

Cyclosporin in the Treatment of Severe Atopic Dermatitis: A Retrospective Study

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Abstract

Introduction: The aims of this study were to determine the clinical profile of patients with atopic dermatitis who were treated with cyclosporin, and to assess the treatment duration, dose and response to cyclosporin therapy. **Materials and Methods:** Casenotes of patients with atopic dermatitis treated with cyclosporin from January 2000 to February 2002 were analysed. **Results:** There were 15 patients (9 males and 6 females) (age range, 1 to 58 years). All had severe disease. The mean initiating dose of cyclosporin was 2.8 mg/kg/day and the mean maximum dose was 3.3 mg/kg/day. Average duration of treatment was 6 months. Rapid improvement was seen within the first 2 weeks and maximum benefit was attained at a mean of 10 weeks. At the end of treatment, 73% of patients had improved from severe to none, mild or moderate disease. Five patients had a flare of eczema during therapy, 3 related to decrease in dose of medication. All patients relapsed within 3 months of cessation of cyclosporin. One patient with borderline hypertension developed worsening of blood pressure, which returned to baseline after cessation of cyclosporin and treatment with atenolol. No patient had sustained rises in serum creatinine. **Conclusion:** Cyclosporin is very useful in patients with severe, recalcitrant atopic dermatitis who have failed conventional therapy. It offers rapid relief of an otherwise disabling skin disease, but its effect is not long-lasting and relapses occur in almost all cases if followed up for long enough.

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Introduction

Cyclosporin is a potent immunosuppressant that inhibits cell-mediated immunity, mainly via inhibition of T helper cells. It has been used successfully in the treatment of severe atopic dermatitis in children and adults, producing a rapid and highly significant improvement in terms of disease activity, pruritus and sleep disturbance.¹ This translates into better quality of life scores for both the patients and their families.² Side effects were infrequently encountered and tolerability is good.

The aims of this study were to determine the clinical profile of patients with atopic dermatitis who were treated with cyclosporin, and to assess the treatment duration, dose and response to cyclosporin therapy in terms of its efficacy and relapse rate on cessation.

Materials and Methods

This was a retrospective study. Casenotes of patients with atopic dermatitis treated with cyclosporin from January 2000 to February 2002 were retrieved and analysed. The severity of atopic dermatitis was graded as mild, where body surface area (BSA) involvement was <10%, moderate where BSA involvement was 10% to 50%, and severe where BSA was >50%, as documented on the body chart.

Eczema was graded as severe if the dermatitis was described as “generalised”, “widespread”, “generalised exfoliative dermatitis”, “extensive” or “severe”. Improvement was graded as poor (0%-25%), fair (25%-50%), good (50%-75%) and excellent (75%-100%). Dermatologists who had treated these patients were consulted on the grading of severity of disease and the response to treatment. Indication of worsening of eczema after initiation or termination of treatment with cyclosporin was taken as relapses.

Results

There were 15 Chinese patients who received cyclosporin therapy for atopic dermatitis. There were 9 males and 6 females; their ages ranged from 1 year to 58 years (mean, 24 years). Four patients were below 12 years of age. All had severe atopic dermatitis prior to cyclosporin treatment, and had failed conventional therapy. Within 6 months prior to starting cyclosporin, all had received, on average, 9 weeks of oral prednisolone, and 93% had received an average of 4 courses of oral antibiotics.

Eighty-two per cent of patients above 12 years of age had been treated with phototherapy. Twenty-seven per cent had, at least, 1 previous hospital admission, while 20% were advised admission but refused.

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The mean duration of treatment with cyclosporin was 6 months, and ranged from 3 weeks to 10 months. The mean initiating dose was 2.8 mg/kg/day, reaching a mean maximum dose of 3.3 mg/kg/day, and achieved a mean dose of 2.7 mg/kg/day for the entire duration of treatment.

