Efficacy and tolerability of cyclosporine microemulsion in chronic idiopathic urticaria. An Italian multicentre collaborative study

Background: Chronic idiopathic urticaria (CIU) is the most common form of urticaria (70-80% of cases). Conventional treatment with either antihistamines and/or corticosteroids is often not satisfactory. A number of studies have suggested the efficacy of cyclosporine (CsA) administered orally in resistant CIU. We evaluated the efficacy and tolerability of CsA in the treatment of CIU over a 6 months period.

Method: We performed an open, non comparative, collaborative multicenter study. One-hundred and twenty adult patients were treated with oral CsA: 5±1 mg/kg/day for 14 days; 4±1 mg/kg/day from day 15 to day 28; then 3±1mg/kg/day up to six months. Symptoms severity and pruritus were evaluated by the Breneman's scale, a 100 mm visual analog scale (VAS) and a 4-point verbal rating scale (VRS).

Results: The actual mean CsA dosage administered was 4.0 mg/kg/day at study beginning, 3.0 mg/kg/day after 1 month and 2.4 mg/kg/day up to 6 months. The Breneman's total score improved significantly (-41%; p=0.0001) by day 14, with further progressive reductions at day 28 (-62% vs. baseline; p=0.0001), month 2 (-79% vs. baseline; p=0.0001) and month 5 (-88% vs. baseline; p=0.0001), then remained stable during month 6. Pruritus (VAS) decreased significantly (-38%; p=0.0001) at day 14 and continued decreasing (up to -86% vs. baseline; p=0.0001). CsA treatment was well tolerated, with only 2 patients discontinuing treatment due to adverse events, which were not severe (mild increase in systolic blood pressure; nausea).

Conclusions: The results suggest good efficacy and tolerability of up to 6 month CsA treatment in resistant CIU.

Key words: Breneman’s total score, Chronic Idiopathic Urticaria, Cyclosporine A, Pruritus, Verbal scale, Visual Analog Score

Introduction

Chronic idiopathic urticaria (CIU) is the most frequent form of urticaria, accounting for 70-80% of the cases (1). CIU is defined as a 6-week or longer history of urticaria in the absence of detectable physical, allergic, vasculitic, infectious or drug-induced causes (2). The presence of autoantibodies directed toward IgE or to the high-affinity IgE Fc receptor, detected by intradermal test with autologous serum, has been reported in approximately 30% of patients with CIU (3). A substantial proportion of patients with chronic urticaria and positive autologous serum skin test (ASST) could be recognized as an autoimmune urticaria auto-reactive subgroup. Symptomatic treatment with antihistamines is the first choice for CIU but these drugs are not always effective. When symptoms are severe, corticosteroids are com-
commonly used, but they are not suitable for chronic treatment due to the high incidence of adverse effects and the risk of inducing more severe attacks after drug discontinuation. The demonstration that chronic urticaria is frequently autoimmune has encouraged a more aggressive therapeutic approach. There is currently little experience in the treatment of chronic urticaria by removal of autoantibodies. Plasmapheresis has been shown to be of temporary benefit in severely affected patients (4). Alternatively, immunological approaches with high-dose immunoglobulin infusions (5) or agents inhibiting antibody production like CsA (6-7) have proven to be helpful. The short term use of CsA in severe CIU not responsive to first line treatments has been investigated by several authors in different countries (8-11). The efficacy of the treatment has always been very satisfactory: pruritus always rapidly decreased, and incidence of adverse events was generally low. Longer treatment courses, i.e. 2 to 4 months, were also studied showing good efficacy and tolerability, and in some cases also showing a trend toward reduction of incidence and severity of relapses (12-15). Further and even more prolonged experience with CsA therapy is required in order to determine the extent of efficacy and tolerability of this approach in the treatment of resistant CIU. This study was aimed at assessing the long term efficacy and safety of CsA treatment (up to 6 months) administered with decreasing dosages (from 5mg/kg/day to 3mg/kg/day) in severe resistant CIU. As severe cases are not so common, a number of centers decided to cooperate following a common treatment schedule and to collect data in a natural clinical setting, i.e. without deviating from each center-specific treatment procedures except for the drug administration regimen and the duration of patients’ follow-up. Therefore, this is a collaborative study aimed at sharing experience to gather a body of data large enough to draw significant clinical conclusions on the use of CsA in severe resistant CIU.

**Subjects and methods**

**Patients and treatment**

After signing a written informed consent, male and female patients, aged ≥ 18 years, meeting the clinical diagnostic criteria for CIU and having failed to respond to first line antihistamines, were admitted to CsA treatment in 20 Italian centers.

