

Response to oral cyclosporine therapy and high sensitivity-CRP level in chronic idiopathic urticaria

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Abstract

Background Chronic idiopathic urticaria (CIU) is often resistant to common treatment of urticaria.

Objective To find out clinical and laboratory findings affecting the response of oral cyclosporine therapy in CIU.

Subjects and methods The response of oral cyclosporine therapy in 15 patients with CIU (male : female = 5 : 10, age 16–60 years old, mean 40.0 years old) was studied. Cyclosporine trough level was measured with an enzyme-multiplied immunoassay, and high sensitivity-CRP was measured with a nephelometric assay. The relation between high sensitivity-CRP level and clinical and laboratory findings in CIU was also studied.

Results All the 15 CIU patients responded to oral cyclosporine therapy. High sensitivity-CRP levels before the start of therapy were elevated in nine of 15 CIU patients. The distributions of treatment duration and basophile leukocytes counts in elevated high sensitivity-CRP patients (8.7 ± 1.3 months, $0.20 \pm 0.05\%$) were significantly shorter and elevated than those in patients showing no elevation (22.7 ± 1.7 months, $0.40 \pm 0.05\%$) ($P < 0.05$, $P < 0.05$), respectively. No other clinical and laboratory findings between patients with elevated and not elevated high sensitivity-CRP showed any significant differences.

Conclusion Chronic idiopathic urticaria patients with elevated high sensitivity-CRP showed good response to oral cyclosporine therapy.

Introduction

Urticaria is a cutaneous vascular reaction induced by immunological or nonimmunological mechanism. Chronic urticaria is characterized by recurrent episodes of transient wheals, frequently associated with angioedema, and present daily or at least twice a week for over 6 weeks. 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 a major role in the pathogenesis of urticaria. Immunosuppressive drugs have been proposed in the treatment of the disease.¹ Cyclosporine has been used when antihistamines fail and prolonged steroid treatment is required. This study evaluated the effectiveness of cyclosporine treatment in CIU. Recently, high sensitivity-CRP has been shown to be useful for potential adjunct for global risk assessment in the primary prevention of cardiovascular disease.² Clinical laboratory findings including high sensitivity-CRP and cyclosporine trough level affecting the treatment were also studied.

Materials and methods

Subjects

Fifteen patients with CIU (male : female = 5 : 10, age 16–60 years old, mean 40.0 years-old) admitted to the outpatient clinics were studied (Table 1). The diagnosis of CIU was made as follows; recurrent episodes of transient wheals, frequently associated with angioedema, present daily or at least twice a week for over 6 weeks. The patients were unresponsive to therapy with antihistamines (epinastine hydrochloride) and difficult to treat even with three times the standard dose (60 mg/d). Patients with infections and those who did not tolerate cyclosporine were excluded from the study. Three patients were thus excluded. Autoreactive patients were patients who have autoimmune urticaria including the patients with a positive autologous serum test and not those who have angioedema caused by foods. All the patients were Japanese. All the subjects were studied for relevant clinical and laboratory findings. Clinical findings studied in CIU patients were age, gender and treatment duration. Laboratory findings studied in CIU patients were serum transaminase (aspartate aminotransferase, alanine aminotransferase), alkaline phosphatase, γ -glutamyl transpeptidase, lactose dehydrogenase, serum total protein,

Table 1 Clinical and laboratory findings in 15 patients with idiopathic chronic urticaria

