

Cyclosporine in chronic idiopathic urticaria: A double-blind, randomized, placebo-controlled trial

Gino A. Vena, MD,^a Nicoletta Cassano, MD,^a Delia Colombo, MD,^b
Elena Peruzzi, BSc,^b Paolo Pigatto, MD,^c and the NEO-I-30 Study Group*
Bari, Origgio, and Milan, Italy

Background: Treatment of severe recalcitrant chronic idiopathic urticaria (CIU) is difficult.

Objective: To assess the efficacy and safety of oral cyclosporin A (CsA) in CIU.

Methods: The response to CsA was evaluated in 99 CIU patients with a double-blind, randomized, three-armed study: 16-week CsA, 8-week CsA +8-week placebo, and 16-week placebo. All patients received cetirizine throughout the study period and were followed-up after 8 weeks.

Results: Fewer therapeutic failures occurred with 16-week CsA ($n = 3$) than with placebo ($n = 11$) and 8-week CsA ($n = 8$). After 8 and 16 weeks, symptom scores significantly improved in both CsA groups over with placebo. Two patients discontinued because of hypertension.

Limitations: During the study period, CsA was not administered at a constant dose; from day 28 the daily dose was 3 mg/kg, which is likely to be less effective and better tolerated than higher dosages.

Conclusion: CsA in addition to background therapy with cetirizine may be useful in the treatment of CIU. (J Am Acad Dermatol 2006;55:705-9.)

Small open-label trials suggest that cyclosporine (CsA), used at a range of different daily dosages (<5 mg/kg) and duration, could be of therapeutic value in patients with chronic idiopathic urticaria (CIU) that is unresponsive to conventional therapy.¹⁻⁹ This double-blind, randomized, between-patients, multicenter study was designed to

Abbreviations used:

CIU: chronic idiopathic urticaria
CsA: cyclosporine
DLQI: Dermatology Life Quality Index
SGA: subject's global assessment

assess the efficacy and safety of CsA and to provide information on the optimal duration of therapy in patients with CIU.

METHODS

The study population, recruited in 18 Italian outpatient clinics, consisted of adult patients suffering from severe relapsing CIU, with persistence of symptoms (total severity score ≥ 8) despite treatment with cetirizine. Severity score was assessed by means of the scale reported by Breneman et al.¹⁰ Exclusion criteria included other concomitant forms of urticaria, any contraindications to cetirizine and CsA, and relevant systemic disorders.

After a 1-week run-in period with cetirizine, 10 mg/d, eligible patients entered a 16-week double-blind period of randomized treatment in addition to the background cetirizine therapy and were randomly allocated to one of the following 3 treatment

From 2nd Dermatology Clinic, MIDIM Department, University of Bari^a; Novartis Farma SpA, Origgio^b; and the Division of Dermatology, University of Milan.^c

*The complete list of all investigators and their sites is given at the end of the article.

Supported by Novartis Farma SpA, Origgio, Varese, Italy.

Disclosure: Dr Colombo and Ms Peruzzi are full-time employees of Novartis Farma SpA. The other authors declare no conflicts of interest.

Presented previously as an abstract at the II International Symposium on Urticaria, November 23 and 24, 2001, Rome, Italy and at the 60th Annual Meeting of the American Academy of Dermatology, February 22-27, 2002, New Orleans, La; also presented as a poster and abstract at the Second 20th World Congress of Dermatology, July 1-5, 2002, Paris, France.

Reprint requests: Gino A. Vena, MD, 2nd Dermatology Clinic, MIDIM Department, University of Bari, Policlinico—Piazza Giulio Cesare, 11, 70124 Bari, Italy. E-mail: g.vena@dermatologia.uniba.it.