Patients were treated with oral CsA microemulsion (Neoral®, Novartis) according to the following schedule: 5±1 mg/kg/day for 14 days; 4±1 mg/kg/day from day 15 to day 28; then 3±1 mg/kg/day up to six months.

**Study design and assessment criteria**

This was an open, non comparative, collaborative, multicentre study. Control visits were scheduled two and four weeks after treatment initiation and then monthly up to six months.

The primary efficacy end-point was the reduction in the Breneman scale total score at week 4 as compared to baseline. Secondary end-points were the Breneman's total score reductions versus baseline at week 8 and at the end of the 6-month follow-up. Safety and tolerability were evaluated by vital signs, laboratory tests and adverse events reporting.

Patients’ history of CIU and demographic data were collected upon treatment initiation. At each visit, weight, diastolic blood pressure (DBP), systolic blood pressure (SBP) and routine laboratory parameters were recorded. Table 1 summarizes the patients’ baseline characteristics.

| Males (%) | 53 (44.2) |
| Females (%) | 67 (55.8) |
| Age, years (mean ± SD) | 44.9 ± 13.5 |
| Weight, kg (mean ± SD) | 69.4 ± 12.1 |
| Breneman score (mean ± SD) | 10.4 ± 7.5 |

**Table 1.**

Patients’ baseline characteristics (n=120).

![Figure 1](image)

**Figure 1.**

Mean CsA dosage at baseline and after 2, 4, 8 weeks and 6 months of treatment.
Results

Patient population and treatment

One-hundred and twenty adult patients (median age 44.8 years, range 16-83; 67 women) were enrolled (Table 1). We report the data collected by March 2003. A total of 17 patients withdrew from the study within the first 8 weeks: 2 withdrew due to adverse events, one for an intercurrent disease, one because of treatment failure and 13 were lost to follow-up. After week 8, a progressively increasing number of patients were lost to follow-up (n=65 at month 5, n=25 at month 6). Anyway, the analysis of efficacy refers to the actual population at each visit. The actual mean CsA dosage administered was 4.0 mg/kg/day at study beginning, 3.0 mg/kg/day after 1 month and 2.4 mg/kg/day up to 6 months (Figure 1).

Efficacy results

Severity of symptoms, evaluated by the Breneman scale total score (16), significantly improved in comparison to baseline as early as by week 2 (n=104): from 10.4±7.5 to 6.1±3.6 (p=0.0001). At week 4 (n=103), which was the primary end-point of the study, the total score dropped to 3.9±3.3 (p=0.0001 vs baseline). At the secondary end-point (week 8; n=103) the score further decreased to 2.1±3.0 (p=0.0001 vs baseline). After 5 months of treatment (n=65) the score was 1.2±1.9 (p=0.0001 vs baseline), and remained stable at 1.2±2.4 at 6 months (n=25) (p=0.0001 vs. baseline). All symptoms included in Breneman’s scale reflected the general trend to a progressive decrease over time. Particularly noteworthy was the effect on pruritus, as evaluated both on a VRS and a VAS. On the VRS, at baseline, 91% of patients classified their pruritus as moderate/severe (36% and 55%, respectively), 2% as absent and 7% as mild at baseline (Figure 3). At week 2, 23% of patients were free from pruritus, 32% classified it as mild, 41% as moderate and only 4% as severe (p=0.0001). At week 4, 41% of patients had no pruritus, 39% classified it as mild, 18% as moderate and only 2% as severe (p=0.0001 vs baseline). A further decrease was reported at week 8: 58% of patients had no pruritus, 32% had mild pruritus, 8% moderate and 2% severe (p=0.0001 vs baseline). After 6 months no patients had seve-
transcriptional activation of several cytokine genes, such as interleukin 3 (IL-3) and IL-5 (4?), and also the genes involved in leukotriene synthesis. All these events require an increase in the concentration of intracellular Ca²⁺.

Furthermore, the cytokine genes that are blocked in mast cells are largely the same as those blocked in T cells, suggesting an effect on a regulatory protein common to mast cells and T cells. The efficacy and safety of CsA in severe resistant CIU have been demonstrated in several clinical studies, but data on more prolonged use are still needed. We investigated the effectiveness and tolerability of a 6 month course of oral CsA treatment at decreasing doses in this non controlled clinical study involving 20 hospitals and outpatient clinics throughout Italy. The first observation concerns the actually administered dosage, which was in the lowest protocol range, i.e. 4 mg/kg/day at treatment start and 2.4 mg/kg/day during the long-term phase, possibly reflecting a prudent attitude of the investigators toward possible long-term side effects of CsA treatment. Anyway, it is worth underlying that these dosages, lower than those usually reported in CIU clinical trials, showed to be effective. Actually, only 2 patients dropped out due adverse events. One patient withdrew because of an increase in blood pressure after two weeks, which however was not severe. The average increase of SBP and DBP was neither clinically nor statistically significant. All other adverse reactions were mild to moderate in severity and did not require treatment discontinuation, except for one case of nausea.

