

SHORT COMMUNICATION

No Major Effect of Cyclosporin A in Patients with Severe Solar Urticaria: A French Retrospective Case Series

Charlotte Hurabielle¹, Christophe Bedane², Martine Avenel-Audran³, Henri Adamski⁴, François Aubin⁵, Michel Jeanmougin¹, Marie-Claude Marguery⁶, Jean-Louis Peyron⁷, Claire Poreaux⁸, Jean-Luc Schmutz⁸ and Manuelle Viguier^{1*}; on behalf of the Société Française de Photodermatologie

Services de Dermatologie, ¹Université Paris Diderot, Assistance Publique-Hôpitaux de Paris, Hôpital Saint-Louis, 1 avenue Claude-Vellefaux FR-75475 Paris,

²Centre Hospitalo-Universitaire (CHU), Limoges, ³CHU, Angers, ⁴Hôpital Pontchaillou, CHU, Rennes, ⁵Université de Franche Comté, EA3181, SFR4234 CHU, Besançon, ⁶Hôpital Larrey, Toulouse, ⁷Hôpital Saint-Eloi, Montpellier, and ⁸Hôpital Brabois, Nancy, France. *E-mail: manuelle.viguier@sls.aphp.fr. Accepted May 11, 2015; Epub ahead of print May 27, 2015

Solar urticaria (SU) is a rare chronic immunoglobulin (Ig) E-mediated photodermatosis that is thought to be mediated by a photoallergen and can significantly impair daily activities (1). The clinical presentation of SU is identical to other forms of urticaria, with erythematous and oedematous wheals usually developing within minutes after exposure to ultraviolet (UV) radiation on exposed areas, and lasting generally <2 h when UV exposure is discontinued. Systemic symptoms include headache, nausea, wheezing, dizziness and, rarely, syncope or anaphylactic shock (2, 3). First-line treatment for SU is based on conventional H1-antihistamines and sunscreens (4). Recently, the efficacy of intravenous Igs has been suggested in patients who are refractory to treatment (5); however, the use of an anti-IgE antibody, omalizumab, has had conflicting results (6, 7).

Cyclosporin A (CsA) is an immunosuppressive drug that has shown efficacy in chronic spontaneous urticaria (CSU); its efficacy in SU has been reported in one case (8). The aim of this study was to evaluate the efficacy of CsA in a larger number of patients with SU.

MATERIALS AND METHODS

A national, multicentre, retrospective study was performed. All 100 members of the French Society of Photodermatology were contacted by email and asked to report all cases of SU treated with CsA, whatever the duration. SU was defined as the occurrence on exposed areas of erythematous, oedematous and pruriginous wheals <15 min after exposure to UV radiation and lasting <2 h when sun exposure was discontinued, with positive phototesting results. Clinical data regarding the characteristics of the SU before and during treatment with CsA were collected using a dedicated questionnaire.

RESULTS

Reports of 11 patients (8 females; median age 39 years; age range 23–51 years) with SU treated with CsA were collected from 8 dermatology departments of French university hospitals from March 2009 to February 2014. The mean duration of SU before CsA treatment was 5 years (range 1–11 years). SU occurred through window glass in all patients, through thin or light clothes in 9/11 (82%) patients, and spread beyond sun-exposed areas

in 6 (55%) patients. Systemic symptoms occurred in 8/11 patients (73%) (Table SI¹). Previous treatments were ineffective and included at least high-protective-index sunscreens together with H1-antihistamines. The eliciting spectra and baseline minimal urticarial doses (MUDs) are shown in Table SII¹.

The CsA received by all patients was Neoral®. The dosage of CsA differed among patients, with starting dosages ranging from 2.5–5 mg/kg/day and increased after 1–4 months in 4 patients (maximal mean dosage 4.2 mg/kg/day). The mean duration of treatment was 14 weeks (median 12 weeks, range 2–48 weeks) (Table SII¹).

In total, 9/11 patients (82%) reported no modification of SU symptoms with treatment; SU was alleviated in 2 patients (18%). In patient 7, partial response occurred after 2 months of 2.5 mg/kg/day CsA, with H1-antihistamines: SU flares still occurred, but after longer sun exposure and without itching; moreover, SU induction was no longer obtained on phototesting. However, symptoms relapsed after 7 months of treatment, without improvement despite an increase to 3 mg/kg/day CsA for 2 months. CsA was stopped and switched to omalizumab, with good efficiency, after 2 months. For patient 9, SU was not alleviated after 2 months of CsA, 2.5 mg/kg/day. Increasing the dosage to 5 mg/kg/day led to clinical and photobiological improvement after 2 months, with complete clinical remission 6 months later, with absence of SU flares and SU induction on phototesting. SU relapsed one month after CsA withdrawal. Five of 11 patients (45%) reported an adverse event during CsA treatment (Table SII¹), which led to CsA discontinuation in only one patient, who experienced chest oppression.

