

Low-dose cyclosporin A in the treatment of severe chronic idiopathic urticaria

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In a limited number of severe chronic idiopathic urticaria (CIU) patients, low-dose cyclosporin A (CsA) treatment was found to be effective. This open study aimed to extend this clinical observation and determine the safety of treatment with CsA. In addition, it aimed to determine the prevalence and characteristics of the autologous serum skin test (AST) in such patients, and whether this test is affected by CsA treatment. Thirty-five patients who suffered from severe CIU (score 3), and who were followed for 6 months (using a clinical urticaria-severity score [range 0–3]) were divided into three groups: 19/35 were treated for 3 months with low-dose CsA, and thereafter followed for an additional 3 months; 6/35 dropped out of protocol treatment; and 10/35 untreated patients (followed for the same period) served as a disease controls. In the treated group, no side-effects were observed, and by the end of treatment, 13/19 (68%) patients were in full remission (score 0) and the remainder scored 1. In contrast, the 10 CsA-untreated patients scored 3 for the whole follow-up period of 6 months. Positive AST was found in 14/35 (40%) of patients, whereas none were detected in 20 healthy control subjects. AST neither correlated with disease activity nor predicted response to treatment. This uncontrolled study shows that low-dose CsA is effective in treating CIU patients, and can be given safely for 3 months. However, CIU patients requiring initially high doses of glucocorticosteroids and with a long clinical history are less amenable to CsA treatment.

Key words: autologous serum skin test; chronic idiopathic urticaria; cyclosporin A.

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Chronic urticaria is a common disabling disorder which may last for many months, and is characterized by recurrent episodes of transient itchy wheals, which are frequently associated with angioedema. In the vast majority of patients, chronic urticaria is idiopathic, since specific triggering of mast-cell degranulation by allergens or physical factors has not been identified (1).

Autologous serum has been shown to elicit an immediate wheal and flare response when injected intradermally in many patients with chronic idiopathic urticaria (CIU). Histologically, the positive autologous serum reaction shows mixed mononuclear, neutrophil, and eosinophil infiltration, reminiscent of a late-phase, IgE-mediated reaction of histamine release (2). This serum activity has been attributed to the presence of IgG anti-IgE (3) or anti-(high affinity)-IgE-receptor autoantibodies (4), thus suggesting that autoimmune mechanisms are involved in the pathogenesis of CIU.

The treatment of severe chronic urticaria poses a major problem in most cases: antihistamines are of limited benefit; short courses of oral glucocorticosteroids provide sufficient relief, but are followed by relapses, whereas prolonged treatment may be associated with unwanted side-effects.

Cyclosporin A (CsA) was reported to be effective in three patients with severe CIU when given in a daily dose of 6 mg/kg, but was associated with deterioration of the renal function (5). Low-dose CsA (3 mg/kg per day) was found to be sufficiently effective in the treatment of 12 patients with severe CIU without causing major side-effects (6). So far, these are the only published uncontrolled data of CsA treatment in CIU, given for 1 month only.

The current open study was designed to examine the effectiveness of low-dose CsA treatment of severe CIU in an extended number of patients (in comparison to a disease control group), and to evaluate its safety over 3 months. In addition, the

prevalence of AST in CIU patients was monitored for both its persistence after CsA treatment and its predictive value for the efficacy of this medication.

Material and methods

Subjects

Thirty-five patients (26 women and nine men, mean age 44 years, range 21–69 years) with severe CIU, suffering almost daily from severe episodes of chronic wheals (mean disease duration 21 months, range 5–60 months), were studied. All patients responded poorly to H₁ antihistamines given either alone or in combination with H₂ antihistamines. Short courses of prednisolone that caused only partial relief were followed immediately by relapses after discontinuation of treatment, and required continued prednisolone medication (10–25 mg/day). Of these 35 patients, 25 were randomly selected for CsA treatment, whereas the remaining 10 patients served as a disease control group.

Urticaria score

Patients recorded daily their urticaria symptoms, rated on a 4-point scale, as detailed previously by Breneman et al. (7): number of lesions, number of separate episodes, average size of lesions, average duration of lesions, and pruritus. Table 1 details the scoring system: 0=no symptoms; 1 (mild urticaria)=1–4 points; 2 (moderate urticaria)=5–9 points; 3 (severe urticaria) ≥10 points. On weekly follow-up visits, physicians used the same rating scale. This recording served as a basis for the final global assessment of treatment: nonresponders scored 3, mild responders scored 2, moderate responders scored 1, and those fully relieved of symptoms scored 0.

