

Report

Different effect of oral cyclosporine therapy and oral antihistamine therapy on serum high-sensitivity C-reactive protein level and thymus and activation-regulated chemokine level in atopic dermatitis in older children and adulthood

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Abstract

Background Many patients with atopic dermatitis (AD) are treated with oral cyclosporine or antihistamine therapy in clinical practice.

Objective To evaluate the effectiveness of oral cyclosporine and antihistamine therapy on clinical and laboratory findings in patients with AD.

Subjects and methods Twenty-five patients with AD (male–female = 11 : 14, age 16–42 years old, mean 26.2 years old) were treated with oral cyclosporine therapy. Twenty-three patients with AD (male–female = 10 : 13, age 15–32 years old, mean 24.2 years old) were treated with oral antihistamine therapy. Laboratory findings including high-sensitivity C-reactive protein (CRP) and thymus and activation-regulated chemokine (TARC) were statistically studied.

Results Serum TARC level after oral cyclosporine therapy (1013 ± 883 pg/ml) was significantly decreased compared to before therapy (38194 ± 4678 pg/ml; $P < 0.02$). Basophil counts in peripheral blood after the therapy ($49.7 \pm 26.4 \times 10^{-3}$ cells/ μ l) were more significantly increased than before therapy ($41.1 \pm 16.7 \times 10^{-3}$ cells/ μ l; $P < 0.05$). Serum high-sensitivity CRP level after antihistamine therapy (0.09 ± 0.08 mg/ml) was significantly decreased compared to before therapy (0.13 ± 0.12 mg/ml; $P < 0.05$). Basophil counts in peripheral blood after the therapy ($33.4 \pm 16.2 \times 10^{-3}$ cells/ μ l) were more significantly decreased than before therapy ($41.5 \pm 23.3 \times 10^{-3}$ cells/ μ l; $P < 0.01$).

Conclusion Different effects of oral cyclosporine therapy and oral antihistamine therapy to serum high-sensitivity CRP level, TARC level, and peripheral blood basophils in adult patients with AD were shown. A combination of these two therapies may be more effective for the treatment of AD in adults.

Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin disease of unknown cause, characterized by pruritus and eczematous skin lesions and often associated with elevated serum immunoglobulin E (IgE) levels and eosinophilia.¹ The prevalence of AD is documented to have increased to 10–20% of children and young adults worldwide.^{2,3} A large variety of laboratory and clinical measurements have been linked to disease severity in AD, which reflects the difficulties in defining a selective and objective marker that is most indicative of disease severity.^{4–6} This has led to a wide variation in the outcome of disease severity measurements in clinical studies.

In dermis with acute lesions of AD, there is a striking infiltration of CD4-activated T cells.⁷ It is well-known

that the accumulation of specific leukocytes migrating from blood to inflamed tissue is highly dependent on the chemokine–chemokine receptor network.⁸ β -chemokines that are important in the skin-specific homing of T cells include thymus and activation-regulated chemokine (TARC) and cutaneous T-cell-attracting chemokine.⁹ TARC acts on CCR4, the chemokine receptor, which is probably important for recruitment and homing in target tissues of T-helper 2 cells.¹⁰ Various cell types, including endothelial cells, dendritic cells, keratinocytes, and activated T cells, have been suggested to produce TARC.^{11–13} Several recent reports suggest that TARC might be a useful marker for disease severity in adult patients with AD.^{14–16} C-reactive protein (CRP) has been used for the monitoring of inflammatory change in several kinds of diseases, including infective and inflammatory diseases in

clinical practice. Conventional CRP, however, has provided limited information for the monitoring of inflammatory change in psoriasis. More recently, high-sensitivity CRP has been shown as a potentially useful adjunct for global risk assessment in the primary prevention of cardiovascular disease.¹⁷

Oral cyclosporine therapy has been shown to be effective for the treatment of moderate to severe adult AD.^{18,19} In the present study, oral cyclosporine therapy and oral antihistamine therapy were compared using laboratory findings, including serum TARC level and serum high-sensitivity CRP level in adult patients with AD.