DISCUSSION

The efficacy of CsA in controlling chronic SU (CSU) has been shown in open studies and in randomized double-blind studies, with control of disease in approximately two-thirds of patients and long-term improvement

¹<http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-2140>

in one-quarter of these (9–12). The immunosuppressive effect of CsA is based on the inhibition of cell-mediated immunity by downregulating T helper 1 lymphocyte responses and T-cell-dependent antibody formation by B lymphocytes. It is also based on inhibiting IgE-induced histamine release from human basophils and skin mast cells and release of cytokines and granular proteins from eosinophils (13–15).

Marked efficacy of CsA was reported in a 23-year-old woman with SU refractory to H1-antihistamines, psoralen plus UVA (PUVA) therapy and chloroquine phosphate. She received CsA, 4.5 mg/kg/day, with minimal skin symptoms observed after one week of treatment, and demonstrated decreased light sensitivity to UVA, UVB and visible light (8).

In our series, with a larger number of patients, the response rate was only 18%, which is much lower than the rate reported previously for CSU (9, 11, 12). One explanation for the discrepancy could be different dosages and shorter treatment. CsA concentrations in blood [AQ1] were not monitored. In CSU, CsA was started at a high dose, 4 mg/kg/day on average, with progressive decrease, for 11 weeks a mean of (range 4–12 weeks) (9–12). In our series, the starting dosage was often lower, and was gradually increased. Nevertheless, most of our patients received at least 4 mg/kg/day CsA for a minimum of one month; a period previously shown to be effective for CSU (9–12). Moreover, CsA was effective within 5 days for CSU (11). In addition, our patient who achieved partial remission of SU received a low dosage of CsA (2.5 mg/kg/day). Therefore, the low response rate to CsA in the present study was more likely due to other factors. A possible reason could be the lack of power of this study due to the small number of patients recruited. More importantly, the patients in whom CsA was prescribed had severe SU, as demonstrated by the very low baseline levels of MUD, high frequency of associated symptoms, and numerous lines of treatments for SU received before CsA. This sample selection bias, with patients with severe and refractory SU, that was more difficult to control, could explain the lower than expected response rate. In these high-need patients, the inhibitory effects of CsA on IgE-induced histamine release from basophils and mast cells may be limited and insufficient.

Although adverse events with CsA were frequent (45%), they were consistent with the usual side-effects and led to its discontinuation in only 9% of patients; no serious adverse event related to CsA was reported.

In conclusion, most of the patients in this study with severe and refractory SU did not benefit from CsA. Ne-

vertheless, a small number of patients (18%) achieved complete or partial remission. CsA may therefore be of use as a salvage therapy, after failure of other available options; however, other optimal therapy remains to be identified.

The authors declare no conflicts of interest.

REFERENCES

1. Kojima M, Horiko T, Nakamura Y, Aoki T. Solar urticaria: the relationship of photoallergen and action spectrum. *Arch Dermatol* 1986; 122: 550–555.
2. Ramsay CA. Solar urticaria. *Int J Dermatol* 1980; 19: 233–236.
3. Miyauchi H, Horio T. Detection of action, inhibition and augmentation spectra in solar urticaria. *Dermatol Basel Switz* 1995; 191: 286–291.
4. Roelandts R. Diagnosis and treatment of solar urticaria. *Dermatol Ther* 2003; 16: 52–56.
5. Aubin F, Porcher R, Jeanmougin M, Léonard F, Bedane C, Moreau A, et al. Severe and refractory solar urticaria treated with intravenous immunoglobulins: a phase II multicenter study. *J Am Acad Dermatol* 2014; 71: 948–53.
6. Müller S, Schempp CM, Jakob T. Failure of omalizumab in the treatment of solar urticaria. *J Eur Acad Dermatol Venereol* 2014 Dec 29. Epub ahead of print. [AQ2]
7. Baliu-Piqué C, Aguilera Peiró P. Three cases of solar urticaria successfully treated with omalizumab. *J Eur Acad Dermatol Venereol* 2015 Jan 30. Epub ahead of print. [AQ2]
8. Edstrom DW, Ros AM. Cyclosporin A therapy for severe solar urticaria. *Photodermatol Photoimmunol Photomed* 1997; 13: 61–63.
9. Toubi E, Blant A, Kessel A, Golan TD. Low-dose cyclosporin A in the treatment of severe chronic idiopathic urticaria. *Allergy* 1997; 52: 312–316.
10. Baskan EB, Tunalı S, Turker T, Saricaoglu H. Comparison of short- and long-term cyclosporine A therapy in chronic idiopathic urticaria. *J Dermatol Treat* 2004; 15: 164–168.
11. Grattan CEH, O'Donnell BF, Francis DM, Niimi N, Barlow RJ, Seed PT, et al. Randomized double-blind study of cyclosporin in chronic 'idiopathic' urticaria. *Br J Dermatol* 2000; 143: 365–372.
12. Vena GA, Cassano N, Colombo D, Peruzzi E, Pigatto P. Cyclosporine in chronic idiopathic urticaria: a double-blind, randomized, placebo-controlled trial. *J Am Acad Dermatol* 2006; 55: 705–709.
13. Cirillo R, Triggiani M, Siri L, Ciccarelli A, Pettit GR, Condorelli M, et al. Cyclosporin A rapidly inhibits mediator release from human basophils presumably by interacting with cyclophilin. *J Immunol* 1990; 144: 3891–3897.
14. Stellato C, de Paulis A, Ciccarelli A, Cirillo R, Patella V, Casolaro V, et al. Anti-inflammatory effect of cyclosporin A on human skin mast cells. *J Invest Dermatol* 1992; 98: 800–804.
15. Chapman I, Mazzoni L. Mechanisms of inhibition by cyclosporin A on pulmonary leukocyte accumulation. *Trends Pharmacol Sci* 1994; 15: 99–101.