Clinical and laboratory findings	Number
Male : Female	5 : 10
Cyclosporine trough level (ng/ml)	122 ± 11 ^a
Treatment duration (months)	11.3 ± 1.6
Aspartate aminotransferase (44 U/l)	23.3 ± 3.4
Alanine aminotransferase (U/l)	28.6 ± 6.9
Alkaline phosphatase (U/l)	232 ± 22.9
γ-glutamyl transpeptidase (U/l)	31.7 ± 7.5
Lactose dehydrogenase (U/l)	410 ± 58
Total protein (g/dl)	7.0 ± 0.1
Immunoglobulin G (mg/dl)	1044 ± 44
High sensitivity-CRP (mg/dl)	0.73 ± 0.26 ^b
Urea nitrogen (mg/dl)	20.4 ± 6.9
Serum creatinine (mg/dl)	0.58 ± 0.05
White blood cells (× 10 ³ /μl)	14 480 ± 4768
Lymphocytes (%)	28.5 ± 2.9
Monocytes (%)	5.5 ± 0.4
Eosinophils (%)	1.9 ± 0.4
Basophils (%)	0.28 ± 0.04
Neutrophils (%)	60.4 ± 2.3
Red blood cells (× 10 ⁴ /μl)	448 ± 17
Platelets (× 10 ⁴ /μl)	23.5 ± 1.2

^aMean ± SEM; ^bData from nine elevated patients.

immunoglobulin-G, high sensitivity-CRP, urea nitrogen, serum creatinine, white blood cell count, lymphocyte count, monocyte count, eosinophils count, basophil count, neutrophil count, red blood cell count, and platelet count. A total of 147 normal subjects ($n = 147$, male : female = 91 : 56, age 53.9 ± 13.6 years old) were also studied. Patients were admitted to my department for cryosurgery of skin tumors. They had no systemic diseases including urticaria, atopic dermatitis, psoriasis, connective tissue diseases, diabetes mellitus, hypertension, and hyperlipidemia.

Autologous serum test in chronic idiopathic urticaria

To perform autologous serum test, 50 μl of autologous serum was injected into the patient's forearm.³ Equal volumes of histamine (0.10 mg/ml; Hollister-Stir Laboratories, Spokane, WA, USA) and saline served as the positive and negative controls. Immediately after injection, the sizes of the wheal and flare in millimeters at each site were recorded. Measurements were made again after 15 min, and in some individuals, readings were also taken at 30 min. All positive reactions were observed within 30 min, and long observation did not alter the results. A positive result was defined as an increase in the wheal reaction size of > 3 mm with no change or reduction in size of the saline control.

Measurement of cyclosporine trough level and monitoring of renal function in chronic idiopathic urticaria

Patients with CIU were treated with cyclosporine (Neoral®, Novartis Pharma, Arnhem, the Netherlands) < 5 mg/kg daily

(divided into two doses), and in which trough level was measured in whole blood. Early morning dose trough level was measured with an enzyme-multiplied immunoassay technique (EMIT kit, SYVA, Dade Behring Inc., Deerfield, IL, USA).^{4,5} 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. After 3 months of treatment, the dose was tapered off during 1 month. Monitoring of renal function was performed by serum creatinine determination at baseline and weeks 2, 4, 8, and 12. Cyclosporine trough levels were measured at 2 weeks after the start of cyclosporine. Cyclosporine trough levels measured at weeks 2 were used for statistical evaluation, because all the patients had the same dose (3 mg/kg daily).

Measurement of high sensitivity-CRP level in chronic idiopathic urticaria

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

The response of oral cyclosporine therapy in chronic idiopathic urticaria

Oral cyclosporine therapy was judged as effective when all the edematous erythema completely resolved and no pruritus was found. The dose of cyclosporine was decreased by 25% when CIU completely resolved. The dose was decreased by 25% succeeding, and finally discontinued.

Statistical analysis

Mann-Whitney's *U*-test was used to evaluate the difference of values between two groups. Chi-square test with Yates' correction was used to evaluate the difference of occurrence rate between two groups.