Autologous serum skin test (AST)

All patients were tested after an "antihistamine wash-out" period of 3 days. A control group of 20 healthy, age-matched subjects (12 women and eight men) was similarly tested. AST was performed as previously described (8) with minor modifications. Briefly, 0.1 cc of sterile autologous serum was injected intradermally. The wheal and flare size was determined at 30 min and followed for a total of 60 min. Saline was used as a negative control, and histamine (1 mg/ml) served as a positive control. The flare/wheal diameter was measured and scored from 0 to +4 as follows: 0=negative control; +1=flare ≤15 mm, wheal=negative control; +2=flare >15 mm, wheal=3–5 mm; +3=wheal 6–10 mm;

Table 1. Patient's and investigator's rating scale of symptom severity

Daily events	Points
No. of lesions	
0	0
1–10	1
11–20	2
>20	3
No. of separate episodes	
0	0
1	1
2 or 3	2
>3	3
Average size of lesion (inches)	
0	0
< $\frac{1}{2}$	1
$\frac{1}{2}$ –1	2
>1	3
Average duration of lesions (h)	
None	0
Up to 4	1
>4–12	2
>12	3
Pruritus	
None	0
Mild	1
Moderate	2
Severe	3

+4=wheal >10 mm with the presence of many pseudopods. In all AST-positive patients, the test was repeated at the end of CsA treatment and again 3 months later.

Ethical approval

Our protocol of treatment was approved by the Helsinki committee of the Israeli Ministry of Health, and included only subjects who had given informed and written consent.

Protocol for CsA treatment

Patients scoring 3 entered the study while receiving their previous treatment. CsA (Sandimmune) was given for a total period of 12 weeks – a daily dose of 3 mg/kg for 6 weeks, followed by 3 weeks of 2 mg/kg per day, and then 3 weeks of 1 mg/kg per day – and then discontinued. Blood pressure, serum creatinine, liver enzymes, white blood cell counts, and serum CsA levels were monitored every 3 weeks. However, treatment was stopped when unwanted side-effects were observed (dropouts) or when no clinical benefit by CsA therapy was obtained after 4 weeks (non-responders).

Statistical analysis

Multiple comparisons were performed between clinical scores at the starting point and those measured at successive time intervals with the nonparametric Friedman's analysis of variance, followed by an appropriate post-hoc test. Categorical data were analyzed by the chi-square test with the Yates correction, and a two-tailed P -value ≤ 0.05 was considered to be statistically significant.

Results

Twenty-five patients with CIU entered the treatment protocol, but six dropped out: two patients (AST-negative) after 2 days due to gastrointestinal side-effects (abdominal pains and diarrhea), and another four patients categorized as nonresponders (two AST-positive and two AST-negative), in whom 4-week therapy was of no benefit. These four nonresponders were patients in whom disease duration was the longest (52–60 months), and two of whom required before CsA treatment 25 mg/day of prednisolone, whereas the remaining two patients required 5–10 mg/day only, as in the rest of the series.

Nineteen patients followed for 6 months were available for protocol assessment. The effectiveness of CsA treatment was rapid: by the end of week 1, the scores of all treated patients dropped to 0–1 ($P < 0.001$), enabling the discontinuation of all other medications including prednisolone. However, at week 4, clinical score fluctuations were still noted, requiring in some patients (scoring 2) the renewal of antihistamine treatment (Fig. 1). At week 12, 13/19 patients (six AST-positive; seven AST-negative) were in full remission, while the remaining six (two AST-positive and four AST-negative) scored 1 ($P < 0.001$), and required only antihistamine treatment. During treatment, in 16/19 patients, serum CsA concentration values were within recommended therapeutic levels (200–400 $\mu\text{g/ml}$); in three patients, levels exceeded those values, though without any notable side-effects. However, in 2/19 patients, mild side-effects were recorded: in one patient (serum CsA 250 $\mu\text{g/ml}$), a mild rise in serum creatinine (1.5 mg%) was detected at the end of treatment, and that value returned to normal (1.0 mg%) within 2 weeks. Another patient (serum CsA 300 mg/ml) complained of agitation and sleeplessness, which disappeared when medication was reduced to 2 mg/kg per day. The 10 CsA-untreated patients scored 3 during the whole period of follow-up and required 10–15 mg of prednisolone plus antihistamines daily.

