The effects of oral cyclosporine in plaque-type psoriasis: the experience of Andreas Sygros Hospital

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Introduction: Several studies have shown the efficacy of cyclosporine in the treatment of chronic plaque-type psoriasis. **Aim:** The aim of this retrospective study was to assess the clinical response and toxicity of cyclosporine in a small cohort of patients with refractory plaque-type psoriasis. **Methods:** A total of 39 patients, including 25 males (64%) and 14 females (36%), with mild-to-severe plaque-type psoriasis were included in this retrospective, chart-based study. Treatment consisted of cyclosporine at a dose of 1.5–5.0 mg/kg/day (mean dose of 2.53 mg/kg/day). The mean duration of therapy was 31.0 weeks (range of 3–227 weeks). **Main outcome measures:** The main outcome measures were the physician's global assessment and the psoriasis area and severity index (PASI). **Results:** Satisfactory clinical response, defined as significant improvement, based on the physician's global assessment, was observed in 31 patients (79.9%). Disease remission was observed in 26 (66.7%) and 29 patients (74.4%), with a reduction in PASI score by 80% and 50% respectively. The mean PASI score decreased by 96% from 12.7 (range of 1–39) at the beginning of treatment to 0.5 (range 0–5) at the end of treatment. Disease recurrence, defined as an increase of PASI score by 50%, was observed in 19 patients (73.1%). The median time-to-relapse was 105 days, according to the Kaplan–Meier curves. No statistically significant change in the arterial blood pressure and serum creatinine levels were noted during treatment (paired t-test, p = 0,556). In five cases (12.8%), there was an increase in creatinine levels by more than 30%. **Conclusion:** Treatment with cyclosporine is well tolerated and provides an effective modality for the control of plaque-type psoriasis.

Keywords: cyclosporine, disease-free interval, psoriasis, relapse rate, side effects

Psoriasis is a chronic cutaneous disease that can seriously affect a patient's psychologic status and quality of life. To control the disease, life-long intermittent treatment is required. Various treatment modalities have been employed to achieve this goal. Mild forms of the disease are usually treated with topical agents, such as topical steroids, calcipotriol (Dovonex®, Leo Laboratories) tar, or dithranol. In more extensive forms of the disease, phototherapy/ultraviolet (UV)B and long-wave ultraviolet radiation photochemotherapy (PUVA) or systemic therapy are considered. Systemic therapies, however, are associated with side effects that limit their use on a chronic basis. PUVA therapy, for instance, has been associated with an increased risk of skin cancer. Methotrexate can cause hepatotoxicity, while systemic retinoids are highly teratogenic. The use of cyclosporine has been shown to be effective in several randomized, controlled studies [1–3], however serious concerns have been raised with regards to its associated nephrotoxicity. It has been recommended that continuous therapy with cyclosporine should not exceed 2 years and that renal function should be monitored throughout treatment.

In this retrospective study, we intended to investigate the efficacy and side-effects of cyclosporine in a small cohort of patients with plaque-type psoriasis who were unresponsive to topical or other systemic therapy.

Methods

Subjects

Our group performed a retrospective analysis of all patients who were diagnosed with psoriasis at the Psoriasis Clinic in Andreas Sygros Hospital (Athens, Greece) over a period of 5 years (January 1997–2002) and who had received systemic cyclosporine. The subjects included in the analysis were aged between 20 and 70 years and had mild-to-severe plaque-type psoriasis that was refractory to other treatments, such as topical steroids, phototherapy/PUVA, methotrexate, or retinoids, or had to discontinue these treatments because of side effects. Of the 39 patients, 14 (35%) had mild-to-moderate disease (psoriasis area and severity index [PASI] < 10), while 25 suffered from moderate-to-severe psoriasis. Patients not included in this study were those who had pustular, erythrodermic or arthropathic forms of psoriasis, an

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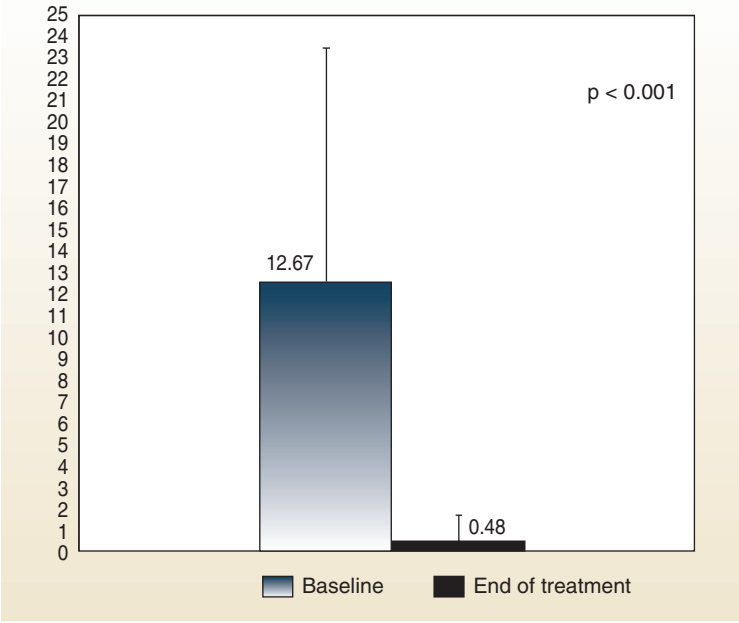
Figure 1. Mean psoriasis area and severity index (PASI) score at baseline and at the end of treatment.



