



Effects of Cyclosporine on Palmoplantar Pustulosis and Serum Expression of IL-17, IL-23, and TNF- α

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ABSTRACT

Introduction: This study aimed to investigate the effects of cyclosporine on palmoplantar pustulosis (PPP) and serum expression of IL-17, IL-23, and TNF- α .

Methods: Patients with PPP ($n = 48$) were recruited and treated with cyclosporine alone. The Palmoplantar Pustulosis Area and Severity Index score was obtained, and ELISA was employed to detect the serum IL-17, IL-23, and TNF- α expression before treatment and after 8 weeks of treatment.

Results: Complete remission was achieved in 16.7% of the patients, remission in 45.8%, an improvement in 31.3%, and the treatment was ineffective in 6.25%, yielding an overall effectiveness of 62.5%. Adverse effects included hypertension ($n = 6$), frequent urination and enuresis nocturna ($n = 6$), gastrointestinal discomfort ($n = 6$), hypertrichosis ($n = 3$), and increased creatinine ($n = 1$). While serum IL-17, IL-23, and TNF- α concentrations were reduced after 8 weeks of treatment, the reductions were

greatest for IL-23 and TNF- α , whereas the reduction in IL-17 was not significant.

Conclusion: Cyclosporine is a safe and effective treatment for PPP with few adverse effects, which might be related to the regulation of IL-23 and TNF- α .

Keywords: Cyclosporine; Palmoplantar pustulosis; IL-17; IL-23; TNF- α

INTRODUCTION

Palmoplantar pustulosis (PPP) is a chronic, recurrent palmoplantar disease that occurs most frequently in patients aged 50–60 years and during the summer. The incidence of PPP is relatively low, and some clinicians speculate that PPP is the palmoplantar manifestation of pustular psoriasis [1]. Currently, PPP is treated with topical corticosteroids, PUVA, acitretin, methotrexate, cyclosporine, tetracyclines, or biological agents. However, the efficacy of each of these drugs in the treatment of PPP and the specific mechanisms that underlie their therapeutic effects are largely unknown. In the present study, patients with PPP who received treatment with cyclosporine alone were recruited, the adverse effects of this treatment were observed, and their serum expression of TNF α , IL-17, and IL-23 was measured in order to explore the mechanism underlying the therapeutic effects of cyclosporine on PPP.

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METHODS

Patients

All procedures performed in studies involving human participants were implemented in accordance with the ethical standards of the Second Hospital of Jilin University research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study. A total of 48 patients with PPP were recruited from the Department of Dermatology of the Second Hospital of Jilin University between June 2017 and March 2018. There were 8 males and 40 females, with a mean age of 49.8 years (range 18–79 years). The mean course of the disease was 2 years (range 15–20 years). 24 patients were smokers. The inclusion criteria were as follows: (1) patients were 18 years or older; (2) patients were diagnosed with PPP; (3) informed consent was obtained before inclusion in the study. The exclusion criteria were as follows: (1) uncontrollable hypertension; (2) severe renal dysfunction; (3) severe infectious diseases; (4) a history of malignant tumors; (5) current malignant tumors (excluding basal cell carcinoma); (6) patients were receiving PUVA treatment; (7) patients received simultaneous active vaccine immunization.

Cyclosporine Treatment and Evaluation of Therapeutic Efficacy

The patients were treated with oral cyclosporine at 3 mg/kg/day, twice daily. At the same time, moisturizer (WINONA's Hyaluronic Acid Repair Biomask) was applied externally. Treatment lasted for 8 weeks, and the skin lesions were photographed before treatment and after 8 weeks of treatment. The symptoms and signs (pustules, erythema, scars, and lesion area) were scored using the Palmoplantar Pustulosis Area and Severity Index (PPPASI) score system (Table 1) [2, 3]. Before treatment, the PPPASI score was 0.6–47.4 (average 12.8). The reduction in the total score after 8 weeks of treatment was used to evaluate the therapeutic efficacy [4]. The therapeutic efficacy was classified as complete remission (reduction \geq 90%), remission (60–89%), improvement (20–59%), or treatment ineffectiveness (< 20%). The complete remission rate was calculated as (number of patients in complete remission/total number of patients) \times 100%, and the overall effectiveness was evaluated as the complete remission rate plus the remission rate.

