Effectiveness and adverse effects of ciclosporin in patients with psoriasis

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Sri Lanka Journal of Dermatology, 2012-2014, **16**, 8-15

Abstract

Objectives: To find out effectiveness and adverse effects of ciclosporin in patients with psoriasis.

Methodology: It was a prospective study designed in accordance with established guidelines and the dose of ciclosporin was 3mg/kg/day. Patients were reviewed at 2, 4 and 8 weeks and data collected included PASI score and adverse events of cyclosporine. Patient's response to the treatment was rated at the end of the study.

Results: A total of 21 subjects (mean age 48) were studied and reduction in mean PASI score was 50% and 67% at 4 weeks and at 8 weeks respectively which were statistically significant. At the end of the study majority of patients (89%) rated the drug as 'good' or 'very good'. Adverse events were reported in 45% of patients and they reflected known side effect profile of ciclosporin

Conclusion: Ciclosporin can improve chronic plaque psoriasis successfully within short period of time and no serious side effects were reported.

Introduction

Although psoriasis is not a life-threatening disease studies have revealed that patients experience a quality of life reduction similar to those with angina or hypertension[1]. It affects between 1-3% of population worldwide[2]. Though exact cause is still not known it is regarded as a T cell driven disease which has genetic predisposition and can be triggered by environmental factors[3].

Ciclosporin is usually indicated in severe and recalcitrant psoriasis which is defined as psoriasis which has failed to respond to at least one systemic therapy or in patients for whom other systemic therapies are contraindicated, or cannot be tolerated[4]. However there are other guidelines which suggest use of cyclosporine in moderate to severe psoriasis[4,5].

This drug has shown to be effective in psoriasis both in short term and long term studies[2,8-13]. Timonen P *et al* has found reduction in PASI score of 60-70% at 4 weeks with ciclosporin treatment and in another study Ho VC *et al* has shown 50% reduction in PASI score at 4 weeks[8,9]. It was compared with other systemic treatments[6,10,11]. In one randomized controlled trial, effectiveness of ciclosporin was compared with that of methotrexate and no significant difference was found between the two[10]. However ciclosporin was found to be superior to methotrexate in the control of psoriasis according to a recent study[6].

Objectives of the study

There were no previous studies done in Sri Lanka in order to determine its efficacy and potential adverse effects in the management of psoriasis by the time this study was initiated. It is a well-known fact that widespread use of this drug has been limited by concerns over adverse effects. Therefore we performed a non-randomised prospective study in keeping with established guidelines[4,5] in order to find out effectiveness and adverse effects of the drug.

Patients and methods

Study design

Subjects were recruited during the period of three months from 01/10/2009 to 31/12/2009 and they were diagnosed patients with chronic plaque psoriasis attending the Dermatology Clinic, General Hospital, Kandy.

It was a non-randomised prospective study involving 21 patients. This study was designed in accordance with established guidelines[4,5].

Each subject was initially assessed with a detailed history, thorough clinical examination and relevant baseline lab studies which included full blood count, fasting blood sugar, renal function tests, liver function tests, chest X-ray and mantoux test.

Inclusion criteria

Patients with extensive (involving more than 20% of body surface area) or disabling plaque psoriasis and with all the following criteria fulfilled were recruited.

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- When other conventional systemic therapies (methotrexate, acitretin) are inappropriate, ineffective or cannot be tolerated
- Age is between 18 years and 60 years
- Subjects who have ability to express informed written consent.

Exclusion criteria

Those who have had at least one of the following criteria were excluded from the study.