Reduction of PASI score (mean + standard deviation) before and after treatment.

abnormal liver or renal function, hyperuricaemia, hyperkalemia, a history of receiving immunomodulatory or cytotoxic drugs, a history of malignancy, uncontrolled hypertension, untreated acute infections or concomitant treatment with potentially nephrotoxic medication.

Treatment dosage & schedule

Cyclosporine (Sandimmune Neoral®, Novartis) was administered at a starting dose of 1.5–3.0 mg/kg daily and was increased by increments of 0.5–1.0 mg/kg daily to a maximum of 5mg/kg/day to achieve clearance (>90% reduction in area affected). With the exception of a few patients that required continuous administration for disease control, most patients received cyclosporine on an intermittent regimen until clearance was achieved. Patients who achieved satisfactory clinical response were instructed to reduce the dose by 1 mg/kg/day each week until stopping within 4 weeks. Dosage reductions were also allowed for elevated creatinine concentrations of more than 30% above baseline or hypertension (> 95 mmHg rise in diastolic blood pressure in two consecutive visits). Topical agents, such as corticosteroids, calcipotriol, salicylic acid preparations and emolients were used concomitantly with cyclosporine in most patients.

Main outcome measures

The physician's global assessment and the PASI were used as the primary efficacy criteria in this study. Secondary criteria included the mean relapse-free interval. The assessment of drug toxicity included adverse effects and, in particular, disturbances in arterial blood pressure, renal function and of further relevant laboratory parameters.

Statistical analysis

Quantitative variables are represented using the mean value, median, standard deviation and range. Qualitative variables are represented using the frequencies and percent. Comparisons of absolute values of variables (creatinine and PASI score) during the observation period were analyzed using the paired-samples t-test or Wilcoxon test in case of violations of assumptions. The median time-to-disease recurrence was estimated using the Kaplan–Meier estimates.

All tests are two-sided with 95% significance level. P-values less than or equal to 0.05 were considered as statistically significant. Statistical analysis was performed using the statistical package SAS 8.1. Sample size was not estimated using statistical methods. Missing data was not estimated nor replaced by the last observation carried forward (LOCF) procedure.

Results

Demographic data

Of the 96 patients who were treated with systemic therapy for their psoriasis, 49 (51%) had received cyclosporine during the study period. Complete data and follow up information were available for 39 of these patients, including 25 males (64%) and 14 females (35.9%).

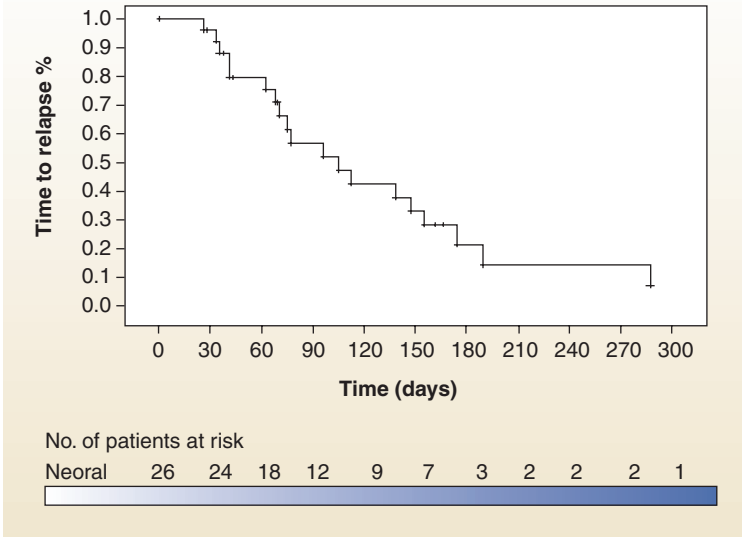
Dosage & duration of treatment

The mean duration of treatment was 31 weeks (range: 3–227 weeks), while the mean dose of cyclosporine used was 2.5 mg/kd/day with a range of 1.5–5.0 mg/kg/day. The median time-to-remission was 60 days.

