

Treatment of Chronic Idiopathic Urticaria and Positive Autologous Serum Skin Test with Cyclosporine: Clinical and Immunological Evaluation

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ABSTRACT

This study evaluates the effectiveness and safety of cyclosporine (CsA) in the treatment of patients with chronic idiopathic urticaria with a positive autologous serum skin test (ASST), who fail to respond to conventional therapy, and requiring long-term oral steroid treatment. In a double-blind study, 40 adults were assigned randomly to receive CsA (5 mg/kg per day for 8 weeks and then 4 mg/kg per day for 8 weeks) or cetirizine (10 mg/day) and then they were followed up for 9 months. After 2 weeks, the study was opened because 16 patients (40%) had daily severe relapses requiring systemic steroids treatment. All of these patients had been receiving antihistamines and, therefore, all patients also were assigned to the CsA treatment regimen (5 mg/kg per day for 8 weeks and then 4 mg/kg per day for 8 weeks). The ASST and clinical severity score were evaluated before and after treatment.

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All of the 40 patients completed the 16-week CsA course without dropping out because of relevant side effects. In three patients, CsA was reduced by 0.5 mg/kg per day after the 1st month of treatment for a mild and reversible increase in serum creatinine. During CsA treatment, 20 patients had relapses resolving spontaneously (8 patients) or with antihistamines (12 patients). During the 9-month follow-up period, 22 patients had relapses resolving spontaneously (10 patients) or with antihistamines (12 patients). Only two patients failed to complete the study because of severe symptoms occurring after 4 and 7 days of follow-up and requiring long-term steroid treatment. After 9 months of follow-up, 16 patients were still in full remission. The clinical severity score of chronic idiopathic urticaria dropped significantly by the end of the 4th month of treatment ($p = 0.002$) as well as by the completion of follow-up ($p = 0.007$). The ASST was negative in 13 patients and positive in 3 of 16 patients, with total remission of symptoms. Significant score reduction also was observed in patients experiencing relapses that resolved spontaneously ($p = 0.005$) or with antihistamines ($p = 0.03$). These results show the long-term efficacy and tolerability of CsA in patients with severe chronic idiopathic urticaria, unresponsive to conventional treatments. (Allergy and Asthma Proc 24:285–290, 2003)

Chronic urticaria is defined as wheals, at times associated with angioedema, present daily or on most days for >6 weeks, with single wheals lasting <24 hours. The

disease is diagnosed as "idiopathic" when no causal factors can be identified. It has been observed that in a subgroup of patients with chronic idiopathic urticaria (CIU), intradermal injection of autologous serum, collected during the active phase of the disease, elicits a wheal-and-flare response (autologous serum skin test [ASST]), whereas the nonactive disease serum usually does not induce such a reaction.¹ These observations suggested the presence of histamine-releasing factors that are able to trigger cutaneous mast cell activation and degranulation in patients with CIU. Subsequently, circulating autoantibodies against the high-affinity immunoglobulin E (IgE) receptor (FcεRI) or against IgE were found in ~30% of patients with CIU.^{2,3} 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.⁴ Additionally, removal of autoantibodies by plasmapheresis produced clinical improvement in patients with CIU.⁵ Western blot analysis and enzyme-linked immunosorbent assay have confirmed the presence of these autoantibodies.⁶

In view of these findings, it has been suggested that autoimmune mechanisms could be involved in the pathogenesis of some forms of CIU. Consequently, immunosuppressive drugs have been proposed in the treatment of the disease. In particular, cyclosporine A (CsA) has been used, when antihistamines fail and prolonged steroid treatment is needed. The aim of this study was to evaluate the effectiveness of 4-month treatment with CsA, its safety, and the duration of clinical benefit over a follow-up period of 9 months in patients with severe CIU and positive ASST.

PATIENTS AND METHODS

Forty consecutive patients (28 women and 12 men) aged from 18 to 60 years (mean, 36.3 years), with severe CIU and positive ASST, referred to the Allergy and Clinical Immunology Section and to the Dermatology Department of the University of Chieti (Italy), were included in the study after giving their informed consent.