- Impaired renal function (serum creatinine above 10% of the upper limit of the reference range)
- Impaired hepatic function (bilirubin or liver enzymes twice the upper limit of the reference range)
- Uncontrolled hypertension
- History of systemic malignancies
- Patients with active infection
- Immunodeficiency or concomitant immunosuppressive therapy
- Pregnancy and lactation
- Arsenical exposure
- Concomitant treatment with nephrotoxins and with drugs that affect the metabolism of ciclosporin e.g. NSAIDS, anticonvulsants
- Malabsorption
- History of epilepsy and tuberculosis
- Radiological evidence of suggestive of pulmonary tuberculosis and strongly positive Mantoux test (>10mm)
- Previous exposure to hepatitis B and C
- Previous serious side effects of ciclosporin and known hypersensitivity
- History of more than 200 PUVA treatment sessions

Women of childbearing age were required to use appropriate method of contraception throughout the study period. Before treatment all patients stopped receiving systemic treatment for psoriasis for at least 14 days and PUVA for at least 30 days. Topical treatments which had been used by patients routinely were allowed to be used. However neither new topical treatment nor systemic treatment was started along with ciclosporin.

Informed written consent was taken before starting treatment and they were assessed by the same investigator and the data collected using interviewer administered questionnaire.

Dose of cyclosporin

Cyclosporine dose of 3 mg/kg/day were given in two divided doses for 8 weeks. Dose of the drug was not increased more than that but allowed to reduce by 0.5-1.0 mg/kg/day in cases of dose related adverse effects. All patients had same brand of cyclosporine (Immunosporin®) throughout the study.

Discontinuation of treatment

Treatment was discontinued at any stage when subjects developed intolerable adverse effects or worsening of psoriasis.

Statistical analysis

Changes in parameters were assessed for significance using paired t-tests or Wilcoxon signed rank sum tests, as appropriate.

Results

Dermographic data

Twenty one patients (male-18, female-3) started treatment and drug was discontinued in three patients within first 2 weeks so that only 19 patients were included in statistical analysis. Out of those nineteen 16 were males and 3 were females. Mean age of the patients was 48 (Table 1).

Indication for cyclosporine

Majority of subjects (48%, n=10) who received cyclosporine were those who has had poor or no response to methotrexate (MTX) and/or phototherapy.

Statistical analysis

Reduction of PASI score

Reduction of mean PASI score is shown in Table 1 and there is a statistically significant reduction at 4 weeks (Wilcoxon signed rank test, p-value <0.001) and at 8 weeks (Wilcoxon signed rank p-value <0.001).

Successful treatment (defined as > 75% reduction of the baseline PASI score, PASI 75) was achieved by 47% (n=9) of the patients. Almost complete clearing (defined as > 90% reduction of the baseline PASI score) was achieved by 5% (n=1) of the patients. Eighty-four per cent of the patients (n=16) achieved > 50% improvement in PASI score at 8 weeks compared with baseline (Figure 1-4).

Table 1. Pre-treatment characteristics of patients treated with ciclosporin

No	*Sex*	*Age*	*Duration of psoriasis (yrs.)*	*Previous systemic treatment*	*Type of psoriasis*	*Indication for cyclosporine*
1	M	51	15	MTX, PUVA	Plaque	Poor response to MTX/PUVA
2	M	38	06	MTX, UVB	Plaque	Poor response to MTX
3	M	60	30	MTX, PUVA, UVB	Plaque	MTX>2g
4	M	52	6/12	UVB, MTX	Plaque	Can't tolerate MTX/UVB
5	M	45	08	PUVA, MTX	Plaque	MTX >1.5g
6	M	42	05	MTX	Plaque	Can't tolerate MTX
7	M	34	06	UVB, MTX	Plaque	MTX >1.5g
8	M	42	04	UVB, MTX	Plaque	Poor response to MTX
9	M	58	10	PUVA, MTX	Plaque	Poor response to MTX
10	F	48	04	UVB, MTX	Plaque	Can't tolerate MTX
11	M	44	02	MTX	Plaque	Can't tolerate MTX
12	M	45	10	MTX, UVB	Plaque	MTX >2g
13	F	58	18	PUVA, MTX	Plaque	MTX >1.5g
14	M	45	03	MTX, UVB	Plaque	Poor response to MTX/UVB
15	M	52	07	MTX	Plaque	Poor response to MTX
16	M	59	08	MTX,UVB	Plaque	Poor response to MTX
17	F	50	2/12	MTX,UVB	Plaque	Can't tolerate MTX/UVB
18	M	45	03	MTX	Plaque	Poor response to MTX
19	M	48	05	PUVA, MTX	Plaque	Poor response to MTX
20	M	50	01	PUVA	Plaque	Poor response to PUVA
21	F	40	05	MTX	Plaque	Can't tolerate MTX

