

**CYCLOSPORIN-A EFFICACY IN CHRONIC IDIOPATHIC URTICARIA**

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Common drugs in the therapy of chronic idiopathic urticaria (CIU) include antihistamines alone or combined with corticosteroids, but severe unresponsive patients require alternative treatments. This retrospective study aims to evaluate clinical response and safety of low-dose and long-term oral Cyclosporin-A (CyA) in unresponsive patients. One hundred and ten CIU patients, unresponsive to a previous treatment (antihistamines plus prednisone 0.2 mg/kg/day), received additional oral CyA 1–3 mg/kg/day for 6 months. The patients were subdivided into three groups (A, B, C) according to the different CyA doses. Parameters of clinical efficacy including pruritus, and size and number of wheals were evaluated at baseline, after three and six months. All adverse events were recorded. The mean total symptom severity score decreased by 63% in Group A, 76% in Group B, and 85% in Group C after 6 months. Total disappearance of the symptoms was recorded in 43 patients (39.1%): 7 (28%) of Group A; 12 (37.5%) of Group B and 24 (45%) of Group C. After a mean of 2 months from CyA suspension, 14 patients (11%) had recurrence of symptoms. Minor side effects were noted in 8 patients (7%). Our study indicates that low-dose, long-term CyA therapy is efficacious and safe in severe unresponsive CIU.

Chronic idiopathic urticaria (CIU) is characterized by wheals, with or without angioedema, recurring daily or almost daily for at least 6 weeks (1) in the absence of physical, allergic, infectious, and drug-related causes or vasculitis (2). Its exact pathogenic mechanism is unknown (3), but many patients show circulating histamine-releasing autoantibodies to the high-affinity IgE receptor (FcεRI) or, rarely, to IgE. However, the role of these autoantibodies remains unclear (4). Antihistamines alone or in combination with corticosteroids are commonly applied, and in the unresponsive patients Cyclosporine-A (CyA)

is used (2). Among dermatologic diseases, CyA is approved for severe psoriasis and atopic dermatitis (5-6), and can be used “off-label” for other diseases, such as CIU (7), in which its effectiveness has been demonstrated (2, 8-9).

In this study we retrospectively evaluate the clinical response in terms of reduction of pruritus, and number and size of wheals together with maintenance of remission after a treatment with low-dose (1-3 mg/kg/die) oral CyA (Sandimmun Neoral®, Novartis Farma S.p.A.) for 6 months in association with prednisone.

*Key words: antihistamines, chronic idiopathic urticaria, corticosteroids, cyclosporin-A*

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## MATERIALS AND METHODS

Of 1,242 patients with urticaria admitted to our Section of Allergology and Clinical Immunology from February 2005 to May 2009, 110 subjects (63 F, 47 M) aged 22 to 73 (median 45.6) years, were diagnosed as having CIU, after ruling out physical causes, insect bites, food allergy or other known causes, history of atopic disease, medication, vasculitis or autoimmune diseases, as well as viral infections or malignant diseases.

Inclusion criteria were: chronic urticaria with or without positive autologous serum skin test, no or poor response to classical antihistamines and/or corticosteroids, and no immunosuppressive therapy at the time of the study. Exclusion criteria were: C1 esterase inhibitor deficiency, epilepsy, use of potentially nephrotoxic drugs, drug or alcohol abuse, pregnancy and lactation, diastolic blood pressure >95 mm Hg, increased serum creatinine, potassium, uric acid, bilirubin or hepatic enzyme levels. All patients provided their informed consent in accordance with the Declaration of Helsinki.

The 110 patients had been under treatment with prednisone (0.1 to 0.3 mg/kg/day) and antihistamines for at least 3 weeks with poor or no response, and they received CyA at different doses according to age, pre-existing low hypertension (i.e., diastolic blood pressure no more than 95 mm Hg), and dysmetabolism, hence to the risk of developing renal or hepatic disease following the CyA treatment. Referring to these parameters, patients were allocated to 3 different therapeutic groups (Table I): Group A, CyA 1-1.5 mg/kg/day (25 patients, 8 of whom were aged over 65 years, with grade 1 hypertension and signs of renal impairment); Group B, CyA 1.6-2 mg/kg/day (32 patients, 9 with grade 1 hypertension), Group C, CyA 2.1-3 mg/kg/day (53 patients with no comorbidity). Prednisone 0.1-0.3 mg/kg/day was continued during the CyA treatment and the dose was adjusted according to the CIU severity; in other patients, in line with the clinical improvement, it was gradually tapered to a maintenance dose of 0.07-0.1 mg/kg/day or suspended (45 patients).