After cessation of treatment, biweekly follow-up visits of patients were continued for an additional

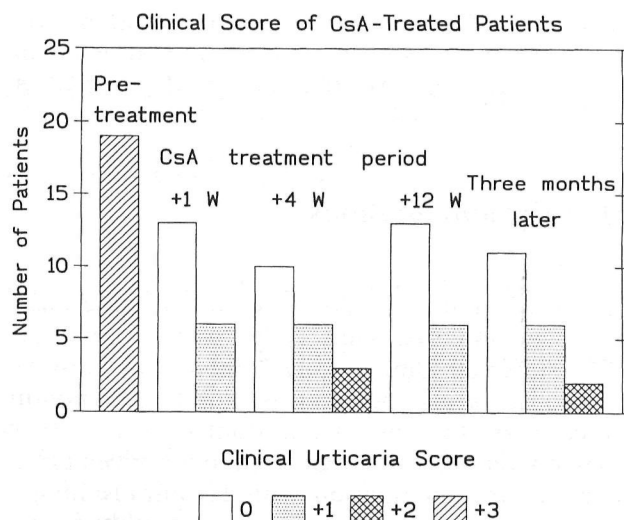


Fig. 1. Clinical score of CsA-treated patients. Investigator's global assessment before, during, and 3 months after treatment.

3 months. Eleven out of 13 (four AST-positive and seven AST-negative) patients, who were in full remission by the end of CsA treatment, remained so for the additional 3 months ($P < 0.001$). In the remaining two, urticaria (score 1) reappeared and required mild antihistamine treatment. Four out of six additional patients who scored 1 at the end of treatment (two AST-positive) remained with this score during follow-up. In the remaining 2/6 patients (all AST-negative), the urticaria score rose from 1 to 2 and could be controlled by antihistamine treatment alone.

Of 35 patients with severe CIU, 14 (40%) demonstrated positive AST, in contrast to healthy controls, all of whom were AST-negative ($P < 0.003$).

In the CsA-treated patients, the following AST results were recorded: 11/19 were negative whereas 8/19 patients were positive, five of whom turned negative at the end of treatment and remained so during follow-up. In the remaining three AST-positive patients, no change in AST took place during the follow-up period, although two were in full remission (score 0) and one patient scored 1 (Table 2).

In the CsA-untreated disease control group, 4/10 were AST-positive and 6/10 were AST-negative. During the follow-up period, AST did not change and a correlation with severity of CIU (which remained at score 3) was not observed.

Discussion

Although the beneficial effect of low-dose CsA treatment was previously demonstrated in an uncontrolled study of a small number of CIU

Table 2. Follow-up of AST-positive patients related to their clinical score

Patients		Pretreatment	End of treatment	3 months later
CsA-treated	Eight AST-positive (scored 3)		Five AST-negative (three scored 0, two scored 1)	Same five AST-negative (two scored 0, three scored 1)
			Three AST-positive (two scored 0, one scored 1)	Same three AST-positive (two scored 0, one scored 1)
	Four AST-positive (scored 3)		Same four AST-positive (scored 3)	Same four AST-positive (scored 3)

patients, it was never administered for longer than 1 month (6). In this prospective open study, a larger group was successfully treated for 3 months, during which no major unwanted side-effects were noted. All patients who participated in this study for its whole duration could gradually discontinue their previous medications (including glucocorticosteroids), and in those patients in whom urticaria partially relapsed after discontinuation of therapy, such episodes were mild and controllable by antihistamines alone. However, patients nonresponding to the CsA regimen seemed to reveal an existing history of long duration, and some an initially increased requirement for glucocorticosteroids.

Although the exact mode of action by which CsA affects urticaria is still unknown, the following mechanisms have been suggested. This drug has been reported to inhibit *in vitro* the production of Ig in activated B cells in the presence of T-cell-derived lymphokines (9). Accordingly, CsA can lower the level of both IgG anti-IgE or anti-Fc ϵ RI autoantibodies (6), but could still suffice to trigger mast-cell degranulation of AST. However, the rapid beneficial effect of CsA in all treated patients raises doubts about the central role of this autoantibody-mediated mechanism in the suppression of CIU activity, since it would not be expected to be effective within 1 week of treatment.

