

ORIGINAL ARTICLE

Low-dose and short-term cyclosporine treatment in patients with chronic idiopathic urticaria: A clinical and immunological evaluation

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ABSTRACT

The present study aimed to evaluate the effectiveness of 2.5 mg/kg/day cyclosporin (CsA) treatment in patients with severe chronic idiopathic urticaria (CIU) and the impact of CsA treatment on several cytokines involved in the etiopathogenesis of CIU. Twenty-seven CIU patients and 24 healthy control subjects were included in the study. The autologous serum skin test (ASST) for autoantibodies and urticaria activity scoring (UAS) were measured for the evaluation of the clinical severity and the response to therapy, and the serum levels of interleukin (IL)-6, IL-8, IL-2 receptor, IL-1 β , tumor necrosis factor (TNF)- α and IL-5 were measured. The mean UAS score was 32.07 ± 7.05 and 6.22 ± 3.84 before and after CsA treatment, respectively. The serum IL-2 receptor, TNF- α and IL-5 levels of patients before CsA treatment were statistically higher than those of the control group ($P = 0.001$), and after 4 weeks of CsA therapy the mean IL-2R, TNF- α and IL-5 levels were significantly decreased. The data from this study demonstrate that CsA therapy is efficient and safe for CIU patients. Increase in clinical efficacy and marked decreases in serum cytokine levels suggest that inhibition of cytokine generation is involved in the action of the drug in this clinical setting.

Key words: chronic idiopathic urticaria, cyclosporine, interleukin, tumor necrosis factor- α .

INTRODUCTION

Urticaria is a cutaneous vascular reaction induced by immunological or non-immunological mechanisms. Chronic urticaria is characterized by recurrent episodes of transient wheals, frequently associated with angioedema, present daily or at least twice a week for over 6 weeks. The disease is diagnosed as “idiopathic” when no causative factor can be identified. Approximately 15–20% of people develop at least one episode of urticaria in their lives and in less than 20% of them an etiological factor has been identified.¹

Chronic idiopathic urticaria (CIU) is occasionally unresponsive to therapy with antihistamines and difficult to treat. Mast-cell degranulation and release of pro-inflammatory mediators and cytokines from

the secretory granules of the mast cells play the major role in the pathogenesis of urticaria. Presence of circulating histamine releasing factors, autoantibodies against the high-affinity immunoglobulin (Ig)E receptor (Fc ϵ RI) or against IgE, were found in approximately 30% of patients with CIU.^{2,3} Clinical improvement after removal of autoantibodies by plasmapheresis⁴ and by immunomodulatory therapy, and demonstration of association with human leukocyte antigen (HLA) DR4, suggest that autoimmune mechanisms could be involved in the pathogenesis of CIU.⁵

In view of these findings, immunosuppressive drugs have been proposed in the treatment of the disease.⁶ In particular, cyclosporine A (CsA) has been used when antihistamines fail and prolonged steroid treatment is required. Therefore, the aim of

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Table 1. Exclusion criteria of the study

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- Chronic urticaria due to physical factors
 - Presence of urticarial vasculitis and C1 esterase inhibitor deficiency
 - History of malignancy (including skin cancer)
 - Systemic steroid use within 2 weeks
 - History of epilepsy
 - Infection
 - Antihypertensive drug use
 - Concomitant use of nephrotoxic drug (aminoglycosides, co-trimoxazol, diclophenac, ketakonazol, ranitidine)
 - Concomitant use of drug that has the possibility to change serum level of cyclosporine
 - Pregnancy
 - Lactation
 - Hypertension (diastolic blood pressure above 95 mmHg)
 - Increased serum creatinine, potassium, uric acid, bilirubin, and hepatic enzyme levels
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this study was to evaluate the effectiveness of CsA treatment, its safety, and the duration of clinical benefit in patients with severe CIU and the impact of CsA treatment on cytokine levels involved in the etiopathogenesis of CIU.

METHODS

Patients

Twenty-seven patients (20 females, 74.07%; seven males, 25.93%) with CIU (an episode of urticaria at least twice a week for over 6 weeks) and 24 healthy control subjects (11 females, 45.83%; 13 males, 54.17%) without a history of atopia, drug use or any systemic disorder, who were admitted to the Dermatology Outpatient Clinic of Gaziantep University, School of Medicine, were included in the study. This study was approved by the local ethics committee and a written consent form was obtained from each subject.

The mean age of the patients was 36.18 ± 11.76 years (range, 17–59). The control group consisted of 11 females (45.83%) and 13 males (54.17%) and the mean age was 32.46 ± 9.52 years (range, 23–39). The disease duration was in the range of 3–180 months (mean, 50.29 ± 48.75). All patients were unresponsive to antihistamines; eight subjects were given systemic steroids but none of them had previously received immunosuppressant therapy.