Results

The response of chronic idiopathic urticaria to oral cyclosporine therapy

All the 15 patients with CIU responded to oral cyclosporine therapy (Table 3). The durations for the resolution

Table 2 The distribution of high sensitivity-CRP measured in normal controls and patients with idiopathic chronic urticaria

Range	Normal controls (n = 15)	Idiopathic chronic urticaria (n = 147)	Risk estimate
0.01–0.07 mg/dl	140 (95.2)	6 (40.0)	Low
0.07–0.11 mg/dl	3 (2.0)	1 (6.7)	Mild
0.12–0.19 mg/dl	2 (1.4)	0 (0)	Moderate
0.20–0.38 mg/dl	2 (1.4)	2 (13.3)	High
0.39–1.50 mg/dl	0 (0)	6 (40.0)	Highest

Values given in parentheses are in percentages.

of wheals were from 2 to 22 weeks, with the mean of 11.3 weeks. Cyclosporine trough levels measured 2 weeks after the start of oral cyclosporine therapy were from 56 ng/ml to 212 ng/ml, with the mean of 121.6 ng/ml.

High sensitivity-CRP level in normal controls and patients with chronic idiopathic urticaria

The distribution of high sensitivity-CRP in normal controls showed 140 low cases (95.2%) (0.01–0.07 mg/dl), 3 mild cases (2.0%) (0.07–0.11 mg/dl), two moderate cases (1.4%) (0.12–0.19 mg/dl), 2 high cases (1.4%) (0.20–0.38 mg/dl) and 0 highest case (0%) (0.39–1.50 mg/dl) (Table 2). The distribution of high sensitivity-CRP in CIU showed six low cases (40.0%), one mild case (6.7%), two high cases (13.3%) and six highest cases (40.0%). High sensitivity-CRP levels before the start of oral cyclosporine

therapy were elevated in nine of 15 patients with CIU (Table 2). The remaining six patients showed no elevation. All nine patients with elevated high sensitivity-CRP showed decrease level after the start of oral cyclosporine therapy. Sensitivity and specificity of high sensitivity-CRP for CIU were calculated as 46.7 and 98.6%, respectively.

The prevalence of clinical and laboratory findings between elevated and not elevated high sensitivity-CRP patients with chronic idiopathic urticaria

The prevalence of clinical and laboratory findings between elevated and not elevated high sensitivity-CRP patients with CIU was studied statistically (Table 4). The positive ratio of autologous skin test between elevated (5/9, 55.6%) and not elevated (3/6, 50%) high sensitivity-CRP patients with CIU showed no significant difference. The distribution of treatment duration in elevated high sensitivity-CRP patients (8.7 ± 1.3 months) was significantly shorter than those in not elevated patients (22.7 ± 1.7 months) ($P < 0.05$). The distribution of basophil leukocyte counts in elevated high sensitivity-CRP patients ($0.20 \pm 0.05\%$) was significantly lower than those in not elevated patients ($0.40 \pm 0.05\%$) ($P < 0.05$). The distribution of cyclosporine trough level, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, γ -glutamyl transpeptidase, lactose dehydrogenase, total protein, immunoglobulin-G, urea nitrogen, serum creatinine, white blood cell counts, lymphocyte counts, monocyte counts, eosinophil counts, neutrophil counts, red blood cell counts, and platelet counts in patients with elevated and not elevated high sensitivity-CRP showed no significant differences, respectively.

Table 3 The changes of high sensitivity-CRP level after oral cyclosporine therapy in patients with idiopathic chronic urticaria

Case no.	Age (years-old)	Gender	Initial (mg/l)	2 weeks (mg/l)	6 weeks (mg/l)	10 weeks (mg/l)	Resolution (weeks)
1	27	Male	1.26	1.09	1.02	0.39	11
2	39	Female	0.29	< 0.07	< 0.07	< 0.07	9
3	47	Male	0.46	0.056	< 0.07		10
4	30	Female	0.096	< 0.07			9
5	61	Female	0.36	0.066	< 0.07		3
6	16	Female	1.26	1.12	0.29		12
7	44	Female	0.451	< 0.07	< 0.07	< 0.07	2
8	47	Male	0.519	0.179	0.158		8
9	35	Female	2.50	< 0.07	< 0.07	< 0.07	14
10	58	Male	< 0.07	< 0.07	0.91	2.51	14
11	29	Female	< 0.07	< 0.07	< 0.07	< 0.07	22
12	19	Female	< 0.07	< 0.07			4
13	38	Male	< 0.07	< 0.07	< 0.07		17
14	59	Female	< 0.07	< 0.07	< 0.07	< 0.07	13
15	51	Female	< 0.07	< 0.07	< 0.07	< 0.07	22

