Solar urticaria treated with intravenous immunoglobulins

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Background: Solar urticaria (SU) is a rare idiopathic photodermatosis induced immediately after sun exposure. This disorder may considerably restrict normal daily life and management is extremely difficult when treatment with oral H1 antihistamines and sun avoidance are ineffective.

Objective: We sought to report the effectiveness of intravenous immunoglobulins (IVIG) in severe SU.

Methods: We performed a retrospective multicentric study via the mailing of a questionnaire to the French photodermatology units to analyze all cases of patients with SU who were treated with IVIG.

Results: Seven patients (5 women) with a mean age of 40 years (range 32-55 years) and a mean disease duration of 5 years (range 2-10 years) received IVIG. The administration schedule differed from one patient to another: 1.4 to 2.5 g/kg were infused over 2 to 5 days. Five of 7 patients obtained a complete remission. The number of courses necessary to obtain clinical remission varied from 1 to 3 courses. Complete remission was maintained during 4 to more than 12 months but antihistamines were still required. In one case, psoralen plus ultraviolet A photochemotherapy was administered.

Limitations: Retrospective study design, limited number of patients, and variations in the IVIG administration schedule could limit the interpretation of the results.

Conclusion: Our case series suggests a beneficial effect of IVIG in severe SU but additional prospective trials including a larger number of patients are needed to demonstrate the effectiveness of IVIG and to specify the optimal modalities of their administration in this disease. (J Am Acad Dermatol 2011;65:336-40.)

Key words: intravenous immunoglobulins; solar urticaria.

Solar urticaria (SU) is a rare idiopathic photodermatosis induced after sun exposure. The incidence of SU is suggested to account for 0.4% of all cases of urticaria.[1] Most commonly SU appears during the third decade and preponderantly in women.[2] The symptoms are characterized by pruritus with erythema and wheals, developing on exposed areas usually within minutes, and lasting for minutes to hours when sun irradiation is discontinued. Although all sun-exposed areas can be involved, SU lesions are most frequently located on the V area of the neck and on the arms. Headache, dizziness, wheezing, nausea, and systemic collapse may occur when large areas of the body are exposed to sunlight for a long period of time. SU is a chronic

Abbreviations used:

IVIG:	intravenous immunoglobulins
MUD:	minimal urticarial dose
SFPD:	French Society of Photodermatology
SU:	solar urticaria
UV:	ultraviolet

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disease and can persist for more than 10 years.[3] This disorder can considerably restrict normal daily life and its management is extremely difficult when treatment with oral H1 antihistamines and sun avoidance are ineffective.[4]

Intravenous immunoglobulins (IVIG) are pure polyvalent antibodies mostly composed of IgG with small amounts of IgA and IgM that are derived from the pooled plasma of healthy donors. IVIG have been successfully used in the management of several dermatologic disorders including chronic urticaria.[5] We report the results of IVIG infusions in 7 patients with severe SU.

CAPSULE SUMMARY

- Solar urticaria is a rare idiopathic photodermatosis. Its management is extremely difficult when treatment with antihistamines and sun avoidance are ineffective.
- Seven patients with severe solar urticaria received intravenous immunoglobulins. Complete remission was achieved in 5 cases. In one patient, psoralen plus ultraviolet A was administered.
- Our case series suggests a beneficial effect of intravenous immunoglobulins in severe solar urticaria but additional prospective trials are needed to demonstrate the effectiveness of intravenous immunoglobulins.

METHODS

The study was performed by the French Society of Photodermatology (SFPD). The goal was to evaluate the effectiveness of IVIG in SU via a retrospective multicentric study. A questionnaire was mailed to all the SFPD members working in 21 different French photodermatology centers to report all cases of patients affected by severe SU who were treated with IVIG. Severe SU was defined as having a poor response to antihistamine use and impairment of the quality of life (impact on daily and professional life). Age, sex, medical history, medications, clinical features, photobiological characteristics, laboratory investigations, and clinical response to IVIG were collected.