MTX- Methotrexate, PUVA- Psoralen+UVA

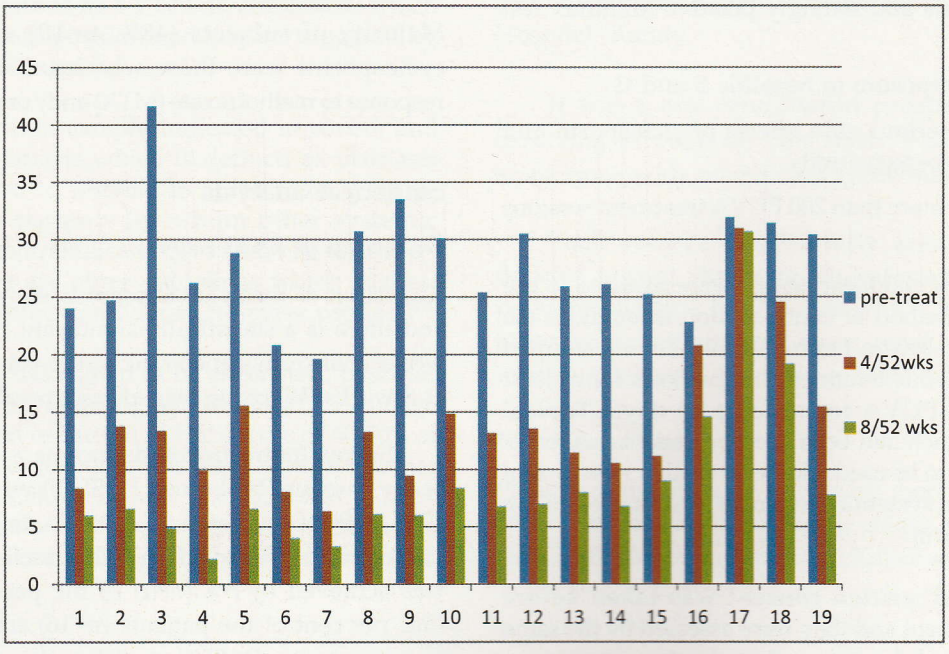

Figure 1. *PASI score measured in each individual before treatment and with treatment at 4 and 8 weeks.*

Figure 2. *Body weight measured before treatment and with treatment at 4 and 8 weeks.*