Adverse Effects

All the patients were tested for liver and kidney function, underwent full blood count and urine tests, and had their serum electrolytes, lipids, glucose, and blood pressure monitored before and during treatment (at 4, 8, 12, and 16 weeks)

Table 1 Calculation of the Palmoplantar Pustulosis Psoriasis Area and Severity Index (PPP PASI)

Score	Erythema (E)	Pustules (P)	Desquamation (D)	Area involved (%)
0	None	None	None	0
1	Slight	Slight	Slight	0–10
2	Moderate	Moderate	Moderate	10–30
3	Severe	Severe	Severe	30–50
4	Very severe	Very severe	Very severe	50–70
5	–	–	–	70–90
6	–	–	–	90–100

The PPP PASI score is calculated as follows: $[(E + P + D) \times \text{area} \times 0.2 \text{ (right palm)}] + [(E + P + D) \times \text{area} \times 0.2 \text{ (left palm)}] + [(E + P + D) \times \text{area} \times 0.3 \text{ (right sole)}] + [(E + P + D) \times \text{area} \times 0.3 \text{ (left sole)}]$

to assess treatment safety. During the treatment, the patients were asked to report adverse effects [blood pressure, kidney dysfunction, gastrointestinal reactions (anorexia, nausea, and vomiting), gingival hyperplasia with bleeding and pain].

Detection of Serum IL-17, IL-23, and TNF- α Concentrations

In the present study, ELISA was employed to detect the serum concentrations of IL-17, IL-23, and TNF- α before and after cyclosporine treatment. Data are expressed as the mean \pm standard deviation (mean \pm SD) and the *t* test was used for comparisons between groups. *P* < 0.05 was considered to indicate statistical significance. The blood was collected from 4 patients in complete remission, 12 in remission, and 8 with improvement.

Statistical Analysis

Statistical analysis was performed with SPSS version 21 (Oracle Co., USA). Data are expressed

as the mean \pm standard deviation (mean \pm SD) and the *t* test was used for comparisons between groups. *P* < 0.05 was considered to indicate statistical significance.

RESULTS

Therapeutic Efficacy

45 of the 48 patients who received cyclosporine treatment showed improvement in their skin lesions. The time taken to achieve this improvement was 15–30 days, and the duration of treatment ranged from 15 days to 6 months. Complete remission was noted in 8 of the 48 patients (16.7%), remission in 22 (45.8%), improvement in 15 (31.3%), and ineffectiveness in 3 (6.25%). Note that the duration of treatment was shorter than 1 month in 3 patients in whom the treatment was ineffective. In those patients, the initial dose of cyclosporine was lower than 2.5 mg/kg/day, and treatment was terminated due to adverse effects (nausea, gastric discomfort, and other adverse effects) and high cost. The overall rate of effectiveness was 62.5% (Figs. 1, 2).