Materials and methods

Subjects

Forty-eight adult patients with AD (male–female = 21 : 27, age 15–42 years old, mean 25.3 years old) admitted to the outpatient clinic were studied. All the patients with AD were given a diagnosis according to the criteria of Hanifin and Rajka.¹ All the patients with AD were Japanese. Childhood-onset AD and patients with mild AD without cutaneous inflammatory change were excluded. All the subjects were studied for relevant clinical and laboratory findings. Clinical findings in patients with AD were studied for age and sex distribution, area, excoriation, itch, and SCORAD score. Laboratory findings in patients with AD were studied for serum TARC level, serum transaminase (aspartate aminotransferase, alanine aminotransferase) level, alkaline phosphatase level, γ -glutamyl transpeptidase level, lactose dehydrogenase level, total bilirubin level, serum total protein level, urea nitrogen level, serum creatinine level, total white blood cell count, counts of red blood cells, neutrophils, lymphocytes, monocytes, eosinophils, basophils, and platelets in peripheral blood, serum immunoglobulin E level, and serum high-sensitivity CRP level.

Oral cyclosporine therapy and oral antihistamine therapy in adult patients with atopic dermatitis

Clinical indications for “cyclosporine + hydrocortisone butyrate propionate” and “bepotastine + hydrocortisone butyrate propionate” were randomly selected irrespective of clinical severity of patients with AD. All the patients with moderate to severe AD were treated with hydrocortisone butyrate propionate. Severity (moderate to severe) was judged by the existence of cutaneous inflammatory change. Patients with mild AD without cutaneous inflammatory change were excluded. All the patients were with hydrocortisone butyrate propionate. Numbers were assigned to each patient with AD, and all those with odd numbers were treated with cyclosporine, and those with even numbers were treated with bepotastine.

Twenty-five of 48 patients with AD (male–female = 11 : 14, age 16–42 years old, mean 26.2 years old) were treated with oral cyclosporine therapy. Patients with AD were treated

with cyclosporine (Neoral®, Novartis Pharma, Arnhem, the Netherlands) <5 mg/kg daily (divided into two doses). Patients previously treated with cyclosporine were excluded, as were patients with concurrent medication and/or comorbidity with a potential influence on cyclosporine trough levels. The initial dose of cyclosporine was 3 mg/kg daily. Twenty-three of 48 patients with AD (male–female = 10 : 13, age 15–32 years old, mean 24.2 years old) were treated with oral antihistamine therapy (bepotastine besilate, 20 mg/day, divided into two doses). All the 48 patients with AD were simultaneously treated with topical application of moderate steroid ointment (hydrocortisone butyrate propionate) twice daily.

The age distribution in 25 patients with AD treated with oral cyclosporine therapy (26.5 ± 2.8 years old, mean $\pm$ SEM) and that in 23 patients with AD treated with oral antihistamine therapy (24.2 ± 1.7 years old, mean $\pm$ SEM) showed no significant difference (Table 1). The male–female distribution in 25 patients with AD treated with oral cyclosporine therapy (male–female = 11 : 14) and that in 23 patients with AD treated with oral antihistamine therapy (male–female = 10 : 13) showed no significant difference. Asthma symptom, irritation by sweat, area, excoriation, itch, and SCORAD score in 25 patients with AD treated with oral cyclosporine therapy and that in 23 patients with AD treated with oral antihistamine therapy showed no significant differences, respectively. All the laboratory findings before therapy in 25 patients treated with oral cyclosporine therapy and 23 patients treated with oral antihistamine therapy, including serum TARC level, serum aspartate aminotransferase level, alanine aminotransferase level, alkaline phosphatase level, γ -glutamyl transpeptidase level, lactose dehydrogenase level, total bilirubin level, total protein level, urea nitrogen level, serum creatinine level, red blood cell counts, total white blood cell counts, lymphocyte counts, monocyte counts, eosinophil counts, platelet counts in peripheral blood, serum immunoglobulin E level, and serum high sensitivity level showed no significant differences, respectively. Four weeks after the start of these therapies, laboratory findings were studied again. Ethical committee in International University of Health and Welfare Hospital approved this study.