Since CsA can inhibit T-cell-mediated autoimmune responses (particularly by suppressing their IL-2 synthesis/release, which is needed to interact with mast cells for their degranulation [10]), it can exert its beneficial effect indirectly on mast cells and/or on the development of the late-phase reaction. However, CsA was also reported to affect degranulation directly *in vitro* by influencing the intracellular Ca²⁺ concentration, and preventing histamine, leukotriene C₄, and prostaglandin D release from human lung mast cells (11, 12). Therefore, the CsA effect in CIU could be attributed mainly to its immediate effect on mast cells and activated T cells and, to a lesser extent, to an effect on humoral autoimmunity.

Although AST was positive in 40% of CIU patients, our findings underline both the lack of

correlation between AST results and urticaria activity (in contrast to the findings of others [13]), and its ineffectiveness in predicting the outcome of CsA treatment (Table 2).

The kinetics of AST after CsA treatment warrant additional clarification: 5/8 AST-positive patients turned negative by the end of successive treatments although in three patients the test remained unchanged. This is a statistically significant change, especially when compared to the disease control group, in whom no change in AST results was noticed. Though we have no direct evidence for this, it is conceivable that CsA treatment affects titers of both anti-IgE and anti-IgE receptor autoantibodies of AST patients selectively: in those turning AST-negative, a significantly lower titer occurs, whereas in those who remain AST-positive, such a reduction does not suffice to suppress AST and may require CsA medication extended beyond 12 weeks.

Currently, we are continuing our clinical evaluation of this open modality by prescribing a second, low-CsA course of treatment to those of our patients in whom the disease severely relapsed after cessation of therapy. In addition, a placebo-control study is planned for new severe CIU patients.

References

1. Champion RH. A practical approach to urticaria syndromes – a dermatologist's view. *Clin Exp Allergy* 1990;20:221-4.
2. Grattan CEH, Boon AP, Eady RAJ, Winkelman RK. The pathology of the autologous serum skin test response in chronic urticaria resembles IgE-mediated late phase reaction. *Int Arch Allergy Appl Immunol* 1990;93:198-204.
3. Gruber BL, Baeza ML, Marchese MJ, Angello V, Kaplan AP. Prevalence and functional role of anti-IgE autoantibodies in urticarial syndromes. *J Invest Dermatol* 1988;90:213-17.
4. Hide M, Francies DM, Grattan CEH, Hakimi J, Kacham JP, Greaves MW. Autoantibodies against the high affinity IgE receptor as a cause of histamine release in chronic urticaria. *N Engl J Med* 1993;328:1599-1604.
5. Fradin MS, Ellis CN, Goldfarb MT, Voorhees JJ. Oral cyclosporin for severe chronic idiopathic urticaria and angioedema. *J Am Acad Dermatol* 1991;25:1065-7.

6. Barlow RJ, Black AK, Greaves MW. Treatment of severe chronic urticaria with cyclosporin-A. *Eur J Dermatol* 1993; 3:273-5.
7. Breneman D, Bronsky EA, Bruce S, et al. Cetirizine and astemizole therapy for chronic idiopathic urticaria: a double-blind, placebo-controlled, comparative trial. *J Am Acad Dermatol* 1995;33:192-8.
8. Grattan CEH, Francies DM, Hide M, Greaves MW. Detection of circulating histamine releasing autoantibodies, with functional properties of anti-IgE in chronic urticaria. *Clin Exp Allergy* 1992;21:695-704.
9. O'Garra A, Warren DJ, Holman M, Popham AM, Sanderson CJ, Clause JJB. Effects of cyclosporin on responses of murine B cells to T cell derived lymphokines. *J Immunol* 1986;137:2220-4.
10. Elias T, Boss E, Kaplan AP. Studies of the cellular infiltrate of chronic idiopathic urticaria: prominence of T-lymphocytes, monocytes and mast cells. *J Allergy Clin Immunol* 1986;78:914-18.
11. Draberova L. Cyclosporin-A inhibits rat mast cell activation. *Eur J Immunol* 1990;20:1469-73.
12. Marone G, Triggiani M, Cerilo R, et al. Cyclosporin A inhibits the release of histamine and peptide leukotriene C₄ from human lung mast cells. *Ric Clin Lab* 1988;18: 53-9.
13. Hide M, Francies DM, Grattan CEH, Barr RM, Winkelman RK, Greaves MW. The pathogenesis of chronic idiopathic urticaria: new evidence suggests an autoimmune basis and implications for treatment. *Clin Exp Allergy* 1994;24:624-7.

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