0190-9622/\$32.00

© 2006 by the American Academy of Dermatology, Inc.

doi:10.1016/j.jaad.2006.04.078

Table I. Baseline characteristics and exposure to study drug of randomized population

	Treatment group		
	16-wk CsA (n = 31)	8-wk CsA (n = 33)	Placebo (n = 35)
Demographics			
Female*	17 (54.8)	17 (51.5)	23 (65.7)
White*	31 (100)	32 (97)	34 (97.1)
Age (y) [†]	44.0 (9.8)	37.1 (11.3)	41.7 (11.5)
Urticaria			
Duration [†]	3.7 (7.1)	6.2 (7.8)	2.4 (3.2)
Severity score [†]	11.1 (2.0)	11.2 (2.2)	11.1 (1.0)
DLQI score [†]	7.9 (5.6)	7.9 (4.6)	7.8 (5.7)
Concomitant disorders			
Gastrointestinal*	3 (9.7)	6 (18.2)	2 (5.7)
Musculoskeletal*	3 (9.7)	0 (0)	2 (5.7)
Infections*	2 (6.5)	0 (0)	3 (8.6)
Exposure to study drug (days of treatment) [†]			
Wk-Wk 8	52.0 (18.1)	52.3 (14.0)	46.6 (21.6)
Wk 9-Wk 16	57.6 (10.9)	50.7 (16.7)	55.3 (12.4)
Compliance <80% or >120% (No. of patients)	4	5	4

CsA, Cyclosporine; DLQI, Dermatology Life Quality Index; Wk, week(s).

*Data expressed as number of patients, with percentage given in parentheses.

[†]Data expressed as mean value, with standard deviation given in parentheses.

arms: CsA (Sandimmun Neoral) for 16 weeks (16-week CsA), CsA for 8 weeks followed by placebo for 8 weeks (8-week CsA), or placebo for 16 weeks. Patients' visits occurred at weeks 2, 4, 8, 12, 16, and after an 8-week treatment-free period (week 24).

CsA was administered at the daily dose of 5 mg/kg from day 0 to day 13, 4 mg/kg from day 14 to day 27, and 3 mg/kg from day 28, in combination with cetirizine 10 mg/d (at bedtime). Rescue treatments for symptoms that were inadequately controlled were recorded.

The primary efficacy parameter was the change in severity score after 8 weeks. Secondary efficacy end points were the change in total score at 16 and 24 weeks; the number of patients requiring rescue therapy at week 24; the subject's global assessment (SGA) of relief of symptoms and the Dermatology Life Quality Index (DLQI)¹¹ over the 24-week postrandomization period. Safety assessments consisted in the reporting of adverse events, monitoring of laboratory parameters, and physical examination.

The Independent Ethics Committee of each center approved the protocol and all participants gave written informed consent.

Twenty-five patients per group were required to detect change from baseline in the primary variable (80% power, 5% level of significance); this number was increased to 32 per group to allow for a 20% drop-out rate. The statistical analyses were performed using SAS (version 8.0). All efficacy analyses were based on the intention-to-treat population and the last-observation-carried-forward approach was used for missing values for any reason. The changes in total score were evaluated by analysis of variance. A proportional odds model was used for comparisons on the SGA. The rate of patients who needed rescue medication was analyzed by chi-square test and the DLQI scores by the Kruskal-Wallis and Wilcoxon tests.

RESULTS

A total of 99 subjects were randomized and received treatment and at least one efficacy evaluation. Baseline characteristics and exposure to study drug are shown in Table I.

Thirty-eight patients did not complete the study: 16-week CsA (n = 8), 8-week CsA (n = 13), and placebo (n = 17). A higher proportion of therapeutic failures both in the placebo group and in the 8-week CsA group during the placebo intake was observed when compared with the 16-week CsA group (Fig 1).

Cumulative efficacy results are summarized in Fig 2. After 8 weeks, the severity score was significantly improved by CsA, and patients experienced significantly greater relief of symptoms and improvement in DLQI scores with CsA compared with placebo. A significantly greater reduction in symptom score versus placebo was still present at 16 weeks in both CsA groups. The difference between CsA and placebo in the secondary end points diminished with time because of the discontinuation of placebo nonresponders. At week 24, there were no longer any significant differences in efficacy parameters among treatment groups. Fewer patients resorted to rescue medication in the 16-week CsA group compared with the other two treatment groups throughout the study.

