintenance CsA doses of 3 mg/kg per day; in the remaining 2 patients, CsA was tapered within 18 months without any further flare up. Of the 3 patients in the control group on PDN alone at 12 months, only 1 was in remission at a PDN dose of 0.21 mg/kg per day at month 24; the other 2 required the addition of CsA and cyclophosphamide, respectively.

## Discussion

SLE is a disease that has remarkably heterogeneous clinical characteristics, presentation, and course; this variability makes it difficult to carry out controlled studies of a large number of patients. As the heterogeneity of the clinical course precludes a standard treatment that can be consistently applied in all patients, the extent and intensity of therapeutic measures should be guided by the activity and severity of the disease in individual cases.

The therapeutic repertoire for the treatment of SLE includes a number of drugs which are thought to inhibit inflammatory pathways in a non-selective manner or to interfere with the underlying autoimmune process. Corticosteroids continue to be irreplaceable in the management of SLE [23]. Since many lupus manifestations respond to intermediate or high doses, they represent the most-important class of drugs for the control of acute manifestations. However, they do not appear to improve long-term outcome [24], and so additional strategies to prevent disease progression and their side effects should be considered. Moreover, although complete discontinuation of corticosteroids is seldom possible, this option should always be evaluated.

Because of its unique selectiveness, CsA has changed the therapeutic praxis in organ transplantation and some autoimmune conditions, particularly now that its toxicity has become less of a problem due to a lower initial dose and early tapering in the case of a significant increase in creatinine levels [25].

A number of non-comparative trials involving patients with severe SLE refractory to conventional treatment have demonstrated that low-dose CsA in combination with steroids (and occasionally additional cytotoxic immunosuppressant agents) can provide long-term disease improvement or remission and a reduction in the use of steroids [8–12]. The CsA/steroid combination has also led to clinical benefits in patients with lupus nephritis, most of whom had failed to respond to conventional treatment [13–16].

CsA nephrotoxicity has been documented in some patients receiving the drug for SLE, but initial biopsy data suggest that this complication is not a limiting therapeutic factor in most cases [13]. Although initial efficacy and tolerability data relating to patients with lupus nephritis are favorable, CsA is more likely to be used in patients whose kidney function remains relatively unimpaired.

The results of this randomized controlled study indicate that CsA can act as a corticosteroid sparer in the maintenance of clinical remission. All of the patients showed good disease control, as indicated by the significant reduction in both the four-point scale of SLE signs and symptoms, and in the SLE-DAI score. Eight patients treated with CsA plus PDN and 7 PDN-treated patients achieved partial remission; 1 patient on the combined treatment achieved complete remission by month 3. These results were maintained throughout the study in all the patients treated with CsA plus PDN, whereas 3 of the PDN-treated patients worsened after remission and were treated with immunosuppressant rescue therapy. In general, clinical benefits were mostly observed within the 1st month as a result of 6-methylprednisolone bolus administration, but the addition of CsA seemed to consolidate and even achieve further improvement for at least 1 year, with a significant and clinically meaningful steroid-sparing effect (a mean of 3 g/year in a patient of 70 kg).

Asthenia, arthralgia/arthritis, cutaneous vasculitis, malar rash, purpura, lymph node enlargement, splenomegaly, hepatomegaly, and thrombocytopenia were all particularly sensitive to the combined treatment. Nephritic manifestations also appeared to be sensitive to CsA treatment: proteinuria responded to the CsA plus PDN combination by month 6, but 3 PDN-treated patients showed no proteinuria response, and proteinuria actually appeared during treatment in 1 patient. Similar results have been reported by other groups [8–17], but it is still uncertain whether this effect on proteinuria reflects a disease-modifying, immunosuppressive effect of CsA or a decrease in the glomerular filtration rate.

No serious signs of kidney dysfunction (i.e., increased creatinine levels) or hypertension were observed in most patients; however, it should be emphasized that patients with renal function or blood pressure abnormalities at entry were excluded from the study, and that the CsA dose never exceeded 5 mg/kg per day. The follow-up period to month 24 showed that even low doses of CsA alone (3 mg/kg per day) were capable of maintaining the clinical results. In such cases, alternating CsA and PDN treatments are likely to maintain remission. In patients who present more-severe Cushing-like effects, the administration of CsA might be further prolonged, provided renal function is carefully monitored. Gradual tapering of the drug might be tried every year or so, in order to identify the few patients who will remain in remission without CsA.

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