All patients recorded their symptoms such as pruritus, size and number of wheals in a daily diary. Every month the patients were interviewed, the diary reviewed, and the physical examination performed, including blood pressure measurement. Evaluations were made by the same two medical investigators.

Efficacy measures were scored as (10): pruritus: 0 (none), 1 (mild), 2 (moderate) and 3 (severe); number of wheals: 0 (none), 1 (1-10 wheals), 2 (11-20 wheals), 3 (>20 wheals); mean diameter of wheals: 0 (no lesion), 1 (<1.27 cm), 2 (1.27-2.54 cm), 3 (>2.54 cm). The value of total symptom severity score (TSSS, or 'overall score') ranged from 0 to 9. The mean of the daily score for each

sign or symptom at time 0, 1 and 2 was recorded.

All patients were assessed for CyA tolerability after 2 and 4 weeks of treatment with renal and liver function tests. Also, the patients were evaluated at time 0 (T0, recruitment), time 1 (T1, after 3 months) and time 2 (T2, after 6 months) for the clinical score, and routine blood exams. The plasma CyA levels (normal therapeutic ranges: 100-300 ng/mL) were measured at T1 and T2. After 1 and 2 months from the end of treatment, the patients were evaluated for possible disease recurrence. Possible adverse events reported by the patients were recorded and relationship with CyA assessed. The treatment was considered effective if the TSSS at T2 was <25%, while relapse was considered as the return of TSSS to >75% of baseline (3).

For the efficacy analyses, the Wilcoxon signed-rank test was used, and a probability value <0.05 considered significant. The Kruskal-Wallis test was used to compare the three groups at T1 and T2.

## RESULTS

The mean TSSS value decreased at T2 by 63% in the Group A, 76% in the Group B and 85% in the Group C compared to the baseline (Fig. 1). At T2, total disappearance of the symptoms was recorded in 43 (39.1%): 7 (28%) of Group A, 12 (37.5%) of Group B and in 24 (45%) of Group C. Compared to the baseline, all patients already showed a reduction of symptoms and signs at T1, and further at T2 (Table II). Specifically, the T2 evaluation shows that the mean pruritus intensity score dropped in Group A by -65.2% ( $p<0.05$ ), in Group B by -77.8% ( $p<0.03$ ), and in Group C by -82.2% ( $p<0.01$ ); the mean score of the wheal size was reduced in Group A by -64.3% ( $p<0.05$ ), in Group B by -76% ( $p<0.02$ ), and in Group C by -88.3% ( $p<0.01$ ); the mean number of wheal score was, again, decreased in Group A by -57.1% ( $p<0.05$ ), in Group B by -73.3% ( $p<0.02$ ), and in Group C by -84.3% ( $p<0.01$ ).

The evaluation of the TSSS improvement in Groups A, B and C with three different doses of CyA showed statistically significant difference between Group A and B at T1, and between Group A and C at T1 ( $p<0.001$ ) and T2 ( $p<0.05$ ).

In 7 Group C patients (13.2%), the CyA was reduced by 0.5 mg/kg/day after two months for a low - and reversible - increase in serum creatinine. Five Group C patients (9.4%) experienced abdominal pain and nausea without blood exam abnormality.

These effects disappeared with CyA administered in three divided doses per day. Of note, the plasma CyA level was lower than the therapeutic range level in all patients: mean levels  $65.4 \pm 10.8$ .

Two months after the withdrawal of the CyA suspension, 14 patients (11%) suffered a relapse, 12 of whom were retreated with the same protocol and responded. Only two patients were resistant, one of whom was treated with weekly methotrexate (10 mg) due to emergence of vasculitis, and the other with omalizumab (compassionate use), both in association with prednisone and antihistamines.