Measurement of serum high-sensitivity C-reactive protein level in adult patients with atopic dermatitis

High-sensitivity CRP was measured from samples drawn on admission, and results were kept blinded from the physicians treating the patients. Blood samples were drawn in vacuum tubes containing lithium heparin, centrifuged, and the remaining plasma stored at -70°C for later measurements. High-sensitivity CRP was measured with a nephelometric assay (Dade Behring Diagnostics, Marburg, Germany). The detection limit was 0.0036 mg/l, linearity from 0.015 to 1.5 mg/l. The coefficient of variation was 3.57% at a concentration of 0.021 mg/dl, 1.06% at a concentration of 0.056 mg/dl, and 3.19% at a concentration of 0.807 mg/dl. The results of

Table 1 The distribution of clinical and laboratory findings before oral cyclosporine therapy and oral antihistamine therapy in adult patients with atopic dermatitis

Clinical and laboratory findings	Oral cyclosporine therapy	Oral antihistamine therapy	Unpaired <i>t</i> -test
Age distribution (years)	26.5 ± 2.8	24.2 ± 1.7	NS ^b
Male/female	11 : 14	10 : 13	NS
Asthma	11 (44%)	9 (39%)	NS
Irritation by sweat	20 (80%)	17 (74%)	NS
Area (%)	24.2 ± 5.1	24.0 ± 4.9	NS
Excoriation (score)	5.2 ± 0.6	5.4 ± 0.8	NS
Itch (mm)	5.6 ± 0.9	5.3 ± 1.0	NS
SCORAD value	71.5 ± 15.5	69.8 ± 13.9	NS
TARC (pg/ml)	38 194 ± 4678 ^a	36 704 ± 660	NS ^c
Aspartate aminotransferase (U/l)	20.6 ± 4.3	22.9 ± 6.2	NS
Alanine aminotransferase (U/l)	18.2 ± 6.1	19.2 ± 11.4	NS
Alkaline phosphatase (U/l)	227 ± 64	219 ± 146	NS
γ-glutamyl transpeptidase (U/l)	19.4 ± 10.7	19.0 ± 18.8	NS
Lactose dehydrogenase (U/l)	255 ± 106	254 ± 91	NS
Total bilirubin (mg/dl)	0.77 ± 0.33	0.77 ± 0.33	NS
Total protein (g/dl)	7.2 ± 0.5	7.3 ± 0.5	NS
Urea nitrogen (mg/dl)	12.4 ± 3.5	11.7 ± 3.0	NS
Serum creatinine (mg/dl)	0.69 ± 0.16	0.67 ± 0.20	NS
Red blood cells (×10 ⁻⁴ cells/μl)	492 ± 34	461 ± 43	NS
White blood cells (×10 ⁻³ cells/μl)	7050 ± 1953	6742 ± 2287	NS
Neutrophils (×10 ⁻³ cells/μl)	4240 ± 1159	4070 ± 1631	NS
Lymphocytes (×10 ⁻³ cells/μl)	1588 ± 442	1577 ± 423	NS
Monocytes (×10 ⁻³ cells/μl)	445 ± 241	438 ± 189	NS
Eosinophils (×10 ⁻³ cells/μl)	737 ± 661	560 ± 443	NS
Basophils (×10 ⁻³ cells/μl)	41.1 ± 16.7	41.5 ± 23.3	NS
Platelets (×10 ⁻⁴ cells/μl)	23.0 ± 3.8	24.1 ± 4.7	NS
Immunoglobulin E (IU/ml)	6512 ± 8054	7600 ± 11 115	NS
High-sensitivity C-reactive protein (mg/dl)	0.14 ± 0.21	0.13 ± 0.12	NS

TARC, thymus and activation-regulated chemokine.

^aMean ± SDV.

^bNS, not significant (chi-squared test with Yates correction).