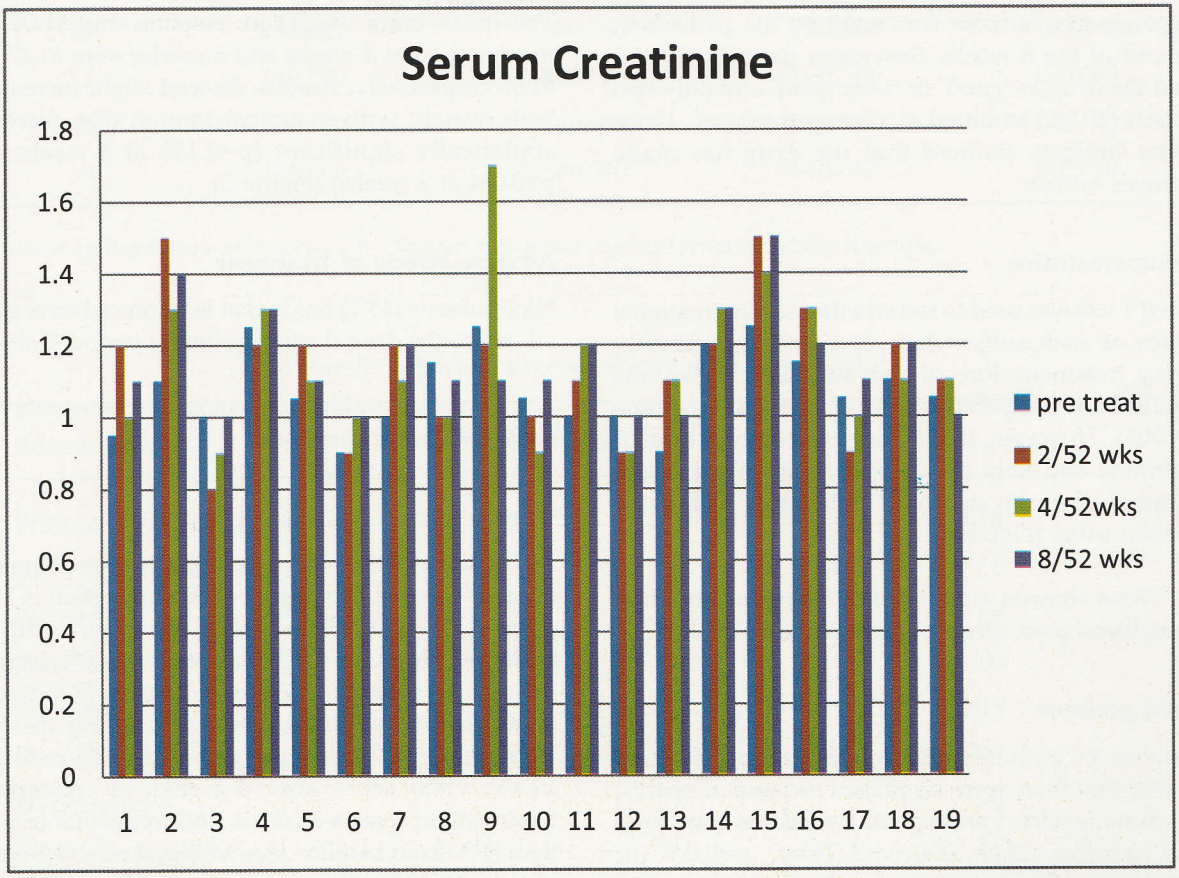

Figure 3. *Serum creatinine measured before treatment and with treatment at 2, 4 and 8 weeks.*