Case 1–9: patients with elevated high sensitivity-CRP level, case 10–15: patients without elevated high sensitivity-CRP level.

Table 4 The distributions of clinical and laboratory findings in patients with elevated and not elevated and high sensitivity-CRP

Clinical and laboratory findings	High sensitivity-CRP		Mann-Whitney's U-test
	Not elevated (n = 6)	Elevated (n = 9)	
Autologous skin test positive (%)	3 (50)	5 (55.6)	NS*
Cyclosporine trough level (ng/ml)	110 ± 13 ^a	130 ± 16	NS**
Treatment duration (months)	15.3 ± 2.8	8.7 ± 1.3	P < 0.05
Aspartate aminotransferase (U/l)	22.7 ± 1.7	23.7 ± 5.8	NS
Alanine aminotransferase (U/l)	38.7 ± 11.7	21.9 ± 8.1	NS
Alkaline phosphatase (U/l)	206 ± 29	249 ± 33	NS
γ-glutamyl transpeptidase (U/l)	43.7 ± 15.9	23.8 ± 6.1	NS
Lactose dehydrogenase (U/l)	411 ± 106	388 ± 71	NS
Total protein (g/dl)	6.8 ± 0.3	7.0 ± 0.1	NS
Immunoglobulin G (mg/dl)	1007 ± 93	1069 ± 44	NS
High sensitivity-CRP (mg/dl)	< 0.08	0.73 ± 0.26	ND ^b
Urea nitrogen (mg/dl)	14.7 ± 1.3	24.1 ± 11.5	NS
Serum creatinine (mg/dl)	0.67 ± 0.05	0.52 ± 0.08	NS
White blood cells (× 10 ⁻³ /μl)	14 400 ± 6088	14 530 ± 7131	NS
Lymphocytes (%)	27.4 ± 6.5	29.3 ± 2.5	NS
Monocytes (%)	6.2 ± 0.7	5.0 ± 0.5	NS
Eosinophils (%)	1.7 ± 0.5	2.1 ± 0.5	NS
Basophils (%)	0.40 ± 0.05	0.20 ± 0.05	P < 0.05
Neutrophils (%)	56.0 ± 3.1	63.4 ± 3.1	NS
Red blood cells (× 10 ⁻⁴ /μl)	414 ± 34	471 ± 13	NS
Platelets (× 10 ⁻⁴ /μl)	23.0 ± 2.9	23.9 ± 1.0	NS

^aMean ± SEM, ^bND, not performed for statistical analysis because six patients showed < 0.08 mg/dl.

*NS, not significant (χ²-test with Yates' correction); **NS, not significant (Mann-Whitney's U-test).

Discussion

This study showed that high sensitivity-CRP level was elevated in nine of 15 (60%) CIU patients. Sensitivity and specificity of high sensitivity-CRP for CIU were 46.7% and 98.6%, respectively. These results established the sensitivity, specificity, positive and negative predictive value of this test. These results excluded the observation by chance. Several studies have shown the effective response of oral cyclosporine therapy in CIU patients.⁶⁻⁹ A study showed that cyclosporine is effective for CIU and provided further evidence for a role of histamine-releasing autoantibodies in the pathogenesis of the disease.⁶ Eight of 19 on active treatment but none on placebo had responded at 4 weeks. Three others on active drug met the criterion for response at 2 weeks but not at 4 weeks. Mean reduction in UAS between weeks 0 and 4 was 12.7 for active and 2.3 for placebo. A double-blinded study showed the long-term efficacy and tolerability of cyclosporine in patients with severe CIU, unresponsive to conventional treatments.⁶ During cyclosporine treatment, 20 patients had relapses resolving spontaneously (eight patients) or with antihistamines (12 patients). During the 9-month follow-up period, 22 patients had relapses resolving spontaneously (10 patients) or with antihista-