^cNS, not significant (unpaired *t*-test).

simultaneous measurements in 89 normal controls showed that the correlation coefficient between conventional CRP and high-sensitivity CRP was 0.999.

Measurement of thymus and activation-regulated chemokine in adult patients with atopic dermatitis

Serum TARC level was measured using commercially available ELISA kits (Shionogi Pharmaceutical, Osaka, Japan), according to the manufacturer's instructions. The minimal detection level of TARC was 125 pg/ml.

Efficacy evaluation

At each visit, the area of active eczema was estimated by the rule of nines, and severity was assessed by scoring the worst area in each of head and neck, upper limbs, lower limbs, and anterior and posterior trunk, for erythema, excoriation, and lichenification (range 0–3).²⁰ Itch and sleep loss were each assessed by marking a 10-cm visual analog scale. The primary efficacy outcome was assessed with the change in the SCORAD value.²¹ This

assessment was made at the start of treatment (week 0) and after four weeks. In addition, SCORAD score was also assessed after two weeks.

Statistical analysis

A paired *t*-test was used to evaluate the difference of values before and after treatment in the same group. An unpaired *t*-test was used to evaluate the difference of values between two groups. The chi-squared test with Yates' correction was used to evaluate the difference of occurrence rate between two groups.

Results

The distribution of clinical and laboratory findings before and after oral cyclosporine therapy in 25 adult patients with atopic dermatitis

The prevalence of clinical and laboratory findings before and after oral cyclosporine therapy in 25 patients with AD were statistically studied (Table 2). Asthma symptoms after

therapy (eight of 25, 32%) showed no significant difference than that before therapy (11 of 25, 44%). Irritation by sweat after therapy (four of 25, 16%) was significantly decreased compared to before therapy (20 of 25, 80%; $P < 0.01$). The area after therapy ($4.7 \pm 1.9\%$) was significantly decreased compared to before therapy ($24.2 \pm 5.1\%$; $P < 0.01$). The excoriation after therapy (2.0 ± 0.5) was significantly decreased compared to before therapy (5.2 ± 0.6). The itch after therapy (2.1 ± 0.6 mm) was significantly decreased compared to before therapy (5.6 ± 0.9 mm; $P < 0.01$). The SCORAD value after two weeks (24.4 ± 4.9) was significantly less than before therapy (71.5 ± 15.5 ; $P < 0.01$). The SCORAD value after four weeks (22.5 ± 3.9) was significantly less than before therapy (71.5 ± 15.5 ; $P < 0.01$). The distribution of serum TARC level after therapy (1013 ± 883 pg/ml) was significantly less than before therapy (38194 ± 4678 pg/ml; $P < 0.02$; Fig. 1). The distribution of basophil counts in peripheral blood after oral cyclosporine therapy ($49.7 \pm 26.4 \times 10^{-3}$ cells/ μ l) was significantly elevated

compared to before therapy ($41.1 \pm 16.7 \times 10^{-3}$ cells/ μ l; $P < 0.05$; Fig. 2). The distribution of serum aspartate aminotransferase level, alanine aminotransferase level, alkaline phosphatase level, γ -glutamyl transpeptidase level, lactose dehydrogenase level, total bilirubin level, total protein level, urea nitrogen level, serum creatinine level, red blood cell counts, total white blood cell counts, lymphocyte counts, monocyte counts, eosinophil counts, platelet counts in peripheral blood, serum immunoglobulin E level, and serum high-sensitivity CRP level before and after therapy showed no significant differences, respectively.

The distribution of laboratory findings before and after oral antihistamine therapy in 23 patients with adult atopic dermatitis

Statistical analysis of the prevalence of laboratory findings before and after oral antihistamine therapy in 23 patients with AD was performed (Table 3). Asthma symptoms after therapy (six of 23; 26%) showed no significant difference compared to that before therapy (nine of 23;

Table 2 The distribution of clinical and laboratory findings before and after oral cyclosporine therapy in 25 adult patients with atopic dermatitis