Fourteen of 15 patients (93%) showed initial improvement upon taking cyclosporin. The patient who had not improved had not been compliant with medication, having found cyclosporin too expensive a drug to take. The earliest beneficial effect was noted at a mean of 2 weeks after starting cyclosporin. Maximum beneficial effect was noted at a mean of 10 weeks of therapy (range, 1 week to 7 months). At the end of treatment, 7 patients had good to excellent response (Figs. 1 and 2), 4 had fair response and the rest had poor response to cyclosporin treatment.

One patient's blood pressure rose from baseline of 130/94 mm Hg to 150/110 mm Hg. Cyclosporin was stopped and atenolol was prescribed, resulting in the blood pressure returning to a baseline of 130/90 mm Hg after 2 months.

Two patients had transient rises of serum creatinine, above 30% of baseline, which returned to normal, 1 month later, without any change in the dose of cyclosporin.

Five patients (33%) had a flare of eczema while on treatment. Two were related to lowered dosage of cyclosporin, 1 had inadequate supply of cyclosporin and 1 patient had a worsening of eczema from secondary bacterial infection. A patient with food allergy and who had a positive radioallergosorbent test to egg white (class 4, high probability), egg yolk (class 3, moderate probability) and peanut (class 4, high probability) developed a flare of eczema after receiving the measles, mumps and rubella vaccination, and after ingesting peanut soup.

Of those who improved at the end of treatment and who were followed up for more than 1 month (13 of 15 patients), all had relapsed within 3 months. The mean duration to relapse post-treatment was 5 weeks (range, 5 days to 12 weeks).

Five patients had good and adequate response and treatment was stopped. In another 5 patients, cyclosporin was stopped due to unsatisfactory control of disease despite an adequate duration. Four patients terminated treatment due to financial reasons. Cyclosporin was stopped in a patient with high blood pressure and in another who developed herpes zoster.

Discussion

Cyclosporin is a drug with potentially serious side effects. Its use, in our centre, in patients with atopic dermatitis was reserved for severe disease that failed to respond to conventional therapy or oral steroids.

In our study, the mean initiating dose of cyclosporin was 2.8 mg/kg/day and the mean maximum dose was 3.3 mg/kg/day. In a Belgian consensus, the recommended initiating

dose was 2.5 mg/kg/day, to be given in 2 divided doses, and not to exceed a maximum dose of 5 mg/kg/day.³ The mean duration of treatment in our patients was 6 months. In another consensus, it was recommended to use the lowest effective dose in the shortest period of time possible. The maximum recommended duration of treatment was 6 months, but treatment seemed safe, up to a year of use.⁴

Most of our patients (93%) improved after being treated with cyclosporin, at least initially. The earliest beneficial effect was noted, on average, within the first 2 weeks of treatment. This early beneficial effect has also been seen in other studies.^{1,2,5} In 1 study, the mean sign score using the 6-area, 6-sign score for severity of eczema decreased from 40 to 31.8 within the first 2 weeks of initiating treatment, then declined more gradually.¹ Cyclosporin has also been shown to decrease itching in atopic dermatitis.⁶ The response of itch, compared to all other aspects of the eczema, was the first to improve after cyclosporin treatment and was also the first to arise after the drug was stopped.⁷

Before treatment, all patients had severe eczema. At the end of treatment, 7 patients had good to excellent response while 4 patients had a fair response to cyclosporin treatment. This translates into 73% of patients showing a definite improvement at the end of treatment. In view of the fact that these patients are difficult to manage, having failed conventional therapy such as oral steroids and phototherapy, the improvement may make a substantial difference to the patient in terms of his or her quality of life.

Apart from 1 patient with hypertension requiring cessation of drug, the tolerability and safety profile of cyclosporin was good. This patient had a blood pressure of 130/94 mm Hg at the start of therapy. Patients with baseline hypertension are at risk of developing worsening of hypertension when placed on cyclosporin treatment and the drug should be used with caution with regular blood pressure monitoring. It is recommended that if the diastolic blood pressure at 2 separate readings is >95 mm Hg, the cyclosporin dose should be decreased by 25% to 50% or antihypertensive treatment instituted, such as using calcium antagonists.³ Increase of serum creatinine to 30% above baseline levels was observed in 2 patients. This resolved without any change in the dose of cyclosporin. These isolated, transient increases in serum creatinine were observed in other studies too, and have been attributed to the daily variation in serum creatinine which is not related to the nephrotoxic effects of cyclosporin.¹ It is recommended that the dose of cyclosporin be reduced by 25% if serum creatinine increases 30% to 50% above baseline at 2 visits a week apart, or be increased by more than 50% above baseline at 1 visit.²