The detailed medical histories of all patients were evaluated together with dermatological examination. The characteristics of urticaria plaque (distribution of lesions, number of lesions, number of separate episodes, size and duration of lesions), coexistence of angioedema, number of recurrences, response to drug therapy, history of atopia and the possible causative factors (foods, drugs, any disease association of lesions, hot, cold, sunlight exposure, pressure, trauma) were established. The serological tests (i.e. acute phase reactants, C-reactive protein, erythrocyte sedimentation rate, C3, C4, IgE, antinuclear antibody [ANA], antistreptolysin O [ASO], hepatitis markers) and routine biochemical tests (i.e. electrolytes, liver functions tests, blood urea nitrogen, creatinine, thyroid function tests), urine analysis, Gaita microscopy, and hemograms were performed. Radiological imaging of systems was also performed if required. The exclusion criteria are listed in Table 1.

Study design and protocol

In this prospective, controlled study, the patients with chronic idiopathic urticaria ($n = 27$) and healthy control subjects ($n = 24$) were enrolled. The patients received oral cyclosporine (Sandimmun Neoral; Novartis, Basel, Switzerland) at a dosage regimen of 2.5 mg/kg/day given in two divided doses for 4 weeks.

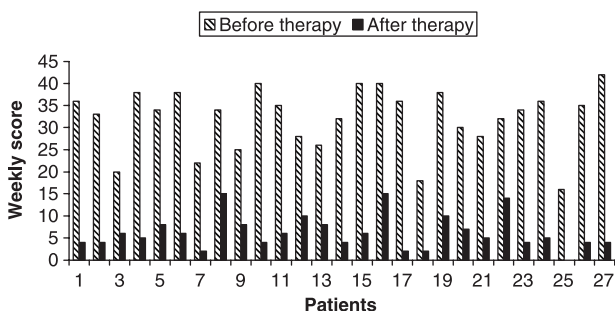
Autologous serum skin test (ASST), a screening test for autoantibodies, was applied to the patients following an “antihistamine wash-out” period of 3 days (7 days for patients treated with ketotifen) as described previously.⁷ Sterile autologous serum and saline (0.1 cc) were injected i.d. 3 cm apart from each other to clinically uninvolved volar forearm skin. The wheal and flare response were evaluated at 30 min. ASST was accepted as positive if the diameter of wheal after autologous serum injection was 1.5 mm greater than the wheal diameter induced by saline injection. The test was assessed by the same physician.

Serum samples were taken from patients before and after drug therapy for the measurement of interleukin (IL)-5, IL-6, IL-8, IL-2 receptor (IL-2R), IL-1 β and tumor necrosis factor (TNF)- α levels. Serum IL-6, IL-8, IL-2R, IL-1 β , TNF- α levels were measured with an Immulite Immunoassay Analyser

Table 2. Serum levels of interleukin-2 receptor (IL-2R), tumor necrosis factor (TNF)- α and IL-5 in control and study groups before and after cyclosporine (CsA) therapy

	Control group	Study groups	
		Before CsA	After CsA
IL-2R (U/mL)	477.12 $\pm$ 166.87	652.66 $\pm$ 213.04†	522.48 $\pm$ 172.8‡
TNF- α (pg/mL)	8.08 $\pm$ 2.44	14.26 $\pm$ 4.17§	7.81 $\pm$ 3.69¶
IL-5 (pg/mL)	98.15 $\pm$ 32.23	244 $\pm$ 67.18††	114.95 $\pm$ 36.61‡‡

Values are expressed as mean $\pm$ standard deviation. † P = 0.001, control group vs study group before CsA treatment. ‡ P < 0.0001, before vs after CsA treatment. § P < 0.0001, control group vs study group before CsA treatment. ¶ P = 0.001, before treatment vs after treatment. †† P = 0.001, before vs after CsA treatment. ‡‡ P = 0.001, control group vs study group before CsA treatment.

**Figure 1.** Urticaria activity score of patients before and after cyclosporine therapy.

(Immulite DPC, Los Angeles, CA, USA) and IL-5 level was measured by an enzyme-linked immunosorbent assay (ELISA) method (Human IL-5 ELISA; Cytimmune Sciences, College Park, MD, USA).

Urticaria activity scoring (UAS) was performed before and after the treatment to diagnose the clinical severity of urticaria and response to therapy. Number and average size of lesions, and pruritus severity were rated on a 3-point scale and the total score was recorded. The patients were evaluated at baseline and weekly for 4 weeks upon completion of the therapy. The treatment was considered effective if the score at completion of the therapy was less than 25% of the score recorded before therapy.