Efficacy

Satisfactory clinical response, defined as significant improvement, based on the physician's global assessment, was observed in 31 patients (79.5%). Disease remission, defined as greater than 80% PASI reduction, was noted in 26 patients (67%), while reductions of PASI 50% were seen in 29 patients (74.4%). The mean PASI score decreased by 96%, from 12.7 ± 10.8 at the beginning of

Figure 2. Kaplan–Meier estimates of recurrence rates (n = 26).



Kaplan–Meier estimates of recurrence rates after 300 days in the study population.

treatment to 0.5 ± 1.2 ($p < 0.001$) at the end of the treatment period (**Figure 1**).

Relapse rate & time to relapse

Relapse, defined as an increase in PASI by 50%, occurred in 19 patients (73.1%) of the 26 remitted cases. The median time to relapse after the end of treatment was estimated to be 105 days (95% confidence interval = 70–155 days) (**Figure 2**).

Safety & tolerability

Common adverse effects included nausea, paresthesias, headache and hypertrichosis. A total of eight patients discontinued treatment because of lack of response. No statistically significant change in arterial blood pressure measurements or serum creatinine levels was observed during the treatment period (paired t-test, $p = 0.556$). The mean creatinine value was 1.0 ± 0.19 mg/dl with a range of 0.6 to 1.4 mg/dl (**Figure 3**). A rise in creatinine levels of more than 30% was observed in five cases, for which a reduction in the dose of cyclosporine was required without any further sequelae.

Discussion

In the mid 1970s the therapeutic efficacy of cyclosporine, observed inadvertently in psoriatic patients undergoing transplantation, revolutionized our concepts on the pathogenesis of psoriasis [4]. It has been demonstrated that activated T-cells play a key role in increased lesional keratinocyte proliferation, accumulation of neutrophils and psoriatic inflammation [5]. Cyclosporine inhibits the phosphatase calcineurin via binding to intracellular cyclophilin A, resulting in increased phosphorylation of the nuclear factor of activated T-cells (NFAT) and, thus, preventing the translocation of NFAT to the nucleus, which is essential for interleukin (IL)-2 gene transcription, IL-2 production and T-cell activation [6].

The therapeutic effect of cyclosporine in psoriasis may be achieved by modulation of the epidermal cytokine network [7], by inhibition of antigen presentation by Langerhans cells [8], or by direct inhibition of the proliferation of keratinocytes [9]. It has also been demonstrated that cyclosporine may also inhibit angiogenesis induced by the vascular endothelial growth factor (VEGF) and improve psoriasis, through angiogenic mechanisms [10].

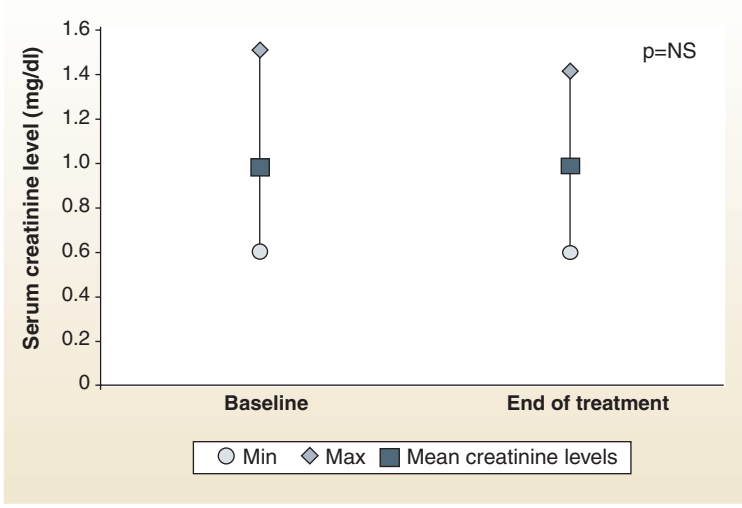
Unquestionably, cyclosporine remains one of the most effective treatments for severe psoriasis. Psoriasis affecting more than 10–20% of the skin or PASI over ten is defined as severe disease [11].

It is important, however, to emphasize that the 'severity' of psoriasis is not always defined by quantitative measures and that other factors, such as quality of life issues and degree of phychosocial impairment can be equally influential. Although our patients presented with a wide range of PASI scores (1–39), the 14 patients (35%) who were defined as having mild-to-moderate disease (PASI < 10), could also be considered to have more severe disease because of the degree of psychosocial impairment and disability due their psoriasis [11].

Low dose short-term cyclosporine has been found at least as effective as high dose etretinate (Tegison®, Hoffmann-La Roche) in severe psoriasis [12]. When used in higher doses (5 mg/kg/day), cyclosporine induces remission more rapidly than etreninate [13]. Compared with methotrexate, cyclosporine at a dose of 3 mg/kg/day appears to be equally efficacious in inducing remission and improving quality of life [14].