## DISCUSSION

In severe CIU patients, high-dose antihistamines, always belonging to first generation, are required, but these drugs make 10% to 15% of the patients unable to maintain daily activities due to asthenia and sleepiness (8). In addition, 40% of the patients are non-responders, thus requiring a more aggressive therapy (11). A second line treatment option is corticosteroid therapy which is frequently used. Therapy may require high doses which produce relevant side effects, i.e., "too much for too long" (12). CyA is either an alternative option to corticosteroids or used when steroids are unsatisfactory, i.e., non-response patients or those needing excessive doses for control (12). We added CyA to steroids in patients who were poorly responsive to these drugs to lower

their dose, hence minimize side affects.

The optimal dose and duration of CyA in CIU still need to be established. Several CyA treatments of different duration in association with antihistamines have been reported: Di Gioacchino et al. administered 5 mg/kg/day for the first 8 weeks, then 4 mg/kg/day for further 8 weeks (1); Grattan et al. studied 30 patients who improved with a 4 mg/kg/day for a 4-week treatment (2), while Serhat Inaloz et al. evaluated 2.5 mg/kg/day for 4 weeks (13). Our retrospective study confirmed the efficacy of low-dose CyA (1–3 mg/kg/day) in three groups of patients in a 6-month treatment. After 6 months (T2), the CyA therapy produced a decrease of the total (TSSS) by -67% in Group A, -76% in Group B and -85% in Group C, although the plasma CyA therapeutic values were not achieved. Complete regression was recorded in 39.1% of patients: similar results were reported by Kessel and Toubi who observed CIU disappearance in 40% of patients given 2-3 mg/kg/day of CyA (8).

The mechanism of action of CyA is not fully known: immunosuppressive along with anti-inflammatory and anti-allergic activity of CyA have been hypothesized (13-14). Perhaps, in CIU the therapeutic effect of CyA is due to the down-regulation of Th1 responses. In fact, CyA reduces the effect of the transcription factor in T cells (nuclear factor of activated T cells) that regulates the transcription of the major activation factor

**Table 1.** Patients' baseline data.

|                                                                            | Group A         | Group B         | Group C         |
|----------------------------------------------------------------------------|-----------------|-----------------|-----------------|
| <b>Male</b>                                                                | 10              | 14              | 23              |
| <b>Female</b>                                                              | 15              | 18              | 30              |
| <b>Median age (years)</b>                                                  | 47.6            | 45.9            | 43.8            |
| <b>Range</b>                                                               | 22-72           | 16-58           | 18-55           |
| <b>Pruritus<sup>a</sup></b>                                                | 2.76            | 2.63            | 2.53            |
| <b>Size of wheals<sup>b</sup></b>                                          | 2.80            | 2.97            | 2.92            |
| <b>Number of wheals<sup>c</sup></b>                                        | 2.52            | 2.81            | 2.74            |
| <b>Total symptom severity score (TSSS, or 'overall score')<sup>d</sup></b> | $8.08 \pm 0.81$ | $8.41 \pm 0.52$ | $8.19 \pm 0.58$ |
| <b>Duration of urticaria (months)</b>                                      | $10.6 \pm 11.7$ | $11.6 \pm 5.8$  | $12 \pm 8.9$    |

<sup>a</sup> Mean pruritus scores ranged 0-3, <sup>b</sup> Mean size of wheals scores ranged 0-3, <sup>c</sup> Mean number of wheals scores ranged 0-3,