Sixty patients (60%) reported adverse events (Table II), with fewer patients in the placebo group than in the CsA groups. The nature of adverse events was similar in the two active treatment groups; gastrointestinal disturbances, paresthesias, and infections were the most common events. Elevated serum creatinine was the most commonly reported laboratory abnormality and increased in 6 patients receiving CsA.

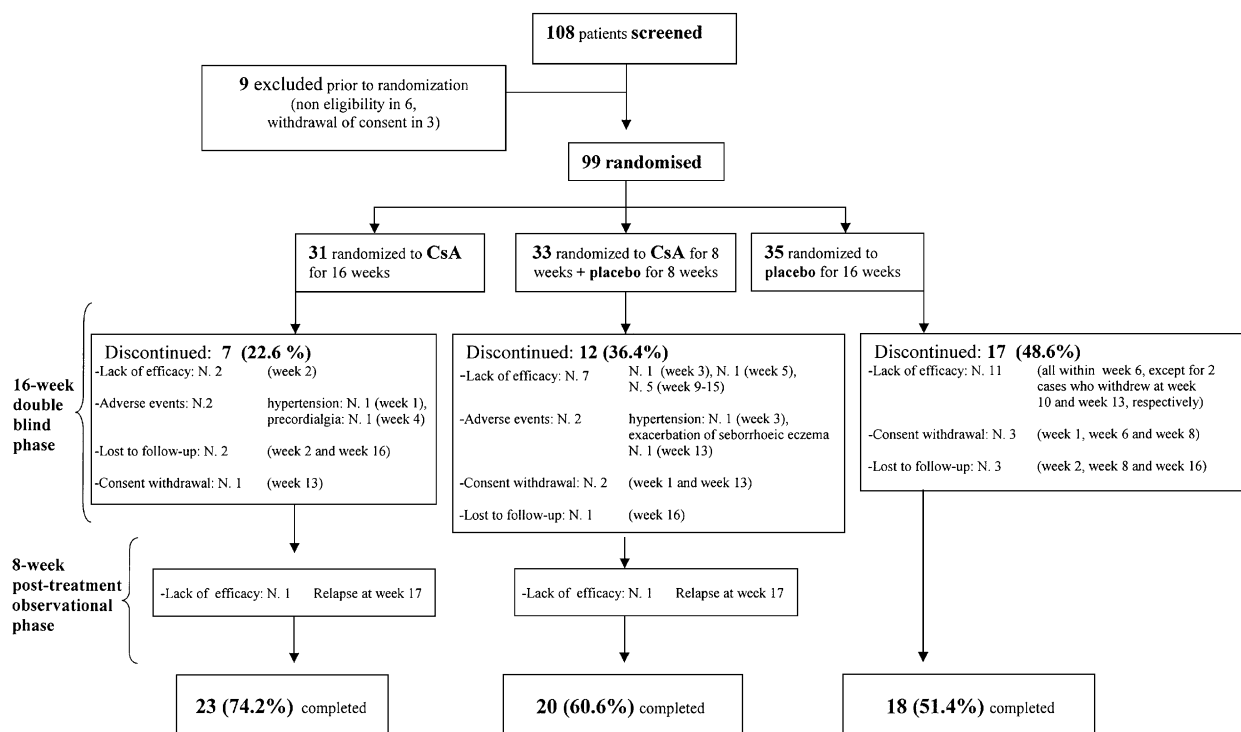


Fig 1. Trial profile.

