

## Original Article

# Safety of short-term cyclosporin in atopic dermatitis

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**Abstract** *Background* Cyclosporin is an immunosuppressive drug, which is also being used in dermatology in different indications. Although its toxicity is very high but in low dose and for short term it can be used relatively safely.

*Patients and methods* 25 male and female patients within age group 15-65 (mean 27.1) were selected. There were 11 males (44%) and 14 females (56%). The study was divided into three periods. Pre treatment period comprising the evaluation period. Treatment period of 10 weeks duration in which cyclosporin was given to all patients in a dose of 3-5mg/kg/day. Fortnightly visits were scheduled in which clinical examination and laboratory profiles were evaluated. Post-treatment follow up period of 12 weeks during which adverse effects were monitored.

*Results* Serum creatinine level remained in normal range in all the patients. There was no change in all the other laboratory parameters evaluated. The mean percentage increase over baseline of serum creatinine concentration remained relatively stable throughout the study. No patient was withdrawn from the study because of elevation of serum creatinine.

*Conclusion* Cyclosporin is safe when used in low dose and for short-term therapy.

**Key words**

Cyclosporin, atopic dermatitis, short term.

## Introduction

Cyclosporin was isolated from the fungus *Tolypocladium inflatum* and became the first clinically useful T-cell active immunosuppressive agent. Since its introduction in the early 1980s, cyclosporin has revolutionized immunosuppressive therapy in transplantation medicine.<sup>1</sup> It is a highly lipophilic cyclic polypeptide, which binds to an intracellular receptor, the

immunophilin cyclophilin and through a complex pathway suppresses the production of IL-2, resulting in the inhibition of proliferation and activation of T cells, thereby reducing the T-cell-mediated immune responses.<sup>2</sup> Thus cyclosporin belongs to the functional substance group of calcineurin inhibitors.<sup>3</sup> The efficacy of cyclosporin in dermatological conditions was accidentally discovered when a renal transplant patient with psoriasis, while receiving cyclosporin was inadvertently cured of his psoriasis. This resulted in an interest in the role of cyclosporin in treating psoriasis and other dermatological conditions with a T cell dysfunction. The

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first account of its efficacy in atopic dermatitis was reported by Van Joost,<sup>4</sup> and since then a large number of cases have been reported. Due to the toxicity of long term cyclosporin as seen in transplant patients, recently interest has been generated in the use of short-term cyclosporin in various dermatological conditions.<sup>5</sup>

### **Patients and methods**

To assess the safety and tolerability of short-term oral cyclosporin in severe refractory atopic dermatitis, an open label clinical trial was carried out. 25 male and female patients within age group 15-65 (mean 27.1) were selected after informed written consent and carefully evaluating the inclusion and exclusion criteria. There were eleven males (44%) and fourteen females (56%). The study was divided into three periods; a pretreatment period of 4 weeks duration during which all systemic therapies were withdrawn and thorough clinical examination and laboratory profile was done to rule out any contraindication to cyclosporin therapy. Ten-week treatment plan was made. Patient's visits were organized biweekly. In case of adverse events or poor response, these visits were increased to once weekly. Recommended dosage was 3-5 mg/kg/day in two divided doses taken at 12-hrly intervals. Dose could be increased at any visit by 1 mg/kg/d up to a maximum of 5 mg/kg/d, in case of unsatisfactory response. Similarly dose could be reduced in case of side effects, to a minimum of 3 mg/kg/day. During last two weeks of treatment, dose was tapered to bring to a minimum of 3mg/kg/d before stopping. During these visits clinical status was determined using SCORAD index.

After completion of 10 weeks of therapy phase, patients entered the follow-up phase of 12 weeks, divided into three visits every four weeks. During this period, response to therapy, relapse rate, any adverse events, serum creatinine and changes in concomitant topical therapy were noted.

### **Assessment of safety**

Blood pressure, hematology, biochemistry, and adverse events were assessed in all patients throughout the study. At the time of enrolment and at fortnightly visits each patient received a complete physical examination and documentation of any adverse events. Blood samples were collected for hematology including a complete cell count with differential, biochemistry including potassium, uric acid, total bilirubin, alkaline phosphatase, aspartate and alanine aminotransferases, gamma-glutamyl transferase, and cholesterol. Serum creatinine and urine for glucose and protein were also measured biweekly.