Clinical and laboratory findings	Oral cyclosporine therapy Before	Paired After	t-test
Asthma	11 (44%)	8 (32%)	NS
Irritation by sweat	20 (80%)	4 (16%)	$P < 0.01$
Area (%)	24.2 ± 5.1	4.7 ± 1.9	$P < 0.01$
Excoriation (score)	5.2 ± 0.6	2.0 ± 0.5	$P < 0.01$
Itch (mm)	5.6 ± 0.9	2.1 ± 0.6	$P < 0.01$
SCORAD value (2 weeks)	71.5 ± 15.5	24.4 ± 4.9	$P < 0.01$
SCORAD value	71.5 ± 15.5	22.5 ± 3.9	$P < 0.01$
TARC (pg/ml)	38194 ± 4678^a	1013 ± 883	$P < 0.02$
Aspartate aminotransferase (U/l)	20.6 ± 4.3	18.7 ± 4.4	NS ^b
Alanine aminotransferase (U/l)	18.2 ± 6.1	16.5 ± 7.6	NS
Alkaline phosphatase (U/l)	227 ± 64	234 ± 70	NS
γ -glutamyl transpeptidase (U/l)	19.4 ± 10.7	18.6 ± 10.6	NS
Lactose dehydrogenase (U/l)	255 ± 106	234 ± 70	NS
Total bilirubin (mg/dl)	0.77 ± 0.33	0.91 ± 0.32	NS
Total protein (g/dl)	7.2 ± 0.5	7.2 ± 0.4	NS
Urea nitrogen (mg/dl)	12.4 ± 3.5	13.7 ± 3.4	NS
Serum creatinine (mg/dl)	0.69 ± 0.16	0.70 ± 0.19	NS
Red blood cells ($\times 10^{-4}$ cells/ μ l)	492 ± 34	490 ± 37	NS
White blood cells ($\times 10^{-3}$ cells/ μ l)	7050 ± 1953	7119 ± 2766	NS
Neutrophils ($\times 10^{-3}$ cells/ μ l)	4240 ± 1159	4398 ± 2194	NS
Lymphocytes ($\times 10^{-3}$ cells/ μ l)	1588 ± 442	1763 ± 511	NS
Monocytes ($\times 10^{-3}$ cells/ μ l)	445 ± 241	445 ± 273	NS
Eosinophils ($\times 10^{-3}$ cells/ μ l)	737 ± 661	645 ± 1032	NS
Basophils ($\times 10^{-3}$ cells/ μ l)	41.1 ± 16.7	49.7 ± 26.4	$P < 0.05$
Platelets ($\times 10^{-4}$ cells/ μ l)	23.0 ± 3.8	22.8 ± 3.9	NS
Immunoglobulin E (IU/ml)	6512 ± 8054	6570 ± 9250	NS
High-sensitivity C-reactive protein (mg/dl)	0.14 ± 0.21	0.08 ± 0.08	NS

TARC, thymus and activation-regulated chemokine.

^aMean $\pm$ SDV.

^bNS, not significant (paired *t*-test).

Figure 1 The distribution of serum thymus and activation-regulated chemokine level after oral cyclosporine therapy (1013 ± 883 pg/ml) was significantly decreased compared to before therapy (38194 ± 4678 pg/ml; $P < 0.02$). The distribution of serum thymus and activation-regulated chemokine level before and after oral antihistaminergic therapy showed no significant differences. NS, not significant