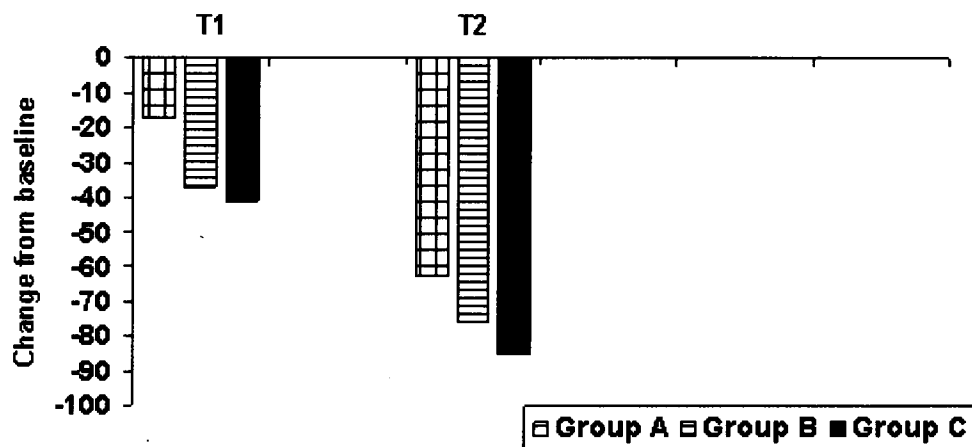
<sup>d</sup> Mean of three domains scored on 0-3 scale.

**Table II.** *Urticaria symptoms scores in the three patient groups.*

| Change from baseline (mean differences)      |         |         |         |          |          |          |
|----------------------------------------------|---------|---------|---------|----------|----------|----------|
|                                              | T1      |         |         | T2       |          |          |
|                                              | Group A | Group B | Group C | Group A* | Group B* | Group C* |
| <b>Pruritus</b>                              | -0.60   | -0.73   | -0.74   | -1.80    | -2.00    | -2.08    |
| <b>Size of wheals</b>                        | -0.32   | -1.31   | -1.45   | -1.80    | -2.31    | -2.58    |
| <b>Number of wheals</b>                      | -0.48   | -1.06   | -1.21   | -1.44    | -2.06    | -2.31    |
| <b>Overall score<br/>(mean of 3 domains)</b> | -1.40   | -3.10   | -3.40   | -5.08    | -6.38    | -6.96    |

Group A, 1-1.5 mg/kg/day; Group B, 1.6-2 mg/kg/day; Group C, 2.1-3 mg/kg/day.

\* $p < 0.05$  or better for each value compared to baseline.

**Fig. 1.** *Total symptom severity score (TSSS) at 3 (T1) and 6 months (T2) of the CyA treatment compared to baseline.*

– namely IL-2 – in various immunological processes (15). Since the pathogenesis of CIU involves the release of numerous potential vasoactive mediators (histamine, lipid-derived vasoactive factors) arising from activation of skin mast cells, the CyA efficacy may be due to inhibition of the release of cell-derived mediators which down-regulates cell adhesion molecules (16). CyA also reduces the

expression of cellular adhesion molecules of dermal capillary endothelial cells, with consequent decrease of both T-cell and neutrophil infiltration (13). CyA provides an inhibitory effect on antigen-presenting cells which are potent stimulators of T cells (13). Overall, these CyA activities justify its effectiveness in reducing the number and size of wheals as well as the itching.

In our study, only 12 patients (10%) presented minor adverse events: 7 showed increased serum creatinine, but a 25% dose reduction led to its regression. Five patients complained of slight gastrointestinal symptoms: the subdivision of the dose in three daily doses resulted in the disappearance of these symptoms. In all cases, no discontinuation of therapy was needed. It should be noted that the side effects, although very low and reversible, occurred only in patients of Group C where the CyA dose was higher. The duration of treatment did not affect the occurrence of side effects. In line with our results, others reported a very low incidence of side effects (mostly gastrointestinal) with 2-3 mg/kg/day, but almost no cases of therapy discontinuation (8). Kessel and Toubi pointed out that some patients with severe CIU were kept on very low doses of CyA (1.5-2.0 mg/kg/day) for 5 to 7 years continuously because they were unable to stop therapy, and showed no important side effects (including malignancy) (8). The treatment with CyA in our patients was efficacious although the plasma level was lower than the therapeutic level required for this drug. In addition, only 11% of patients had a relapse.

According to our results, Group C had the best value with a significant reduction of TSSS at T2. However, we suggest that CyA at 1-3 mg/kg/day according to patients co-morbidity is safe, and should be considered earlier when CIU is very severe and unresponsive to standard treatment, although the optimal use and its dosage remain to be defined.

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