Cyclosporine has been employed in psoriasis both in the form of intermittent short courses and as continuous long-term treatment. At doses 2.5–5 mg/kg/day given for 12–16 weeks it has been found to rapidly produce marked improvement or complete clearance of the disease in 80–90% of patients [13,15–20]. In all randomized trials a reduction in PASI of greater than 50% has been observed [12–20]. Intermittent short courses may also achieve sustained remission in up to 45% of patients for 4 months and in 30% of patients for

Figure 3. Mean serum creatinine levels at baseline and at the end of treatment.



Mean serum creatinine levels at baseline and at the end of treatment.

6 months [19]. To maintain remission, cyclosporine may be administered continuously at a dose 3 mg/kg/day or even lower [21].

Our results demonstrating a reduction of PASI greater than 50% in 74.4% of our patients taking cyclosporine 2.5–5 mg/kg/day, with a median time to remission of 60 days, are consistent with other studies. We elected to taper cyclosporine during a 4-week period, although there is only sparse data in the literature favoring a tapered cessation of therapy. No rebound effect has been noted by abrupt discontinuation of therapy and the time to remission does not differ between patients who ceased treatment abruptly and those who did so in a tapered fashion [19]. Others have found only a slight difference in the two modes of discontinuation [18].

Highlights

- We conducted a retrospective analysis of all patients with mild-to-severe plaque-type psoriasis who had received cyclosporine and were followed at our clinic over a period of 5 years.
- Disease remission, defined as a greater than 80% reduction of the psoriasis area and severity index (PASI) score, was observed in 67% of patients, while 74.4% of patients were noted to have a 50% PASI reduction.
- The relapse rate in our cohort was 73% with a median time-to-relapse of 105 days.
- No statistically significant changes in the arterial blood pressure or serum creatinine levels were noted during treatment.
- Cyclosporine has an excellent therapeutic effect in plaque-type psoriasis without any serious side effects provided that appropriate guidelines are closely followed.

In our study the relapse rate was 73.1% and the median time-to-relapse was 105 days, which is consistent with observations in other series. Ho and colleagues [19] and Berth-Jones and colleagues [17] found a median time to relapse of 115 and 72 days respectively.

In a double-blind study comparing different doses of cyclosporine it was noted that the therapeutic effects of cyclosporine are dose-dependent [22]. Higher doses (5 mg/kg/day) have been shown to be more effective than lower doses (1.25–2.5 mg/kg/day) [22]. However, in other studies this observation has not been confirmed, although a markedly more rapid onset of action has been shown with cyclosporine at a dose of 5 mg/kg/day [20]. Our patients responded to a relatively low dose, as the mean cyclosporine dose needed to induce remission was 2.53 mg/kg/day.

The major cyclosporine adverse events ie, nephropathy and hypertension, were shown to be dose-dependent, occurring at prolonged exposure to the drug and at doses greater than 5 mg/kg/day [23,24]. Cyclosporine causes increased vascular resistance, resulting in reduced renal plasma flow and decreased creatinine clearance, which manifests as a rise in serum creatinine [25]. If serum creatinine increases by 30% above the baseline value, then cyclosporine dose should be reduced [25]. Only a small percentage of patients (10–27%) experience a transient elevation in serum creatinine, which is typically amenable to dose reduction [17–19]. It has also been demonstrated that only 5–12% of patients develop new onset hypertension with intermittent cyclosporine therapy responding to dose reduction or antihypertensive medication [18,20].

In this study we detected a rise in creatinine over 30% above baseline and a rise in blood pressure in only 13 and 10% of our patients respectively, returning to pretreatment values with dose reduction and not requiring discontinuation of the medication. Those observations are consistent with previous studies.

Other adverse events observed in our series (gastrointestinal and neurological events, hypertrichosis and metabolic abnormalities) have been well described with cyclosporine treatment [11]. Only one of our patients had to discontinue the medication due to increased liver enzymes and serum lipids.

Certain limitations are evident in study, such as its retrospective nature and the relatively small number of examined patients. Our hospital is a large referral center for skin diseases in Greece and thus, a much larger number of patients with

various forms of psoriasis is being evaluated and treated annually, either at the in- or the outpatient setting. The Psoriasis Clinic is a more specialized unit operating once weekly that manages a limited number of selected psoriasis patients who have recalcitrant disease. Even though we could have included other patients, our small cohort of patients was evaluated by the same physicians and was followed closely resulting in a more accurate comparison of clinical response to cyclosporine.

Our 5-year experience on cyclosporine for mild-to-severe plaque-type psoriasis provides useful clinical data on the efficacy and safety of this therapeutic modality. We conclude that cyclosporine has an excellent therapeutic effect in psoriasis without any serious side effects, provided that appropriate guidelines are closely followed.

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