Author queries

Article no: ADV SP114552

Author: Charlotte Hurabielle et al. E-mail: manuelle.viguier@sls.aphp.fr.

Article title: No Major Effect of Cyclosporine A in Patients with Severe Solar Urticaria: A French Retrospective Case Series

Dear Author,

Some questions have arisen during the preparation of your manuscript for typesetting. These are marked in the text by [AQ#]. Please consider the points below and make any corrections required.

AQ1: “CsA concentrations in blood were not monitored.” Was added. OK?

AQ2: Epub – do you have full details now?

Many thanks

Table SI. *Characteristics of patients*

Patient	Sex; age, years	SU duration, years	Extracutaneous symptoms during SU flare	Previous treatment for SU
1	F; 44	11	Fever, dizziness, headache	H1-AH, PUVA, IVIG, rituximab
2	F; 28	6	Bronchospasm, syncope	H1-AH, montelukast, IVIG
3	F; 37	1	–	H1-AH, IVIG
4	M; 47	9	Anaphylactic shock, syncope	H1-AH, hydroxychloroquine, IVIG
5	F; 34	1	Bronchospasm, syncope, nausea, vomiting, headache	H1-AH, hydroxychloroquine, IVIG
6	F; 40	6	–	H1-AH, IVIG
7	F; 25	0.5	–	H1-AH
8	F; 39	8	Bronchospasm, syncope, headache	H1-AH, PUVA, glucocorticoids, IVIG, plasmapheresis, methotrexate
9	M; 47	8	Headache	H1-AH, hydroxychloroquine
10	F; 51	2	–	H1-AH, hydroxychloroquine, montelukast
11	M; 23	2	Syncope	H1-AH

SU: solar urticaria; H1-AH: H1-antihistamines; PUVA: psoralen plus UVA, IVIG: intravenous immunoglobulins.

Table SII. Cyclosporine administration schedule and outcomes in patients with solar urticaria

Patient (sex; age, years)	CsA dosage, mg/kg/day; duration	Clinical outcome	MUD before CsA, J/cm ² (action spectrum)	MUD after CsA, J/cm ² (action spectrum)	Adverse events due to CsA
1 (F; 44)	4; 3 months	Unchanged	2 (UVA) <0.5 (UVB)	ND	None
2 (F; 28)	3; 3 months, then 5; 3 months	Unchanged	0.5 (UVA) 0.03 (UVB)	ND	Acne
3 (F; 37)	3; 2 weeks	Unchanged	1 (UVA) 0.18 (UVB)	ND	Chest oppression
4 (M; 47)	2.5; 1 month, then 5; 1.5 months	Unchanged	0.6 (UVA) 0.03 (UVB)	ND	None
5 (F; 34)	4; 1 month	Unchanged	0.8 (UVA)	ND	Nausea, myalgia, arthralgia, paraesthesia, severe asthenia
6 (F; 40)	2.5; 1 month, then 3; 4 months	Unchanged	6 (UVA)	3 (UVA)	None
7 (F; 25)	2.5; 4 months, then 5; 7 months	CR; relapse 1 month after CsA withdrawal	1 (UVA) 0.1 (UVB)	>8 (UVA) >0.18 (UVB)	None
8 (F; 39)	5; 3 months	Unchanged	24 (UVA) 4.8 (UVB) 0.03 (polyC)	0.03 (polyC)	Nausea, acne
9 (M; 47)	2.5; 7 months, then 3; 2 months	PR	5.6 (UVA)	>20 (UVA)	None
10 (F; 51)	5; 1 month	Unchanged	8 (UVA)	4 (UVA)	Abdominal pain, diarrhoea, gingival hypertrophy
11 (M; 23)	5; 1 month	Unchanged	2 (UVA)	1.5 (UVA)	None

MUD: minimal urticarial dose; UV: ultraviolet; polyC: polychromatic solar spectrum including 95% UVA and 5% UVB; ND: not done; CR: complete remission; PR: partial response.