Statistical analysis

All statistical analyses were carried out by using a statistical package, SPSS for Windows ver. 6.0 (SPSS Software, Chicago, IL, USA). The results were expressed as mean $\pm$ standard deviation. The

comparison of UAS, IL-2R, TNF- α and IL-5 values of patients before and after therapy was analyzed by paired Student's *t*-test, and comparison of these values between patients and controls was analyzed by an independent samples Student's *t*-test. The level of statistical significance was set at P = 0.05.

RESULTS

An ASST was performed in all patients before and after therapy, and ASST positivity was found in 11 (three males, eight females,) of 27 patients (40.74%). The mean UAS score was 32.07 ± 7.05 (range, 16–42) and 6.22 ± 3.84 (range, 0–15) before and after CsA treatment, respectively. In a total of 19 patients (70.37%), the score reduced by 25% after CsA treatment. Thus, these patients were considered to be in total remission. The reduction of the UAS score after CsA treatment was statistically significant in all patients (P < 0.005) (Fig. 1).

Serum IL-6, IL-8 and IL-1 β levels in the control and study groups before and after CsA therapy were less than 5 pg/mL. Serum IL-2R, TNF- α and IL-5 levels of the control and study groups before and after therapy are shown in Table 2. The serum IL-2R level of patients before CsA treatment was found to be statistically higher than that of the control group (P = 0.001). After 4 weeks of therapy, the serum IL-2R levels of patients showed a statistically significant decrease (652.66 ± 213.04 and 522.48 ± 172.80 U/mL, before and after therapy, respectively; P < 0.0001). There was no significant difference between the serum IL-2R levels of control and study patients (P = 0.274). The serum TNF- α levels of the patients in study and control groups

before treatment were 14.26 ± 4.17 pg/mL (range, 5.6–30.1) and 8.08 ± 2.44 pg/mL (range, 4.6–10.9), respectively ($P < 0.0001$). The mean TNF- α level showed a significant decrease after treatment with CsA (7.81 ± 3.69 pg/mL; range, 4.1–16.5; $P = 0.001$). The serum TNF- α levels did not show a significant change before and after CsA treatment in the control group ($P = 0.139$).

The mean IL-5 level of the study patients was significantly higher than that of the control subjects (244 ± 67.18 pg/mL [range, 12.76–737.00] and 98.15 ± 32.23 pg/mL [range, 24.36–266.24], respectively ($P = 0.001$). After CsA therapy, IL-5 was noted to be 114.95 ± 36.61 pg/mL (range, 2.91–281.31) in the study group and this reduction was significant compared to the level before CsA therapy ($P = 0.001$). No significant difference was observed between the IL-5 levels of the control group before and after CsA therapy ($P = 0.284$).

During the treatment with CsA, only one patient experienced abdominal pain and nausea. This patient showed no laboratory abnormality and this adverse effect disappeared in 2 days when omeprazole was added to CsA therapy.

DISCUSSION

In the present study, 2.5 mg/kg/day CsA treatment for 4 weeks was found to be effective in terms of lowering the serum levels of cytokines IL-2R, IL-5 and TNF- α , which have been shown to be higher in patients with chronic idiopathic urticaria.

The pathogenesis of CIU involves primarily the mast cells and histamine as the main mediator. Approximately 30–60% of patients with CIU have circulating histamine releasing autoantibodies to the high-affinity IgE receptor Fc RI on basophils and mast cells or, less commonly, antibodies to IgE. ASST is the *in vivo* clinical test for detection of *in vitro* basophil histamine-releasing activity. Mast cell activation results in the release of both preformed (histamine) and newly formed (prostaglandins) mediators from cytoplasmic granules, which cause wheal formation, vasodilatation and erythema. Mast cell degranulation also releases various chemokines and cytokines that are involved in wheal formation. Immunohistochemical findings support the involvement of these factors in the disease

pathogenesis.^{6–13} Inflammatory cell infiltration and mast cell increase have been shown in skin biopsy specimens from urticarial lesions of CIU patients. In the initial stage of lesions, the predominant cell type is the CD4 T cells and the cytokine and chemokine release contribute to the inflammatory process.¹⁴ It was also shown that IL-4, IL-8 and TNF- α cytokines are produced by dermal mast cells.^{8,5,15}

Piconi *et al.* reported increased levels of cytokines such as TNF- α , IL-10 and macrophage inhibitor protein (MIP)-1 α in CIU patients when compared to healthy controls.⁵ A high TNF- α level was also demonstrated in skin biopsy specimens of these patients in various studies^{16,17} Ying *et al.* noted eosinophil and neutrophil infiltration in biopsy examinations as compared to non-atopic subjects and also high CD3⁺, CD4⁺, CD8⁺, CD25⁺ T-lymphocytes and IL-4, IL-5 and γ -interferon (IFN- γ) levels in these patients.¹⁴ Supporting these findings, in our study, we found statistically higher IL-2R, TNF- α and IL-5 levels of CIU patients before CsA treatment when compared to controls. These cytokines were also reported to be high in serum and skin biopsy samples of CIU patients in previous studies. The consistency of our findings with other studies supports the hypothesis that cytokines derived from T cells play an important role in CIU etiopathogenesis.