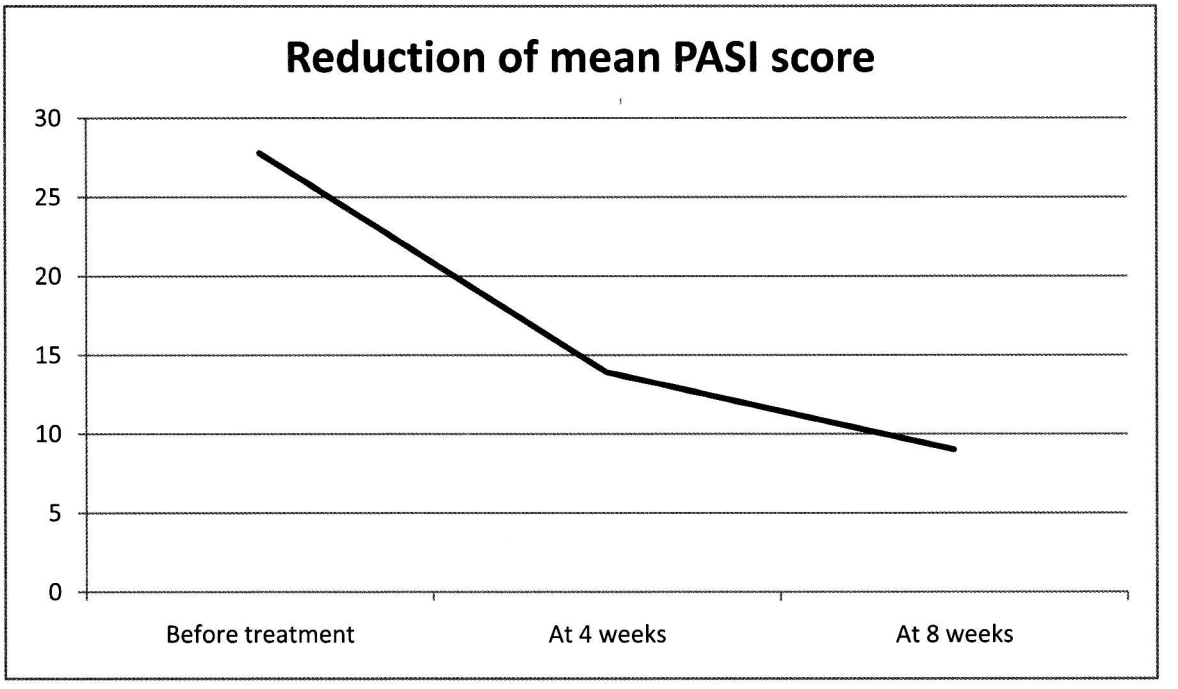

Figure 4. *Mean PASI score during treatment.*

Subjective evaluation of treatment

Response to treatment was rated by the patients at the end of the 8 weeks. Seventeen patients (89.4%) rated the drug as 'good' or 'very good' and only two subjects (10.5%) admitted as 'no improvement'. None of the subjects claimed that the drug has made psoriasis worse.

Serum creatinine

Paired T test was used to test whether serum creatinine values of each subject has increased significantly during treatment. Rise of creatinine at 8 weeks was significant as compared with baseline values (p-value = 0.006). However there were variable values of creatinine and only one subject showed persistent elevation of serum creatinine more than 30% above baseline value (Figure 4).

None showed significant changes in full blood count, blood urea, serum electrolyte, SGOT and SGPT.

Blood pressure

Analysis of both systolic and diastolic pressures showed that there were significant increase in systolic and diastolic blood pressure at 2 weeks as compared with baseline values (Paired T-Tests, p=0.007 for systolic pressure, p=0.016 for diastolic pressure) (Table 2).

Body weight

The mean body weight at baseline was 61.05 and mean values at 4 weeks and 8 weeks were 61.47 and 61.55 respectively. Results showed slight increase in body weight with treatment though they were not statistically significant (p=0.111 at 4 weeks and p=0.084 at 8 weeks) (Figure 3).

Adverse effects of treatment

Nine subjects (45%) has had at least one adverse event related to the drug during treatment period (Table 3).

No serious or life threatening adverse events were recorded during the study.

Discussion

Reduction of PASI score was the main outcome in our study and the results show 50% reduction in PASI score at 4 weeks which was in accordance with the finding of Ho VC *et al*[8] who has shown a 50% decrease in modified Psoriasis Area Severity Index (PASI) score from baseline within 4 weeks of starting therapy. However Griffith C E M *et al* reported a 72% reduction in the PASI score after 4 weeks of ciclosporin treatment. In a meta-analysis PASI reduction of more than 50% from baseline was achieved after 4.3 weeks of ciclosporin treatment at a dose of 5.0 mg/kg/day[5].

Table 2. Blood pressure reading at 2, 4 and 8 weeks

	Blood pressure			
Case no	*Pre treatment*	*2/52 wks*	*4/52wks*	*8/52 wks*
1	130/85	130/85	130/90	130/90
2	100/70	110/70	120/80	120/80
3	120/80	120/80	120/80	120/70
4	140/90	140/90	150/95	140/95
5	120/80	125/80	110/80	120/85
6	130/80	130/80	140/85	140/85
7	135/85	140/90	140/90	140/90
8	110/80	110/80	110/70	110/80
9	120/80	150/100[A]	140/95	140/90
10	130/80	150/90	140/90	150/90
11	140/80	170/100[B]	140/90	140/90
12	120/80	120/90	130/90	130/90
13	110/70	110/80	110/80	110/80
14	130/90	140/95	150/95	150/100
15	130/80	140/80	135/80	135/80
16	140/85	160/100[B]	130/80	130/80
17	140/90	140/90	140/90	150/90
18	130/80	140/80	140/80	140/90
19	130/90	140/90	140/90	140/90

A – Dose of cyclosporine was reduced B – Treated with blood pressure lowering tablets Nifedipin

Table 3. Reported adverse events with ciclosporin

Adverse event	*Number of patients*	*As a %*
With at least one adverse event	09	45
Gastrointestinal symptoms	04	21
Fatigue	03	16
Headache	02	10
Tremors	01	05
Paraesthesia	01	05
Hypertension	03	16
Elevated creatinine	01	05
Elevated cholesterol	01	05