Urticarial lesions involved >50% of their body surface at different times. Symptoms (pruritus and wheals) were present daily and did not respond to H1 antihistamines (cetirizine, loratadine, or fexofenadine), given either alone or in combination with H2 antihistamines. Short courses of oral steroids gave only partial resolution of symptoms and were followed by relapses immediately after discontinuation of treatment, requiring continuous prednisone medication (8–16 mg/day). Urticaria had been present for at least 6 months and in seven subjects it was associated with angioedema of lips and eyelids. All patients had severe deterioration of their quality of life because of their disease. Patients underwent a careful clinical examination. Physical urticarias, as symptomatic dermatographism and delayed pressure urticaria, were excluded by appropriate challenge testing.

No concomitant skin diseases were present. An accurate screening for inhalants and food allergies was performed by

skin-prick test (Allergopharma, Hamburg, Germany) and specific immunoglobulin E (IgE; CAP-Feia Pharmacia-Upjohn, Uppsala, Sweden). Food allergy also was investigated with a 2-week elimination diet, which failed to identify any food as the cause of symptoms. In addition, patients were prescribed a food salicylate and additive-free diet to exclude those substances provoking the disease.

Laboratory analysis included immune assays (rheumatoid factor, antinuclear, antimitochondrial, antismooth muscle, antimicrobial, antithyroid peroxidase, and antithyroglobulin autoantibodies; circulating immune complexes [CIC]; total IgG, IgA, IgM, and IgE), liver and kidney profile, study of the complement system (C3, C4, and C1q), blood cell count, urine analysis, ESR, CRP, FT3, FT4, and TSH.

Exclusion criteria included the presence of central nervous system, liver, and kidney diseases; infectious diseases; hypertension; treatment with drugs interfering with CsA; and previous or actual malignancy.

Patients were randomly assigned to two groups receiving, respectively, CsA (Neoral; Novartis Pharmaceuticals, East Hanover, NJ) and cetirizine (10 mg/day). Patients assigned to the CsA group were treated with 5 mg/kg per day for 8 weeks and then CsA was reduced to 4 mg/kg per day for an additional 8 weeks and then stopped. After 2 weeks, 16 patients (40%) had daily severe relapses requiring systemic steroid treatment and it was found that all 16 patients had been receiving antihistamine. Therefore, these patients also were assigned to the CsA treatment regimen (5 mg/kg per day for 8 weeks and then 4 mg/kg per day for an additional 8 weeks and then stop). Every 2 weeks for the first 2 months and then monthly, blood pressure, serum creatinine, and liver enzymes were monitored. CsA dosage was reduced by 0.5 mg/kg per day to prevent values from increasing above the normal range, and CsA treatment would have been stopped if these values remained abnormal even after the dosage reduction or when no clinical benefits by CsA therapy were obtained after 3 weeks. Moreover, patients were examined in the outpatient clinic monthly during and at the end of follow-up or when relapses occurred.

The clinical severity of the disease during CsA treatment and follow-up was scored as follows: 0, constant remission of symptoms (pruritus and wheals); 1, occurrence of relapses resolved spontaneously within 24 hours; 2, occurrence of relapses resolved by H1 antihistamines (when no spontaneous resolution occurred after 24 hours); and 3, occurrence of relapses resolved by steroids (after failure with antihistamines for 48 hours). ASST was performed during the active phase of the disease, as previously described,³ after 3 days of washout from antihistamines. Fifty-microliter autologous serum, saline, and histamine (1 mg/mL of histamine base in saline) were injected intradermally into clinically uninvolved volar forearm skin. A positive ASST was defined as a 30-minute wheal (with or without erythema) of 1.5-mm diameter greater than a saline control skin test. ASST positivity provides indirect evidence of histamine-releasing activity (HRA) in the serum.⁷ Hista-