mines (12 patients). After 9 months of follow-up, 16 patients were still in full remission. Several other studies also showed the efficacy of oral cyclosporine treatment in CIU patients.^{8,9} Accordingly, oral cyclosporine therapy in CIU patients unresponsive to conventional treatment is an alternative choice for the patients.

Recently, high sensitivity-CRP has been shown to be useful for potential adjunct for global risk assessment in the primary prevention of cardiovascular disease.² With the recognition that inflammation is a critical component in determination of plaque stability^{10,11} and with the availability of highly sensitive assay systems, CRP levels in the low-normal range were found to have predictive value for individuals admitted to the hospital with acute coronary ischemia.¹² Population distribution of hs-CRP based on analysis of > 5000 Americans without known cardiovascular disease showed 5 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.² These reports showed that CRP levels in the low-normal range have predictive value for acute coronary ischemia. Elevated serum level of CRP has also been shown to be an independent predictor of cardiovascular events in Japanese patients with coronary artery disease.¹³ This study found

out that CRP levels in the low-normal range have predictive value for the response to oral cyclosporine therapy even in CIU patients.

The reason for high sensitivity-CRP elevation in CIU remains unknown. Chronic urticaria patients are a heterogeneous group of patients who require an individualized approach to evaluation and management.¹⁴ A study showed findings supporting the CIU autoimmune pathogenetic hypothesis.¹⁵ Before therapy, all patients showed activated B cells (CD19+CD23+ cells) and among B CD19+ cells, about 20% was CD5+. After treatment with prednisone, a significant reduction in CD4+ lymphocytes was observed. Serum IL-2 receptor, TNF- α , and IL-5 levels of patients before cyclosporine treatment were statistically higher than those of the control group, and after 4 weeks of cyclosporine therapy, the mean IL-2R, TNF- α , and IL-5 levels were significantly decreased.¹⁶ A histological examination of CIU revealed a perivascular nonnecrotizing infiltrate of CD4+ lymphocytes consisting of a mixture of TH1 and TH2 subtypes, plus monocytes, neutrophils, eosinophils, and basophils.¹⁷ These cells were recruited as a result of interactions with C5a, cell priming cytokines, chemokines, and adhesion molecules. Autologous serum test and anti-thyroid antibodies were found positive in 28 and 12% of patients, respectively, compared with none of the normal individuals.¹⁸ The study demonstrated that chronic urticaria duration was associated with clinical parameters such as severity and angioedema, and with laboratory parameters such as autologous serum test and anti-thyroid antibodies. The factors affecting the occurrence of CIU remain to be elucidated including severity of angioedema, disease duration, and other clinical factors. Disease duration should be studied in detail, because the result of this study showed the relation between high sensitivity-CRP and treatment duration.

The basophil leukocyte counts in elevated high sensitivity-CRP patients were significantly lower than those in not elevated patients. The presence of autoantibodies to basophil degranulation phenotypes and to disease status was compared.¹⁹ There was an enhancement in basophil function as subjects evolved into a state of remission, which appears independent of the presence of autoantibody. Patients with CIU with a basophil responder phenotype reported longer disease duration, a higher frequency of emergency department use, and significantly higher itch severity.²⁰ Accordingly, the results of this study may show that CIU activity could be represented by an elevated high sensitivity-CRP and decreased basophil leukocyte counts.

In conclusion, an elevated high sensitivity-CRP could be predictive and early response to oral cyclosporine therapy. This finding in this pilot study needs to be confirmed in a larger systematic study.

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