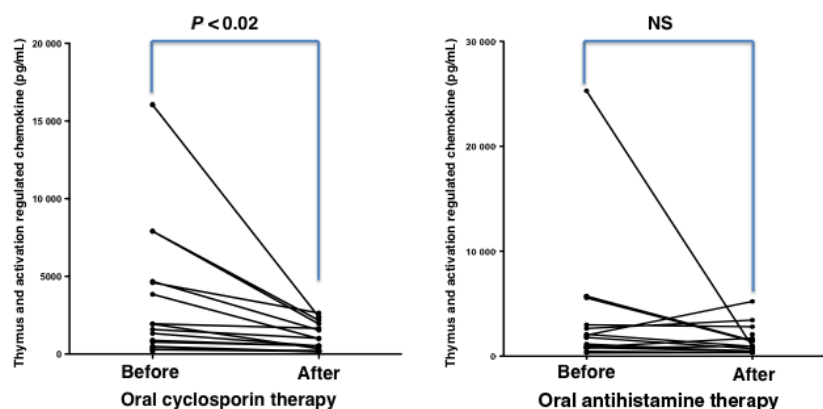
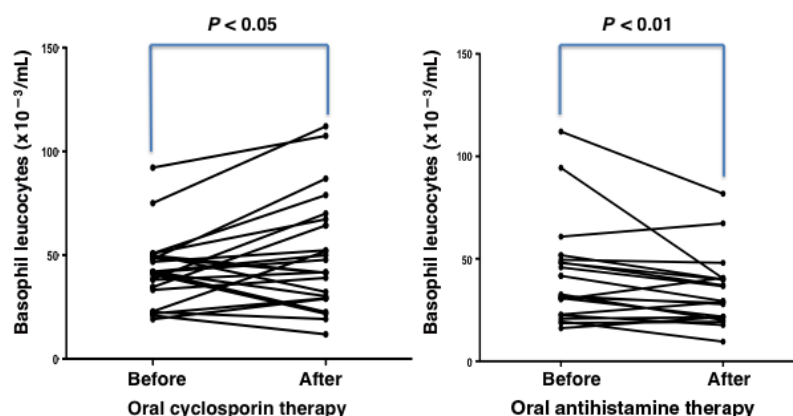


Figure 2 The distribution of basophil counts in peripheral blood after oral cyclosporine therapy ($49.7 \pm 26.4 \times 10^{-3}$ cells/ μ l) was significantly increased compared to before therapy ($41.1 \pm 16.7 \times 10^{-3}$ cells/ μ l; $P < 0.05$). The distribution of basophil counts in peripheral blood after oral antihistamine therapy ($33.4 \pm 16.2 \times 10^{-3}$ cells/ μ l) was significantly elevated compared to before therapy ($41.5 \pm 23.3 \times 10^{-3}$ cells/ μ l; $P < 0.01$)



39%). Irritation by sweat after therapy (eight of 23; 74%) was significantly less than before therapy (17 of 25; 80%; $P < 0.02$). The area after therapy ($5.6 \pm 2.0\%$) was significantly less than before therapy ($24.0 \pm 4.9\%$; $P < 0.01$). The excoriation after therapy (2.4 ± 0.7) was significantly less than before therapy (5.4 ± 0.8). The itch after therapy (2.6 ± 0.8 mm) was significantly decreased compared to before therapy (5.3 ± 1.0 mm; $P < 0.01$). The SCORAD value after two weeks (48.9 ± 14.9) showed no significant difference compared to before therapy (69.8 ± 13.9). The SCORAD value after four weeks (27.5 ± 4.8) was significantly less than before therapy (69.8 ± 13.9 ; $P < 0.01$). The distribution of serum high-sensitivity CRP level after therapy (0.09 ± 0.08 mg/ml) was significantly less than before therapy (0.13 ± 0.12 mg/ml; $P < 0.05$; Fig. 3). The distribution of basophil counts in peripheral blood after therapy ($33.4 \pm 16.2 \times 10^{-3}$ cells/ μ l) was significantly elevated compared to before therapy ($41.5 \pm 23.3 \times 10^{-3}$ cells/ μ l; $P < 0.01$; Fig. 2). The distribution of serum TARC level, serum aspartate aminotransferase level, alanine aminotransferase level, alkaline phosphatase level, γ -glutamyl transpeptidase level, lactose dehydrogenase level, total bilirubin

level, total protein level, urea nitrogen level, serum creatinine level, red blood cell counts, total white blood cell counts, lymphocyte counts, monocyte counts, eosinophil counts, platelet counts in peripheral blood, and serum immunoglobulin E level before and after therapy showed no significant differences, respectively.