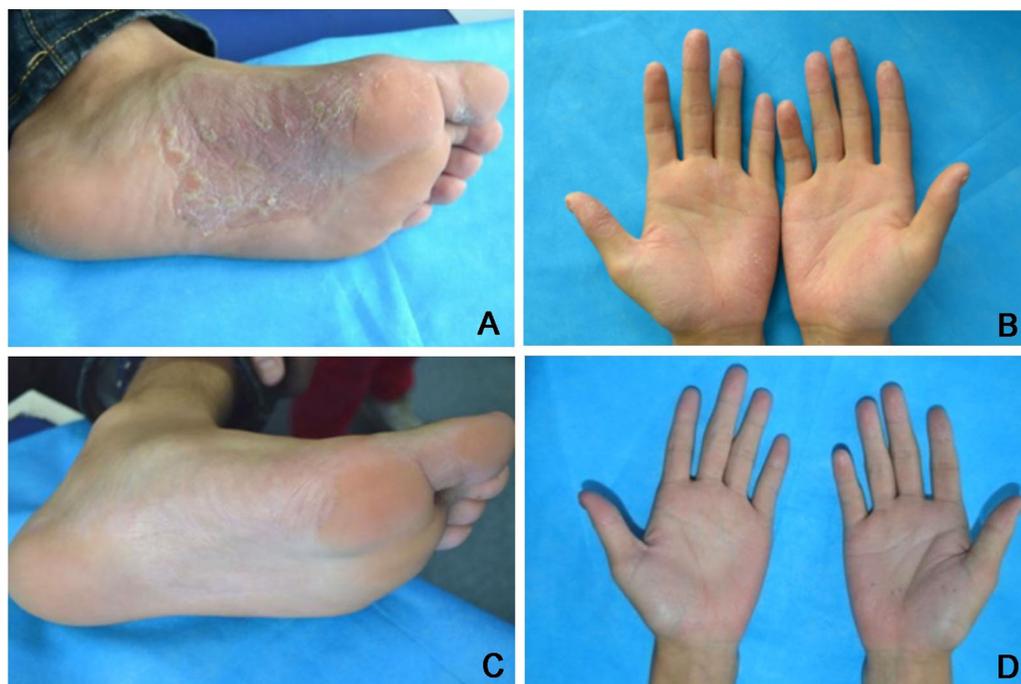


Fig. 1 The hands and feet of case 1 before and after treatment. **a, b** Before treatment, **c, d** after treatment

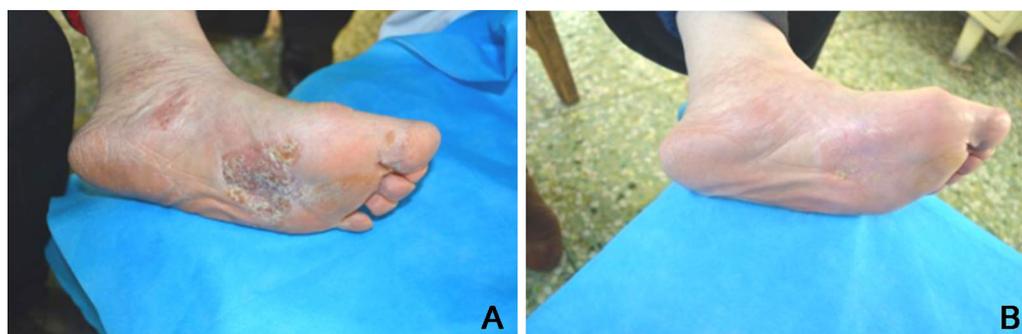


Fig. 2 The feet of case 2 before and after treatment. **a** Before treatment; **b** after treatment

Adverse Effects

The adverse effects observed included hypertension ($n = 6$), frequent urination and enuresis nocturna ($n = 6$), gastrointestinal reactions (nausea and gastric discomfort) ($n = 6$), hypertrichosis ($n = 3$), and increased creatinine ($n = 1$). They resolved after cyclosporine dose reduction or termination of cyclosporine treatment, although the hypertrichosis improved slowly.

Serum Concentrations of IL-17, IL-23, and TNF- α

Our results showed that the serum concentrations of IL-17, IL-23, and TNF- α reduced after 8 weeks of cyclosporine treatment. Significant reductions in IL-23 and TNF- α were noted, but there was no marked reduction in serum IL-17 (Table 2).