	16-week CsA	8-week CsA	Placebo
Week 8			
Improvement of severity score (mean)	62.5% (p=0.03 vs placebo)	62.1% (p=0.02 vs placebo)	23.3%
Improvement of DLQI (mean)	60.2% (p=0.03 vs placebo)	65.7% (p=0.008 vs placebo)	26.1%
SGA of relief * (odds)	3.2 (p=0.01 vs placebo)	3.9 (p=0.02 vs placebo)	1.1
Week 16			
Improvement of severity score (mean)	52.9% (p<0.01 vs placebo)	45.6% (p<0.05 vs placebo)	25.0%
Improvement of DLQI (mean)	63.9% (p=0.05 vs placebo)	68.4% (p=0.04 vs placebo)	33.9%
SGA of relief * (odds)	2.3 (p>0.05 vs placebo)	1.5 (p>0.05 vs placebo)	1.5
Week 24			
Improvement of severity score (mean)	41.7% (p>0.05 vs placebo)	46.9% (p>0.05 vs placebo)	30.2%
Improvement of DLQI (mean)	62.2% (p>0.05 vs placebo)	63.6% (p>0.05 vs placebo)	34.6%
SGA of relief * (odds)	1.7 (p>0.05 vs placebo)	0.9 (p>0.05 vs placebo)	1.7
24-Week post-randomization period			
Rescue therapy (% patients)	19.4 (p>0.05 vs placebo)	42.4 (p>0.05 vs placebo)	31.4

Fig 2. Summary of efficacy results. Where not specified, the difference between 16-week CsA and 8-week CsA was not significant ($P > .05$). Asterisk, SGA of relief consists of a 5-item scale used by patients to rate change of symptoms as follows: 0 = completely relieved; 1 = considerably relieved; 2 = somewhat relieved; 3 = unchanged; 4 = worse; results of SGA of relief are reported in this figure as odds. DLQI, Dermatology Life Quality Index; SGA, subject's global assessment.

Table II. Adverse events throughout the study period

	Treatment group		
	16-wk CsA (n = 31)	8-wk CsA (n = 33)	Placebo (n = 35)
Adverse events			
Upper abdominal pain	5 (16.1)	5 (15.1)	2 (5.7)
Paresthesia	5 (16.1)	4 (12.1)	0
Flushing	3 (9.7)	1 (3.0)	1 (2.9)
Headache	3 (9.7)	3 (9.1)	3 (8.6)
Arthralgia	2 (6.4)	1 (3.0)	2 (5.7)
Back pain	2 (6.4)	1 (3.0)	1 (2.9)
Conjunctivitis	2 (6.4)	0	0
Gastroenteritis	2 (6.4)	1 (3.0)	0
Hypertrichosis	2 (6.4)	1 (3.0)	0
Dizziness	2 (6.4)	1 (3.0)	0
Hypertension	1 (3.2)	2 (6.1)	0
Migraine	1 (3.2)	3 (9.1)	2 (5.7)
Pruritus	1 (3.2)	2 (6.1)	2 (5.7)
Pyrexia	1 (3.2)	2 (6.1)	1 (2.9)
Flu syndrome	0	5 (15.1)	3 (8.6)
Tremor	0	2 (6.1)	0
Urticaria	0	2 (6.1)	0
Urticaria aggravated	0	2 (6.1)	2 (5.7)
Gastritis	0	0	2 (5.7)
Other	9 (29.0)	8 (22.8)	3 (8.6)
Serious adverse events*			
Precordialgia	1 (3.2)	0	0
Acute gastroenteritis	0	1 (3.0)	0
Total (patients)[†]	20 (64.5)	24 (72.7)	16 (45.7)

Data expressed as number of patients experiencing adverse events, with percentage given in parentheses.

*Reason for "seriousness" of event was hospitalization for both; the patients recovered completely and the events were not drug related.

[†]Some patients experienced more than one adverse event.

DISCUSSION

Our results show that oral CsA treatment (5 mg/kg/d progressively reduced to 3 mg/kg/d), in addition to background therapy with cetirizine, is significantly more effective than placebo and cetirizine in reducing the severity of CIU after 8 weeks. There was also a higher incidence of withdrawals because of inefficacy in the placebo group than in the two CsA groups. The amelioration of severity score over placebo still persisted at week 16.