Flares during treatment were seen in 5 (33%) of 15 patients. Two patients had flares directly related to decrease in dosage of cyclosporin, and 1 patient experienced a flare when the medication ran out. To avoid possible flares

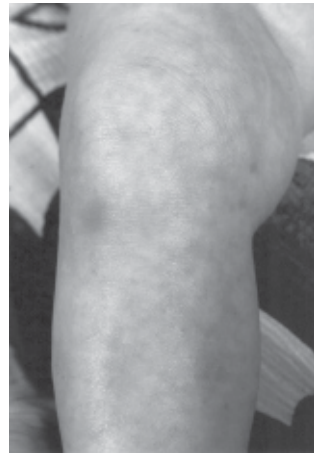


Fig. 1a. Before treatment.

Fig. 1b. At 6 weeks of treatment.

Fig. 1. The lichenified, thickened plaques of eczema seen in this 1-year-old girl improved remarkably after cyclosporin therapy.

during treatment, the dosage of cyclosporin should be tailed down gradually.

All patients, when followed up for sufficiently long duration, had a relapse of atopic dermatitis post-cyclosporin treatment. Various studies have shown that the majority of patients do relapse after cyclosporin therapy has ceased.^{2,5,7} These studies defined relapse as severity of eczema at or >75% of baseline severity prior to starting cyclosporin. Relapse was rapid and occurred within 2 to 4 weeks after cessation of cyclosporin.^{5,7} There have, however, been a few case reports where there was sustained remission after cyclosporin use.^{8,9} To prevent or decrease the severity of relapse post cyclosporin therapy, patients are advised to maintain their daily topical application of steroid creams and emollients during and after cyclosporin treatment.⁴ Since the mean duration to relapse post-treatment was 5 weeks in our study, we would recommend that patients be seen within a month after cessation of cyclosporin therapy. Aggressive topical therapy, oral antibiotics with *Staphylococcus aureus* cover, and intermittent courses of oral steroids are often sufficient to treat the acute attacks of eczema encountered. If eczema is still not controlled, swab cultures of the skin should be done to exclude resistant strains of bacteria such as methicillin-resistant *Staphylococcus aureus*, and treated with appropriate antibiotics. Other modalities of therapy used at our centre post cyclosporin therapy include phototherapy, methotrexate, azathioprine and repeat courses of cyclosporin. These have been used with variable success.

It is interesting to note that 4 patients (27%) stopped treatment because of financial reasons. For a 60-kg person, the cost of cyclosporin ranges from S\$400 to S\$600 a month. This is often the main reason for non-compliance to treatment or request by patients to stop cyclosporin treatment.

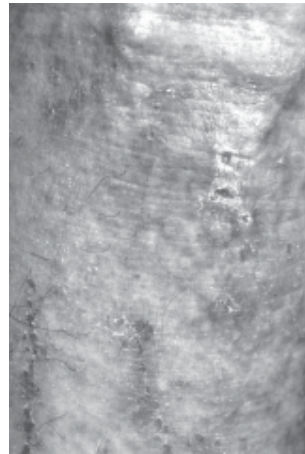


Fig. 2a. Before treatment.

Fig. 2b. At 3 months of treatment.

Fig. 2. The lichenified, excoriated plaques of eczema seen in the popliteal fossa of this 27-year-old male patient resolved after cyclosporin therapy.

Conclusion

Cyclosporin is very useful in patients with severe, recalcitrant atopic dermatitis who have failed conventional therapy. The potential for serious adverse effects necessitates regular monitoring during its use. It offers rapid relief of an otherwise disabling skin disease, but its effect is usually not long-lasting and relapses occur in almost all cases, when followed up for a sufficient length of time.

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