### **Results**

Out of 25 patients who entered the study there was one dropout after 2 weeks of therapy (due to personal reasons) and 11 dropouts during follow-up period. Drop out rate was more in females, (7 females, 4 males). Serum creatinine level remained in normal range in all the patients. There was no change in all the other laboratory parameters evaluated. No known or new adverse effects of cyclosporin were observed. 4 patients (16%, all females) developed photosensitive rash after 2-3 hours of inadvertent sun exposure, which

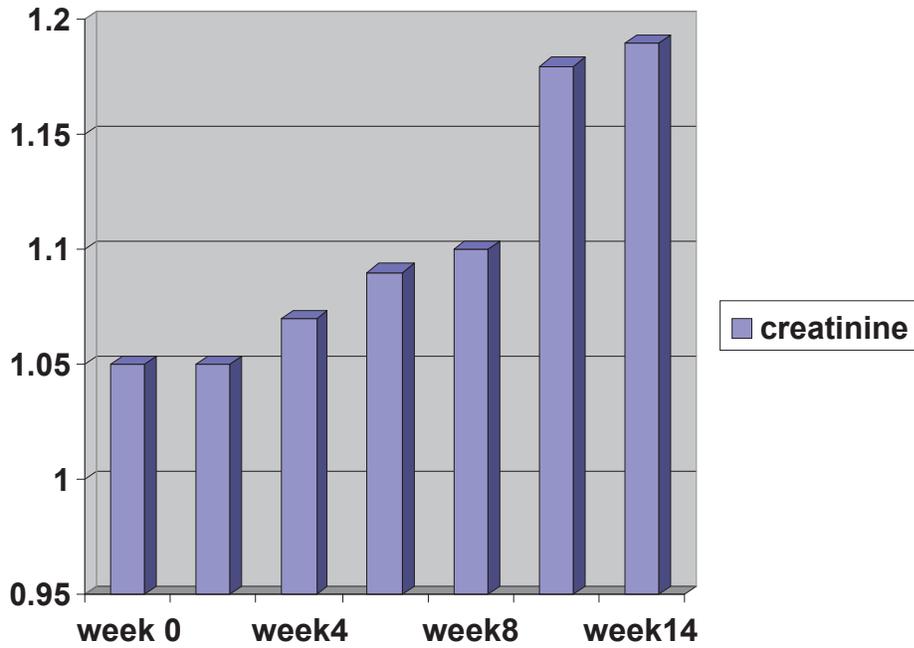


Figure 1 Average serum creatinine (mg/dl) values during the study period.

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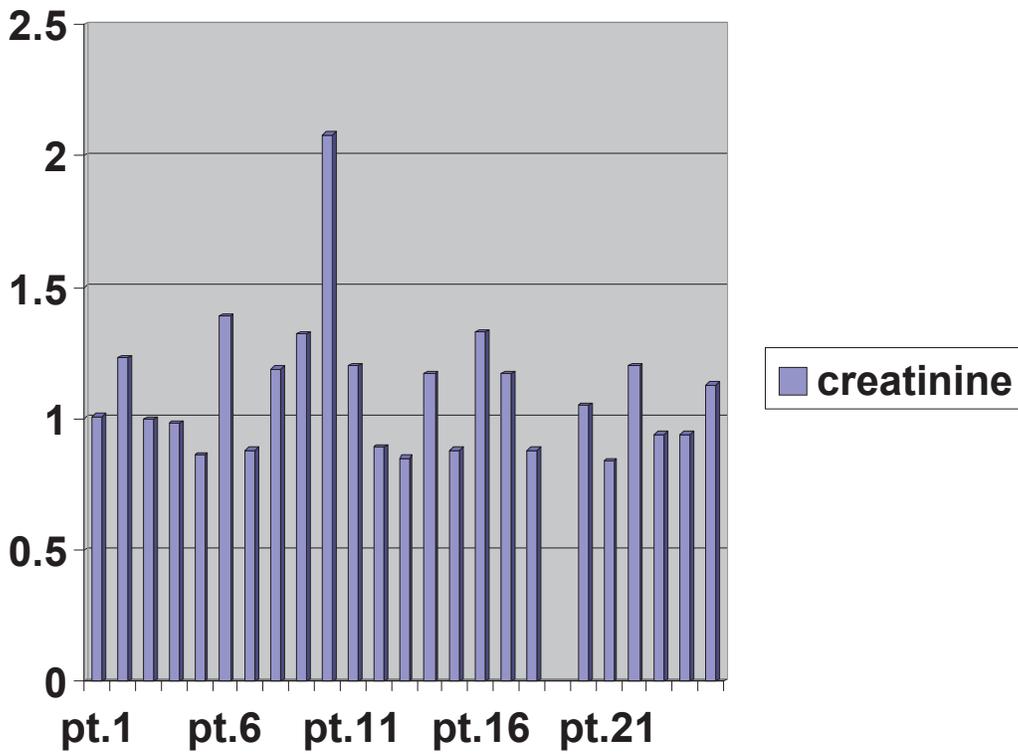