After 8 weeks of treatment mean PASI score decreased from its baseline by 67.42% in our study. There were no comparable studies where PASI measured at 8 weeks; however we came across two previous studies where outcome of ciclosporin were measured at 12 weeks. In one study in which dose of the ciclosporin was allowed to increase up to 5 mg/kg/day PASI score was reduced by 72% at 12 weeks[6]. In a dose finding study done by Timonen P *et al* reported 57% reduction of PASI score at 12 weeks in a group of patients whose initial dose of the drug was 2.5-3.0mg/kg/day[9].

Only one patient suffered from psoriatic arthritis in our study and ciclosporin didn't have much impact on arthritis as evaluated by the investigator and the patient. Obviously numbers of patients with arthritis are not enough to come to a conclusion with regard to psoriatic arthritis. Only two subjects (10%) didn't show the improvement as expected in our study. We believe that they probably would have improved if they were treated with higher dose of ciclosporin which was not allowed in our study. Patient's overall satisfaction was quite encouraging. More than 80% have rated the treatment as 'good' or 'excellent'. This is in agreement with the findings of Berth-Jones *et al* who showed 'considerable improvement' rated by more than 80% of subjects in their study where average duration of treatment was less than 8 weeks 14. Ho VC *et el* also reported similar results at the end of their study[8].

Safety and tolerability

Adverse effects considered by the investigator to be related to the medication were reported by 45% of subjects (n=9). This was in accordance with the findings in Ho VC *et al* study where 50% of patients developed adverse events considered by the investigators to be probably or definitely related to the study medication[8]. That study was carried out for maximum period of 12 weeks and dose was allowed to increase up to 5 mg/kg/day. However in an another study number of subjects who reported adverse effects were much higher[6].

It is important to note that significant number of subjects showed a rise in both systolic and diastolic blood pressure at a dose of 3 mg/kg/day. However only three subjects (16%) developed hypertension (defined as systolic blood pressure more than 160 mmHg or diastolic pressure more than 95 mmHg on two or more occasions) and they required either dose reduction of ciclosporin or antihypertensive treatment. Ho VC *et al*[8] reported that 12% of their patients had new onset of hypertension while there were other studies which showed similar results [5,14,15].

During this study mean serum creatinine rose as expected at 8 weeks. Only one subject (5%) showed persistent elevation of creatinine more than 30% above baseline and that is in contrary to the finding of Berth-Jones *et al* where 17% of patients showed increased (defined as >30% increase above baseline) serum creatinine[14]. In a meta-analysis this occurred in only 4% of treatments[5]. One patient in our study required dose reduction and his subsequent creatinine level came back to normal. However there were varying results of serum creatinine and in some patients creatinine level was reduced while on treatment.

Subjects were expected to have their lipid profile done at 4 weeks. Only one subject reported substantial elevation of total cholesterol and triglycerides which required treatment.

Significant number of patients seems to gain weight while on treatment although they were not statistically significant. However weight gain is a documented side effect and need to be cautious in obese people if they were to be treated with long term ciclosporin.

None of the subjects suffered from severe bacterial or viral infection during treatment period and special attention paid for the signs and symptoms of pulmonary tuberculosis at each clinic visit. Documented adverse effects such as hypertricosis, gum hypertrophy and non-melanocytic skin cancers were not reported and possible reasons would be short duration of treatment, low dose of the drug and small size of the sample.

Duration of remission once it is induced is another important aspect which we didn't include in this study. After 8 weeks of treatment dose of the drug was gradually reduced in our study. We need to conduct further studies on long term efficacy and safety of treatment.

Conclusion

We have concluded that ciclosporin can improve psoriasis within short period of time and the patients are quite happy with the results. Results of our study are similar to that of previous studies done in other parts of the world. Reported side effects in this study reflected the known side effect profile of ciclosporin and they were mild to moderate in severity.

Acknowledgment

We are grateful to Dr M. R. U. N Bandara for his assistance given in statistical analysis.

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