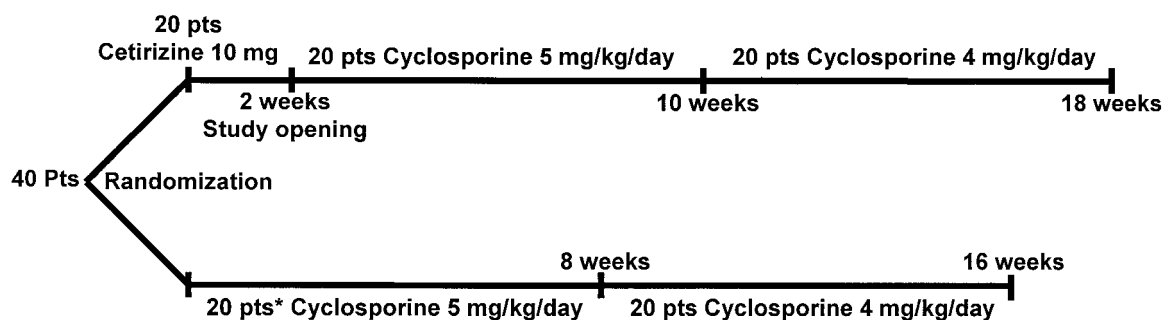


Figure 1. Study plan showing the CsA regimen after randomization (*CsA reduction in three patients after a mild and reversible creatinine increase). Cetirizine-receiving patients also assigned to the CsA regimen after a 2-week treatment.

TABLE I

Immune Parameters Characterizing Enrolled Patients		
Immune Parameter	Values	No. of Patients
Total IgE	>200 kU/L	6/40
Skin-prick test	Positive for inhalants	2/40
CICs	Positive, ranging from 4.8 to 7.6	22/40
C3	<70 mg/dL	5/40
C4	<12 mg/dL	8/40
Rheumatoid factor	>25 IU/mL	15/40
Antinuclear auto-Ab	>2.2 U.F. (FIAX)	2/40

TABLE II

Immune and Functional Thyroid Profile of Enrolled Patients		
Parameter	Values	No. of Patients
Thyroid peroxidase auto-Ab	>30 U/mL	22/40
Thyroglobulin auto-Ab	>325 IU/mL	13/40
TSH	>4.9 μ /mL	3/40
FT3	<2 pg/mL	2/40
FT4	<5 pg/mL	2/40

mine served as the positive control. ASST was scored from 0 to ++++ as follows: 0, weal equal to saline control; +, weal ≥ 1.5 mm than a saline control; ++, weal equal to histamine reaction; +++, weal greater than histamine reaction; +++++, weal with pseudopodes. ASST was repeated at the completion follow-up and at least once during relapses of the disease.

Statistical Analysis

Statistical analysis was performed by a multiple comparison of clinical severity scores before treatment, after 4 months of treatment, and at the end of follow-up. The Wilcoxon matched pairs test was applied to compare ASST scores before and after treatment.

RESULTS

After assigning the cetirizine group to the CsA treatment, all enrolled patients completed the 16-week course (Fig. 1).

Laboratory Data

The diagnostic flow chart failed to identify a known cause of urticaria. Results of immunological investigations are reported in Table I. High total IgE concentrations were observed in six patients, two of whom had positive skin-prick tests to common inhalants (grass and *parietaria* pollen) not correlated with clinical manifesta-

tions. Weak positivity for CIC was observed in 22 patients, 8 of whom also had reduced levels of serum C3 and C4. Reduced levels of C3 and C4 also were detected in four patients without CIC. In patients with reduced levels of C3 and C4, a skin biopsy excluded the presence of urticarial vasculitis. We observed a high percentage of patients with thyroid autoantibodies (22/40), but laboratory and clinical evidence of thyroid disease was observed only in 3 of these patients (Table II). Positivity for rheumatoid factor was detected in 15 patients who had neither clinical evidence of arthritis nor increase of inflammatory markers (ESR and CRP). In two other patients, antinuclear autoantibody positivity at low titer again was an isolated immunologic finding.

Clinical Response

Pruritus disappeared within 1–3 days of treatment and was followed by the resolution of wheals and flares within the 1st week in 33 patients (82.5%). In seven patients (17.5%), pruritus disappeared within 8–10 days of treatment and the full remission of the disease was obtained during the 3rd week.