These findings are consistent with the results of another controlled trial conducted in 29 patients with CIU treated with the old formulation of CsA (Sandimmun) at the constant dosage of 4 mg/kg per day for 4 to 8 weeks.¹² The difference versus placebo was considerable at week 8 (63% of patients improved vs none in the placebo group). Improvement

persisted, but in a smaller number of patients (25%) over the long-term (6 months).

The design of the study did not allow the detection of a dose-dependent response to CsA,¹³ although this was somewhat suggested by the greatest reduction from baseline in both symptom score and SGA of relief in the first 2 weeks detected in the active groups (data not shown).

Our study also confirms that CIU affects patients' quality of life^{14,15} and that DLQI score changes correlate with clinical outcome in CIU.¹⁶

A secondary objective of the study was to establish the best duration of therapy. There was no significant difference in therapeutic efficacy of the two periods of therapy in terms of the various efficacy parameters recorded, in apparent agreement with the results previously obtained in an open study comparing two regimens with different duration in a small case series.⁹ However, CsA for 8 weeks instead of 16 weeks was associated with a 15% greater drop-out rate for inefficacy, although the overall therapeutic efficacy appeared to be similar. These results appear to confirm the impression of Toubi, Bamberger, and Kessel,¹⁷ who, on the basis of sporadic case reports, suggested the possibility of reducing the risk of CIU relapses with prolonged CsA treatment.

Treatment with CsA was well tolerated. Although adverse events were common, they led to discontinuation of treatment in only 6% of patients in both CsA groups. Most abnormalities in laboratory examinations were occasional findings. The only exception was serum creatinine, which increased in 6 cases with active treatment. However, the increase remained within the normal range or just above it and promptly regressed upon discontinuation of treatment. There was no important difference in the safety profile of the two durations of treatment, but the sample size was not sufficiently large to reach any definitive conclusions.

In conclusion, oral CsA, at the dosage of 5 mg/kg per day progressively reduced to 3 mg/kg per day in addition to background therapy with cetirizine, may be useful in the management of CIU.

Investigators and Co-Investigators of the NEO-I-30 Study Group: G. A. Vena, N. Cassano, V. D'Argento (2nd Dermatology Clinic, University of Bari); A. Tursi, E. Nettis, E. Cavallo, L. D'Oronzio (Section of Allergology and Clinical Immunology, University of Bari); C. Varotti, A. M. Costa, O. Calderoni (Institute of Dermatology, University of Bologna); C. Tosoni, M. T. Branzini (Unit of Clinical Immunology, Spedali Civili, Brescia); G. S. Del Giacco, G. Piludu (Unit of Allergology, University of Cagliari); S. Masci, M. G.

Andreassi (Unit of Dermatology, University of Chieti); A. F. Finzi, P. Pigatto, A. Bigardi (2nd Dermatologic Clinic, University of Milan); A. Giannetti, A. Conti (Unit of Dermatology, University of Modena); F. Fabbri, M. Caproni (2nd Dermatologic Clinic, University of Florence); S. Romagnani, L. Emmi, F. Ligobbi (Institute of Allergology and Immunology, University of Florence); F. Ayala, N. Balato, F. Suppa (Institute of Dermatology, University "Federico II" of Naples); G. Marone, A. De Paulis, G. Spadaro (Institute of Allergology and Clinical Immunology, University "Federico II" of Naples); L. Andreassi, M. L. Flori, A. Molinu, M. Pellegrino (Institute of Dermatology, University of Siena); P. Lisi, L. Stingeni (Unit of Dermatology, University of Perugia); B. Santucci, C. Valenzano (Istituto San Gallicano, IRCCS, Rome); O. De Pità, A. Zaffiro (Istituto Dermopatico dell'Immacolata, IDI, IRCCS, Rome); L. Fontana, F. Galas, S. Modica (Unit of Allergology and Clinical Immunology, University "Tor Vergata" of Rome); V. Bottari (Unit of Allergology and Clinical Immunology, Hospital "San Filippo Neri," Rome).