Figure 2 Average serum creatinine values of each patient at the end of study period.

subsided in two weeks. Photosensitivity is not a known adverse effect of cyclosporin, and we think it might be unrelated to the drug unless more reports come in.

### **Serum creatinine**

The mean percentage increase over baseline of serum creatinine concentration remained relatively stable throughout the study, as shown in figure 1. As it can be appreciated from the figure, there is an upward trend of serum creatinine during the treatment phase but it remains within the normal range and quickly settles down once the patient is taken off the treatment. None of our patients had a rise in serum creatinine levels more than 30% of the baseline as shown in figure 2, which was a criterion for reduction or termination of treatment. It can be seen that in all patients the serum creatinine at end of study remained within normal values. No patient was withdrawn from the study because of elevation of serum creatinine.

### **Discussion**

Cyclosporin was the first T-cell active immunosuppressant approved for the systemic treatment of severe psoriasis and atopic dermatitis. In addition, a variety of other inflammatory skin diseases are also responsive.<sup>3</sup> The majority of data concerning efficacy, long-term safety, and adverse effects of the calcineurin inhibitors refer to cyclosporin. Although its systemic use is effective, especially in atopic dermatitis and psoriasis, predictable adverse effects such as hypertension and nephrotoxicity limit its systemic use.<sup>5</sup> Because of the immunomodulatory effects of cyclosporin, there is also an inhibition of tumor defense

mechanisms, as supported by a higher incidence of skin cancers in cyclosporin-treated organ transplant patients.<sup>6</sup> There are fewer data on dermatologic patients on a low-dose regimen, but the incidence of lymphoma is less than 0.2%.<sup>3</sup> These adverse effects help explain why, although highly effective, systemic cyclosporin should be restricted to patients with severe inflammatory skin diseases only.

The combination of high efficacy and severe adverse effects compelled many researchers to look for alternative methods of using cyclosporin. One of these was low dose and short therapy. Several reports have established the fact that short-term therapy with cyclosporin results in marked improvement in patient condition without the risk of too many side effects in many conditions including psoriasis and atopic dermatitis.<sup>7,8,9,10</sup> This research has opened a new chapter in the cyclosporin research in dermatology. The minimum effective dose is being searched for, as well as the shortest possible duration of treatment.<sup>7</sup> Similarly the results are encouraging in other dermatoses.<sup>11,12</sup>

Our study was done to evaluate the safety and tolerability of cyclosporin in our population. Our results are in confirmation with the current literature. During the 10-week treatment period, we have seen excellent tolerability of the drug. None of our patients had to stop the drug due to side effects. Serum creatinine remained within normal limits during the treatment period with an upward trend but returned to baseline on stopping treatment. Another consideration in our setting is the cost. Cyclosporin is an expensive drug. Long-

term dosage makes it unaffordable for a lot of our patients. Intermittent dosage brings it within reach of many more.

### **Conclusion**

Cyclosporin, a potent and expensive immunosuppressant, can be safely used as short-term therapy for atopic dermatitis.

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