By the end of treatment ($p = 0.002$) as well as by the completion of follow-up ($p = 0.007$), the clinical score of treated patients was significantly lower with respect to baseline (Fig. 2). During CsA treatment, 8 patients (20%) had an average of three relapses (range, 2–5 relapses) resolving spontaneously (clinical score, 1) and 12 patients (30%) had an average of 4 relapses (range, 1–6 relapses),

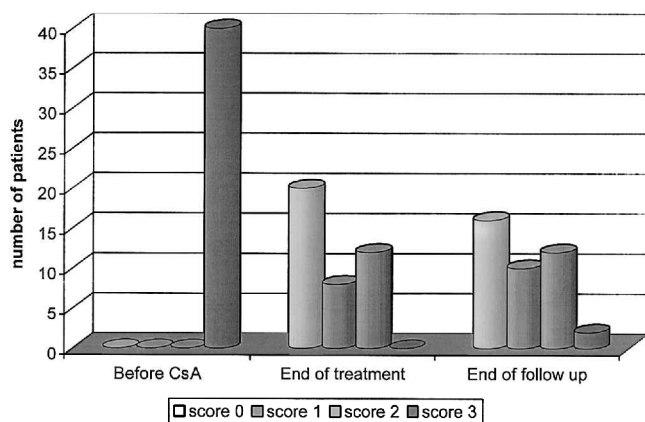


Figure 2. Clinical severity score before CsA, at the end of treatment (4th month) and at the end of 9 months of follow-up. Score 0, no relapses after treatment; score 1, occurrence of relapses spontaneously resolving; score 2, occurrence of relapses resolved by H1 antihistamines; score 3, occurrence of relapses resolved by steroids. Before treatment, all patients were assigned score 3, requiring long-term steroid treatment. Significant statistical differences were found among clinical severity scores of the three groups; $p < 0.005$ (Wilcoxon matched pairs test).

which resolved with the use of antihistamines (clinical score, 2).

In the 9-month follow-up period, 10 patients (25%) had an average of 11 relapses (range, 7–14 relapses) resolving spontaneously (clinical score 1) and 12 patients (30%) had an average of 15 relapses (range, 10–18 relapses) that resolved with antihistamines (clinical score, 2). After 4 and 7 days of follow-up, two patients (5%) had severe symptoms requiring long-term steroid treatment (clinical score, 3). After 9 months of follow-up, 16 patients (40%) were still in full remission (clinical score, 0; Table 3).

Change in ASST

Before treatment, the mean ASST score was 3 (range, 2–4). Of the 16 patients with total remission of disease (Table 3), at the completion of follow-up, the ASST was negative in 13 patients and positive in 3 patients (score, 1, 2, and 2, respectively).

The reduction of the ASST score after CsA treatment was statistically significant in all patients ($p = 0.002$; Fig. 3). All patients with relapses continued to have positive ASST but with a significant reduction of score ($p < 0.002$). Particularly, in patients with relapses resolving spontaneously, ASST (performed during the 1st relapse) had an average score of 1.6, compared with the previous score of 2.5 ($p < 0.005$). In the patients with relapses resolved by antihistamines, the ASST score was lower at the end of follow-up (average, 2.75) compared with at the start of treatment (average, 3.3; $p = 0.03$). No change in ASST score was observed in patients requiring steroid treatment (Table 3).

CsA Tolerability

CsA was well tolerated with no dropouts for relevant and irreversible side effects such as permanent changes in blood pressure, renal function, and liver enzymes. After the 1st month of treatment, three patients had mild increases in serum creatinine (1.8, 1.9, and 2.2 mg/dL, respectively; normal range, 0.8–1.5 mg/dL), and their values returned within the normal range after CsA reduction of 0.5 mg/kg per day. Four patients reported side effects such as headache, abdominal pain, and diarrhea, but symptoms were mild and disappeared after the first 2 weeks of treatment; therefore, CsA dosage was not reduced.

DISCUSSION

This study shows the efficacy and tolerability of CsA and confirms its usefulness as an alternative drug in patients with severe chronic urticaria that is unresponsive to conventional treatments. The studied population was selected for strongly positive ASST, which suggests the presence of circulating histamine-releasing factors or autoantibodies against the high-affinity IgE receptor (FcεRI) or against IgE.^{2–4} These patients were treated successfully for 16 weeks, without relevant side effects. Only two patients did not respond to CsA and had severe relapses requiring prolonged steroid treatment. These two patients did not show any evidence of distinctive clinical, immunologic, and blood chemistry alterations. All of the other patients could discontinue their previous medications, and in those in whom urticaria relapsed after CsA therapy, episodes were mild and either spontaneously resolving or resolved by antihistamines alone.

The full remission of CIU and the negativity of the ASST after 9 months of follow-up suggest the long-term action of CsA is likely because of its interference with the pathogenetic mechanisms of the disease. Although relapses were observed after CsA withdrawal in other patients who continued to have a positive ASST, CsA affected the natural history of the disease in these cases also, because episodes were mild, did not occur daily, and were easily controlled by antihistamines.