We thank Jennifer Hartwig, MD, for her contribution to the drafting of the manuscript.

REFERENCES

1. Fradin MS, Ellis CN, Goldfarb MT, Voorhees JJ. Oral cyclosporine for severe chronic idiopathic urticaria and angioedema. *J Am Acad Dermatol* 1991;25:1065-7.
2. Barlow RJ, Kobza Black A, Greaves MW. Treatment of severe, chronic urticaria with cyclosporin A. *Eur J Dermatol* 1993;3:273-5.
3. Vena GA, Curatoli G, Fiordalisi F, Foti C, D'Argento V. La ciclosporina A nel trattamento dell'orticaria cronica idiopatica severa. Studio clinico su otto casi. *Boll Dermatol Allergol Profess* 1993;8:309-18.
4. Curatoli G, D'Argento V, Fiordalisi F, Vena GA. Trattamento dell'orticaria cronica: chetotifene versus cetirizina in schema sequenziale con ciclosporina A. *Boll Dermatol Allergol Profess* 1996;11:113-8.
5. Toubi E, Blant A, Kessel A, Golan TD. Low-dose cyclosporin A in the treatment of severe chronic idiopathic urticaria. *Allergy* 1997;52:312-6.
6. Ilter N, Güner MA, Akkoca MA. Short-term oral cyclosporine for chronic idiopathic urticaria. *J Eur Acad Dermatol Venereol* 1999;12:67-9.
7. Loria MP, Dambra PP, D'Oronzio L, Netti E, Pannofino A, Cavallo E, et al. Cyclosporin A in patients affected by chronic idiopathic urticaria: a therapeutic alternative. *Immunopharmacol Immunotoxicol* 2001;23:205-13.
8. Di Gioacchino M, Di Stefano F, Cavallucci E, Verna N, Ramondo S, Paolini F, et al. Treatment of chronic idiopathic urticaria and positive autologous serum skin test with cyclosporine: clinical and immunological evaluation. *Allergy Asthma Proc* 2003;24:285-90.
9. Bulbul Baskan E, Tunali Ş, Turker T, Saricaoglu H. Comparison of short-and long-term cyclosporine A therapy in chronic idiopathic urticaria. *J Dermatol Treat* 2004;15:164-8.
10. Breneman D, Bronsky EA, Bruce S, Kalivas JT, Klein GL, Roth HL, 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.
11. Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI)—a simple practical measure for routine clinical use. *Clin Exp Dermatol* 1994;19:210-6.
12. Grattan CE, O'Donnell BF, Francis DM, Niimi N, Bralow RJ, Seed PT, et al. Randomized double-blind study of cyclosporin in chronic 'idiopathic' urticaria. *Br J Dermatol* 2000;143:365-72.
13. Cassano N, D'Argento V, Vena GA. Cyclosporin A in chronic idiopathic urticaria: An update. *Int J Immunopathol Pharmacol* 2002;15(Suppl. Jan-Apr):13-8.
14. Poon E, Seed PT, Greaves MW, Kobza-Black A. The extent and nature of disability in different urticarial conditions. *Br J Dermatol* 1999;140:667-71.
15. Thompson AK, Finn AF, Schoenwetter WF. Effect of 60 mg twice-daily fexofenadine HCl on quality of life, work and classroom productivity, and regular activity in patients with chronic idiopathic urticaria. *J Am Acad Dermatol* 2000;43:24-30.
16. Lennox RD, Leahy MJ. Validation of the Dermatology Life Quality Index as an outcome measure for urticaria-related quality of life. *Ann Allergy Asthma Immunol* 2004;93:142-6.
17. Toubi E, Bamberger E, Kessel A. Prolonged cyclosporin-A treatment for severe chronic urticaria. *Allergy* 2003;58:535-6.