Cyclosporine forms a complex with the cytosolic immunophilin, cyclophilin, which binds to and inhibits the activity of the intracellular enzyme calcineurin phosphatase. This reduces the effect of the transcription factor in T cells (nuclear factor of activated T cells) that regulates transcription of a number of cytokine genes, the most significant being IL-2. IL-2 serves as the major activation factor for T cells in numerous immunological processes. CsA also inhibits histamine release from mast cells and downregulates various cellular adhesion molecules.^{18–21} Reduced expression of cellular adhesion molecules on dermal capillary endothelium decreases both T-cell and neutrophil infiltration. CsA also has an inhibitory effect on antigen-presenting cells, such as Langerhans and dendritic cells, which are potent stimulators of T cells. Additionally, IL-2, IL-2R, IL-3, IL-4, TNF- α and IFN- γ production are also inhibited by CsA.²² The IL-3, IL-4 and IL-5 lowering effect of CsA was also detected in various studies.^{23–26}

In a previous study with CsA therapy for atopic dermatitis, the patients received CsA at a dose of 3.5 mg/kg/day for 3 months. In these patients, IL-2R, CD30⁺ and IL-4 levels were found to be decreased after CsA therapy. Moreover, a negative correlation between decrease in IL levels and clinical recovery was observed in the same study.²⁷ In another study, CsA therapy was shown to reverse high IL-2R and TNF- α levels in patients with atopic dermatitis.²⁸ Consistent with these findings, in our study, we observed a marked increase in clinical efficacy as serum IL and cytokine levels decreased with the use of CsA. The evaluation of the severity of the disease and efficacy of therapy via UAS revealed a 25% decrease in score after 2.5 mg/kg/day CsA therapy indicating a total remission.²⁹

The release of mast cell-derived mediators may be caused by both immune and non-immune mechanisms. Fc ϵ R1a on the mast cell surface is a high-affinity IgE receptor that binds the Fc portion of IgE, resulting in histamine release. IgG autoantibodies against this receptor appear to be the etiological factor in as many as 25% of patients with CIU. Other agents, such as aspirin, opioids and adenosine, cause mast cell degranulation directly through non-immunological means. The functional activity of these autoantibodies, suggested *in vivo* by ASST, has been confirmed *in vitro* by the basophil and mast cell histamine release assays.³⁰ Additionally, removal of the autoantibodies by plasmapheresis produced clinical improvement in patients with CIU.⁴ Western blot analysis and ELISA have confirmed the presence of these autoantibodies.³¹ ASST positivity provides indirect evidence of histamine-releasing activity (HRA) in the serum.⁷

Recent findings suggest that in 25–45% of patients, CIU is not idiopathic but is an autoimmune disease. Coexistence of other autoimmune diseases and recovery after immunosuppressive therapy imply that autoimmunity plays a role in the etio-pathogenesis. In our study patients, the ASST positivity was found to be 40.7% and was consistent with the autoimmune nature of the disease.

Chronic idiopathic urticaria is sometimes unresponsive to therapy with antihistamines and is difficult to treat.¹² If antihistamines fail to treat CIU patients, the corticosteroids are used as alternative agents to control acute exacerbations. However,

frequent recurrences and adverse effects related to long-term use of steroids are the limiting problems in the management of CIU.^{8–12} Thus, the treatment protocols including immunosuppressive agents have been used for patients with severe CIU which is resistant to conventional therapies and were found to be effective.^{32,33}

Although several studies have reported the effectiveness and tolerability of CsA in the management of severe forms of chronic urticaria, the precise mechanism of action of the drug is not understood completely. Experimental studies suggest that this drug, along with its immunosuppressive action, has anti-inflammatory and anti-allergic properties as well.^{18,34}

The incidence of side-effects associated with low-dose cyclosporine is rare. In previous studies, it was reported that because no adverse effect was seen at the dose of 3–5 mg/kg/day, monitoring of drug level was not necessary.³⁵ In our study, only one patient experienced nausea and abdominal pain which is consistent with previous studies demonstrating minor side-effects.^{36–38}

In conclusion, the data of this study demonstrate that CsA therapy is efficient and safe for CIU patients. However, it is necessary to observe long-term CsA treatment in future studies because it may help patients maintain long periods of remissions. Increase in clinical efficacy with a concomitant decrease in serum cytokine levels suggests that inhibition of cytokine generation is involved in the action of the drug in this clinical setting.

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