The precise mechanism of action of CsA in urticaria is not understood completely, although several studies have reported CsA effectiveness and tolerability in the management of severe forms of chronic urticaria. Experimental studies suggest that this drug, along with an immunosuppressive action, has anti-inflammatory and antiallergic properties as well.^{8,9}

CsA was first reported by Fradin *et al.*¹⁰ to be effective in three patients with severe CIU when given at a daily dose of 6 mg/kg, but treatment was associated with a deterioration in renal function that resolved after CsA withdrawal. Barlow *et al.*¹¹ treated 12 severe CIU patients with low-dose CsA (3 mg/kg per day) for 1 month, obtaining resolution of symptoms in 9 of these patients without causing major side effects. After 3 months of follow-up, five patients had

TABLE III

Score of ASST Before and After Treatment

ASST Score	Before CsA No. of Patients	After CsA No. of Patients			
		No Relapse	RSR	RRA	RRS
++++	12				2
+++	17			9	
++	11	2	6	3	
+		1	4		
0		13			
Mean ASST score	3.025	(3*) 0.31	(2.5*) 1.6	(3.3*) 2.75	(4*) 4

ASST after CsA was performed at the first relapse and at the end of follow-up in patients with full remission. Relapses were divided in RSR (spontaneously resolving), RRA (resolved by antiH1), and RRS (resolved by steroids).

Statistically significant differences between ASST scores before and after treatment in all patients, $p < 0.002$.

ASST is scored from 0 to +++++: 0, weal equal to saline control; +, weal ≥ 1.5 mm than a saline control; ++, weal equal to histamine reaction; +++, weal greater than histamine reaction; +++++, weal with pseudopodes.

*Mean ASST score of each group before CsA treatment is shown.

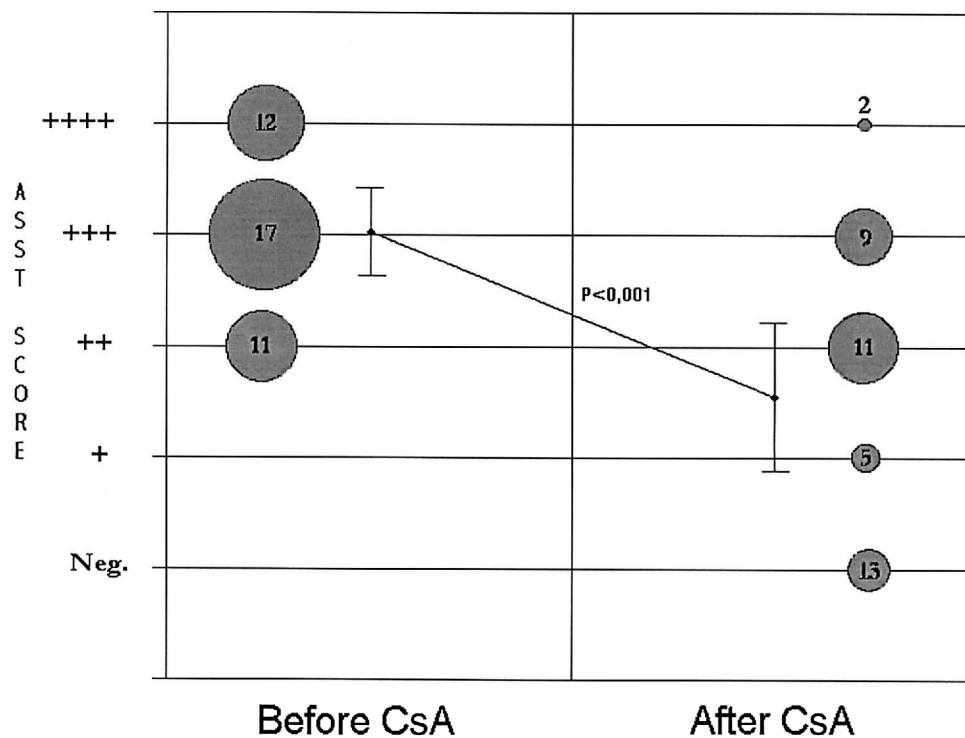


Figure 3. ASST before and after CsA therapy. Extension of the area of each circle represents the number of subjects with the specific ASST score. Statistical significance of ASST score reduction before versus after CsA treatment; $p = 0.002$ (Wilcoxon matched pairs test).