Discussion

The present study showed that serum TARC levels after oral cyclosporine therapy were significantly decreased compared to before therapy. Serum high-sensitivity CRP level after antihistamine therapy was significantly less than before therapy. Basophil counts in peripheral blood after oral cyclosporine therapy were significantly more than before therapy, but after antihistamine therapy, they were significantly less than before therapy. These results showed different effects of oral cyclosporine therapy and oral antihistamine therapy to serum high-sensitivity CRP level, TARC level, and peripheral blood basophils in compared to adult patients with AD.

In an animal model using guinea pig allergic conjunctivitis, bepotastine besilate significantly inhibited conjuncti-

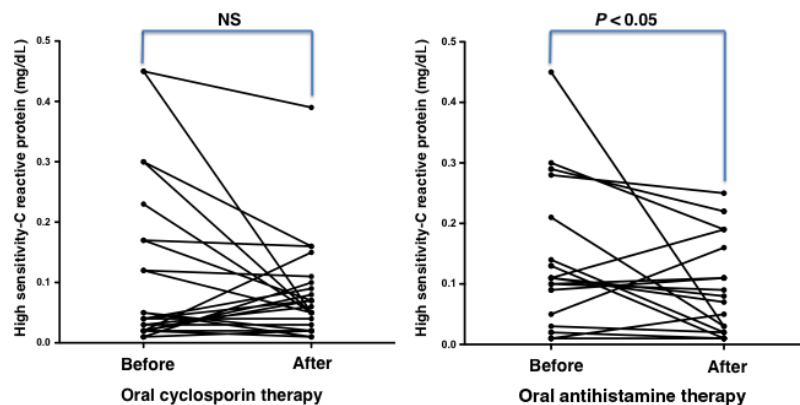
Table 3 The distribution of laboratory findings before and after oral antihistamine therapy in 23 adult patients with atopic dermatitis

Clinical and laboratory findings	Antihistamine therapy Before	Paired After	t-test
Asthma	9 (39%)	6 (26%)	NS
Irritation by sweat	17 (74%)	8 (35%)	$P < 0.02$
Area (%)	24.0 ± 4.9	5.6 ± 2.0	$P < 0.01$
Excoriation (score)	5.4 ± 0.8	2.4 ± 0.7	$P < 0.01$
Itch (mm)	5.3 ± 1.0	2.6 ± 0.8	$P < 0.01$
SCORAD value (2 weeks)	69.8 ± 13.9	48.9 ± 14.9	NS
SCORAD value	69.8 ± 13.9	27.5 ± 4.8	$P < 0.01$
TARC (pg/ml)	$36\,704 \pm 660^a$	1337 ± 1209	NS ^b
Aspartate aminotransferase (U/l)	22.9 ± 6.2	21.2 ± 6.3	NS
Alanine aminotransferase (U/l)	19.2 ± 11.4	18.7 ± 11.1	NS
Alkaline phosphatase (U/l)	219 ± 146	237 ± 217	NS
γ -glutamyl transpeptidase (U/l)	19.0 ± 18.8	23.3 ± 22.4	NS
Lactose dehydrogenase (U/l)	254 ± 91	231 ± 81	NS
Total bilirubin (mg/dl)	0.77 ± 0.33	0.92 ± 0.37	NS
Total protein (g/dl)	7.3 ± 0.5	7.3 ± 0.5	NS
Urea nitrogen (mg/dl)	11.7 ± 3.0	11.9 ± 3.0	NS
Serum creatinine (mg/dl)	0.67 ± 0.20	0.60 ± 0.10	NS
Red blood cells ($\times 10^{-4}$ cells/ μ l)	461 ± 43	468 ± 46	NS
White blood cells ($\times 10^{-3}$ cells/ μ l)	6742 ± 2287	6175 ± 1830	NS
Neutrophils ($\times 10^{-3}$ cells/ μ l)	4070 ± 1631	3769 ± 1280	NS
Lymphocytes ($\times 10^{-3}$ cells/ μ l)	1577 ± 423	1493 ± 400	NS
Monocytes ($\times 10^{-3}$ cells/ μ l)	438 ± 189	367 ± 124	NS
Eosinophils ($\times 10^{-3}$ cells/ μ l)	560 ± 443	512 ± 616	NS
Basophils ($\times 10^{-3}$ cells/ μ l)	41.5 ± 23.3	33.4 ± 16.2	$P < 0.01$
Platelets ($\times 10^{-4}$ cells/ μ l)	24.1 ± 4.7	23.9 ± 4.3	NS
Immunoglobulin E (IU/ml)	7600 ± 11115	5913 ± 9350	NS
High-sensitivity C-reactive protein (mg/dl)	0.13 ± 0.12	0.09 ± 0.08	$P < 0.05$