Table 2 Serum IL-17, IL-23, and TNF- α concentrations before and after cyclosporine treatment (ng/L, mean \pm SD)

Cytokine	Before treatment (week 0)	After treatment (week 8)
IL-17	46.36 \pm 15.72	44.87 \pm 15.95
IL-23	287.66 \pm 109.84	259.24 \pm 109.47**
TNF- α	323.10 \pm 119.51	295.90 \pm 118.76**

** $P < 0.01$ vs before treatment

DISCUSSION

PPP is a chronic disease with a high recurrence rate and a poor response to treatment. It occurs most often in patients aged 50–60 years [1]. In the present study, a total of 48 patients diagnosed with PPP were recruited, including 8 males and 40 females. The mean age was 49.8 years (range 18–79 years). Plantar involvement was more frequent than palmar involvement, which was consistent with previously reported cases [1, 5]. This suggests that PPP is frequently found in the palmoplantar region. In Olazagasti et al.'s retrospective review of 215 patients with PPP, systemic agents that elicited a complete response included acitretin (6 of 24 patients; 25%), methotrexate (2 of 20 patients; 10%), and cyclosporine (2 of 4 patients; 50%). Several treatments—dapsone (3 patients), etanercept (3 patients), and prednisone (5 patients)—elicited no response [5]. In the present study, 48 patients with PPP received monotherapy with cyclosporine. The PPPASI score was 0.6–47.4 before treatment (mean 12.8). After 8 weeks of treatment, the efficacy was evaluated. Results showed complete remission in 8.3% of patients, remission in 41.7%, improvement in 22.9%, and treatment ineffectiveness in 20.8%, with an overall effectiveness rate of 50%. These results are consistent with relevant results in the literature [5–7] and they confirm that cyclosporine is an effective treatment for PPP.

Cyclosporine A is safer than other commonly used systemic treatments. Adverse reactions disappeared after cyclosporine reduction

or withdrawal, and increased body hair recovery was relatively slow. These findings indicate that cyclosporine is an effective treatment for PPP with few adverse effects, and that these adverse effects are mild and may resolve after treatment termination. However, routine monitoring is necessary and the dose of cyclosporine should be determined according to the guidelines in order to reduce or avoid the adverse effects of cyclosporine.

The pathogenesis of PPP is still poorly understood. Smoking, emotional stress, focal infection, certain drugs, genetics, immunity, and metal sensitization are reported to be involved in the occurrence or aggravation of pustulosis [5]. Smoking plays a particularly important role in the pathogenesis of PPP. Tobacco smoke is considered to be a possible trigger of PPP, and it may increase the expression of IL-17 and IL-22 [8]. Recent studies have shown that IL-17, IL-23, and TNF- α play crucial roles in the pathogenesis of psoriasis [9], and PPP is closely related to this pathogenesis [10, 11]. Several reports have reported an over-expression of IL-17 in periodontitis [12, 13]. IL-17 is expressed not only in Th17 cells but also in inflamed tissues such as gingiva [12, 13]. Elevated IL-17 expression has been noted in the skin lesions and sera of PPP patients, and TNF- α is significantly increased in the sera of PPP patients, but IL-23 is not [14]. As a result of this low IL-23 expression in the sera of PPP patients, it was assumed that the expression of IL-17 in inflamed tissues such as gingiva may relate to the pathogenesis of PPP [14]. Our results showed that the serum concentrations of IL-17, IL-23, and TNF- α decreased after 8 weeks of cyclosporine treatment in PPP patients. Significant reductions were noted in IL-23 and TNF- α , while the serum IL-17 concentration decreased slightly. This implies that the therapeutic effects of cyclosporine may be related to the down-regulation of IL-17, IL-23, and TNF- α expression, especially that of IL-23 and TNF- α . Note that the sample size was small in the present study, and the specific mechanisms underlying the therapeutic effects of cyclosporine were not investigated further. Thus, more clinical studies with elegant designs and large sample sizes are needed to confirm the etiology and

pathogenesis of PPP as well as the mechanisms underpinning the therapeutic effects of cyclosporine.

CONCLUSIONS

Cyclosporine is a safe and effective treatment for PPP with few adverse effects, which may be related to the regulation of IL-23 and TNF- α .

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Compliance with Ethics Guidelines. All procedures performed in studies involving human participants were in accordance with the ethical standards of the Second Hospital of Jilin University research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Data Availability. The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

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