relapses, all responding to a second course of CsA therapy. Toubi *et al.*¹² showed that low-dose CsA (3 mg/kg per day for 6 weeks then 2 mg/kg/day for 3 weeks and finally 1 mg/kg/day for 3 weeks) is sufficiently effective and can be given safely for 3 months, with less relapses occurring during 3 months of follow-up. In Toubi's study, the majority of ASST⁺ CsA-treated patients (62.5%) turned negative at the end of treatment. In our study, CsA appears less effective; in fact, 13/40 patients (32.5%) had a negative ASST at the end of therapy. Toubi reported that ASST

positivity neither correlated with disease activity nor predicted response to treatment, comparing results with those of ASST⁻ patients. In our study, it is impossible to confirm these data because only ASST⁺ patients had been enrolled. Moreover, the ASST use in clinical practice is still limited by the absence of studies investigating its reproducibility.

The efficacy of CsA was confirmed by Vena *et al.*,¹³ who used 5 mg/kg per day with reversible side effects. Grattan *et al.*¹⁴ studied 30 patients with CIU and positive ASST, obtaining disease control in about two-thirds and long-term

improvement in one-quarter of these patients with 4 mg/kg per day of CsA for 4 weeks. Patients who experienced relapses were withdrawn from the study, and it was not assessed if CsA had restored responsiveness to conventional treatment with antihistamines.

The recent identification of histamine-releasing IgG autoantibodies directed against the α -chain of Fc ϵ RI and/or IgE may support the autoimmune nature of a subgroup of CIU. A high percentage of patients with positivity for CICs (together with reduced serum levels of C3 and C4), rheumatoid factor, and thyroid autoantibodies was observed. The meaning of these findings is still uncertain and needs additional investigation. However, the association of urticaria with autoimmune thyroiditis has been described.¹⁵

In this study, most patients had a very rapid resolution of itching, confirming reports of other trials.^{10–13} This is particularly difficult to explain, considering only the immunosuppressive action of CsA. It has been shown that CsA can lower the level of both IgG and anti-IgE or anti-Fc ϵ RI autoantibodies.¹¹ However, this immunosuppressive action would be expected to be effective at least after 1 week of treatment, and the rapid resolution of itching, wheals, and erythema might be caused by different effects. CsA has been reported to prevent histamine, leukotriene C4, and prostaglandin D release from human mast cells.^{8,9} On the other hand, it has been shown that cyclosporine has no effect *in vivo* on skin mast cell releasability.¹⁴ Recently, it has been shown that CsA can inhibit the release of interleukin-4 from human basophils.¹⁶ In addition, CsA could affect indirectly mast cells by suppressing T-cell interleukin-2 synthesis/release, which is needed for mast cell degranulation.¹⁷

In patients with CIU and positive skin responses to autologous serum, the presence of anti-IgE autoantibodies in circulation was found in ~80% of the subjects and also in ~70% of patients with atopic dermatitis and 25% of healthy control subjects.¹⁸ Moreover, anti-Fc ϵ RI autoantibodies were found in ~30% of patients with CIU, as well as in a small percentage of patients with dermatomyositis and pemphigus vulgaris, although in these two latter diseases the autoantibodies did not seem to have a functional activity in terms of histamine releasability.¹⁸ On the other hand, patients might have nonantibody histamine-releasing factors¹⁹ because the anti-Fc ϵ RI α may belong to the natural antibodies, which have a restricted and conserved set of self-antigens.²⁰ Recently, some authors have identified endogenous proteins that act as superantigens and induce the secretion of histamine from human Fc ϵ RI⁺ cells.^{16,21}

A greater effectiveness of CsA was observed in this study compared with other trials,^{10–13} probably because patients were enrolled only if ASST was positive and a full dose of long-lasting CsA formulation was administered. The role and optimal use of CsA in the management of severe chronic urticaria remains to be defined more clearly. Controlled studies are needed to evaluate the optimal dosage, the length of therapy, and the usefulness of an associated or

sequential therapy with antihistamines to further reduce the dosage of CsA without losing any clinical efficacy.

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