TARC, thymus and activation-regulated chemokine.

^aMean $\pm$ SDV.

^bNS, not significant (paired *t*-test).

**Figure 3** The distribution of serum high-sensitivity C-reactive protein level after oral antihistaminergic therapy (0.09 ± 0.08 mg/ml) was significantly decreased than before therapy (0.13 ± 0.12 mg/ml; $P < 0.05$). The distribution of serum high-sensitivity C-reactive protein level before and after oral cyclosporine therapy showed no significant differences

val vascular hyperpermeability in a dose-dependent manner.²² Bepotastine besilate further suppressed platelet-activating factor-induced eosinophil infiltration into

conjunctival tissue. Chemotaxis of guinea pig peritoneal eosinophils and histamine release from rat peritoneal mast cells *in vitro* were also inhibited by the addition of bepo-

tastine. Mast cell function and eosinophil chemotaxis were also inhibited *in vitro* with bepotastine, suggesting bepotastine acts as an inhibitor of allergic response through multiple mechanisms: histamine H(1) receptor antagonism, mast cell stabilization, and inhibition of eosinophil migration to ocular inflammatory sites. Numerous short- and long-term clinical trials and surveillance studies have shown that twice-daily bepotastine is an effective and generally well tolerated antihistamine in the treatment of patients with allergic rhinitis, chronic urticaria, or pruritus associated with skin conditions (eczema/dermatitis, prurigo, or pruritus cutaneus).²³ In a noncomparative trial in patients with pruritus associated with skin diseases, the majority of bepotastine recipients in the overall population, as well as in the specific skin disease subgroups (eczema/dermatitis, prurigo, or pruritus cutaneus), had a final global improvement rating of moderate or greater. Bepotastine was generally well tolerated in adult and pediatric patients with allergic conditions.

Several recent reports suggest that TARC might be useful markers for disease severity in adult patients with AD.^{14–16,24–26} The pathophysiology of AD includes disturbed skin barrier functions, frequent allergic responses against allergens, defects in the antimicrobial immune defense, and a genetic predisposition. Advances in our understanding of the complex interdependent network of members of the rapidly growing protein superfamilies of cytokines and chemokines led to the development of AD.

Recently, high-sensitivity CRP has been shown to be a potentially useful adjunct for global risk assessment in the primary prevention of cardiovascular disease.¹⁷ Population distribution of high-sensitivity CRP based on the analysis of >5000 Americans without known cardiovascular disease showed five quintiles, which could be considered, in clinical terms, to represent individuals with low, mild, moderate, high, and highest relative risks, respectively, for future cardiovascular disease.¹⁷ More recently, patients with chronic idiopathic urticaria with elevated high-sensitivity CRP were found to show good response to oral cyclosporine therapy.²⁷ Serum interleukin-6 has been reported as elevated in patients with systemic sclerosis. These elevated serum interleukin-6 levels were reflected as elevated high-sensitivity CRP levels in patients with systemic sclerosis.²⁸ These observations showed that CRP levels in the low-normal range reflected the activities in many kinds of inflammatory skin diseases.

The results of the present study show that CRP levels in the low-normal range responded well to antihistamine therapy, but serum TARC levels responded well to oral cyclosporine therapy. In addition, basophil counts in peripheral blood showed different responses to oral cyclosporine therapy and antihistamine therapy in adult

patients with AD. These results may indicate that a combination of these two therapies may be more effective for the treatment of adult AD.

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