The analysis of efficacy revealed a dramatic effect of CsA on symptoms severity, as assessed
by the Breneman’s total score, as early as after 2 weeks and a continuous further improvement until the 5th month. At the 6th month, the score remained stable around 1. Other reports had suggested the efficacy and safety of CsA on CIU during 2 to 4 months of treatment (12, 14, 15). Anecdotal positive experiences were reported up to 6-8 months of low dose CsA treatment (13). On the other hand, Baskan et al. suggested that CsA therapy for more than one month provides little further benefit (17). Our results seem to confirm that prolonged CsA administration induces continuous improvement in CIU symptoms, at least up to 5 months. On the other hand, we think that the early clinical response to CsA treatment probably induced a number of patients to discontinue the drug before the 6 months end-point and not to attend the further scheduled visits.

Our patients were not tested for autologous serum skin test (ASST) at the beginning of the study because some authors reported that CsA works very well in all types of patients (12). Our data seem to confirm this observation. We are aware that this survey suffers from the limitations of an open non controlled design and of the lack of rigorous study procedures. However, as stated before, we aimed at obtaining a very large number of patients treated in a natural clinical practice setting to evaluate the current management of CIU in Italy. Unfortunately, a small number of patients reached the 6-month treatment end-point, but it is a quite common experience in outpatient studies to lose patients to follow-up upon the resolution of symptoms. For the above mentioned reasons our results do not allow to draw definite conclusions, however they reflect the everyday clinical practice in CIU and suggest that CsA can be effectively and safely used up to 6 months in patients with CIU not responding to antihistamines. A further large properly controlled clinical trial is required to confirm the efficacy and safety of long-term CsA in the treatment of resistant CIU, which also addresses the issue of the relapse rate after treatment discontinuation.
References


International-Italian Society of Plastic-Aesthetic and Oncologic Dermatology

ISPLAD

Journal of Plastic Dermatology

Editor
Antonino Di Pietro (Italy)

Editor in Chief
Francesco Bruno (Italy)

Associate Editors
Francesco Antonaccio (Italy)
Mariuccia Bucci (Italy)
Franco Buttafarro (Italy)
Ornella De Pi(à Italy)
Giulio Ferranti (Italy)
Andrea Giacomelli (Italy)

Alda Malasoma (Italy)
Steven Nisticò (Italy)
Elisabetta Perosino (Italy)
Andrea Romani (Italy)
Nersys Roberts (UK)

Paolo Fabbri (Italy)
Salvador Gonzalez (USA)
Ferdinando Ippolito (Italy)
Giuseppe Miceli (Italy)
Martin Charles Jr Mihm (USA)
Joe Pace (Malta)
Lucio Pastore (Italy)
Gerd Plewig (Germany)

Eady Robin AJ (UK)
Abel Torres (USA)
Umberto Veronesi (Italy)

English editing
Rewadee Anujapad

International-Italian Society of Plastic-Aesthetic and Oncologic Dermatology

Direttore Responsabile
Pietro Cazzola

Direzione Marketing
Armando Mazza

Rapporti con ISPLAD
Antonio Di Maio

Consulenza grafica
Piero Merlini

Impaginazione
Clementina Pasina

Registra: Tribunale di Milano n. 102 del 14/02/2005
Scripta Manent s.n.c. Via Bassini, 41 - 20133 Milano
Tel. 0270608091/0270608060 - Fax 0270606917
E-mail: scriman@tin.it

Abbonamento annuale (3 numeri) Euro 39,00
Pagamento: conto corrente postale n. 20350682
intestato a: Edizioni Scripta Manent s.n.c.,
via Bassini 41 - 20133 Milano
Stampa: Arti Grafiche Bazzi, Milano

E vietata la riproduzione totale o parziale,
con qualsiasi mezzo, di articoli, illustrazioni
e fotografie senza l'autorizzazione scritta dell'Editore.
L'Editore non risponde dell'opinione espressa dagli
Autori degli articoli.

Ai sensi della legge 675/96 è possibile in qualsiasi
momento opporsi all'invio della rivista
comunicando per iscritto la propria decisione a:
Edizioni Scripta Manent s.n.c.
Via Bassini, 41 - 20133 Milano