RESULTS

Patient characteristics

Seven patients with severe SU received IVIG in France between August 1998 and July 2009. Three of these cases (patients 1-3) have been previously reported.[6-8] There were 5 female and 2 male patients with a mean age of 40 years (range 32-55 years). The mean SU duration before IVIG treatment was 5 years (range 2-10 years). The previous treatments were ineffective (Table I). All patients had a daily history of urticaria confined to sun-exposed areas occurring within seconds to minutes after sun exposure (including through glass) (Fig 1). On several occasions, headache, dizziness, and dyspnea were associated. Day-to-day outdoor activities were limited for all patients. Patients 2, 3, and 4 were declared unable to work. No photoactive medication was taken.

Laboratory investigations

In all patients, routine biochemical analysis and blood cell count were normal except in patient 3, who presented diabetes with hypertriglyceridemia. Serologic test for antinuclear antibodies produced negative findings. Anti-beta 2 glycoprotein 1 antibodies with type III mixed cryoglobulinemia were detected in patient 2.

Photobiological investigations

Phototesting was performed using a solar simulator (Dermolum UM-UW, Müller Elektronik, Moosinning, Germany) in patients 1 to 5: polychromatic spectrum including 95% ultraviolet (UV) A and 5% UVB, and UVA radiations were filtered with the WG 305 and 345 filters (Schott, Clichy, France) respectively. Patients 6 and 7 were tested with UVB source (Waldmann, Reischtett, France) and UVA high-pressure lamp (Dixwell, Lyon, France). For visible illumination, a slide projector emitting in 400 to 800 nm with a peak of 500 nm (Kodak, Rochester, NY) was used in patient 1. Results for eliciting spectra and minimal urticarial dose (MUD) are shown in Tables I and II, and Fig 2, *A*. Polychromatic (patients 1-5) and UVB (patients 6 and 7) minimal erythema doses were evaluated 24 hours after exposure in normal values.

Modalities of administration, effectiveness, and safety of IVIG in patients with SU

The details of treatment and outcome are set out in Table II. The administration schedule of IVIG differed from one patient to another with doses ranging from 1.4 to 2.5 g/kg infused over 2 to 5 days. The number of courses varied from 1 to 3 with different time lags between the infusions (2-9 months). Five of the 7 patients had a clinical complete remission of SU (71%) with dramatic MUD increase after IVIG (Table II, and Fig 2, *B*). Patient 2 was also treated with psoralen plus UVA photochemotherapy after the third course, because clinical improvement obtained with IVIG was only partial. Complete remission was maintained during 4 to more than 12 months. Antihistamines were still required, owing to the occurrence of pruritus after sun exposure when the treatment was forgotten. The improvement in the quality of life was noted with the possibility of outdoor activities.

Table I. Characteristics of patients before receiving intravenous immunoglobulins for solar urticaria

Patient	Sex/age, y	Medical history	Duration of SU, y	Previous medications for SU	Action spectrum of SU
1	F/55	Vasomotor rhinitis, asthma	3	Sunscreen use, carotenoid, antihistamines*, UVB then PUVA therapy + corticosteroid, hydroxychloroquine	polyC, UVA, visible
2	F/32	Antiphospholipid syndrome, stroke during pregnancy	2	Sunscreen use, antihistamines*, PUVA after UVA desensitization	polyC, UVA
3	M/41	Type 2 diabetes	5	Sunscreen use, antihistamines*	polyC, UVA
4	F/34		5	Sunscreen use, antihistamines*, PUVA, corticosteroid	polyC, UVA
5	F/37	Varicella myelitis	6	Sunscreen use, antihistamines*, hydroxychloroquine UVA desensitization	polyC, UVA
6	F/42		5	Sunscreen use, antihistamines*, UVA desensitization	UVA, UVB
7	M/41		10	Sunscreen use, antihistamines*, UVA desensitization	UVA, UVB

F, Female; *M*, male; *polyC*, polychromatic solar spectrum including 95% ultraviolet A and 5% ultraviolet B; *PUVA*, psoralen plus ultraviolet A; *SU*, solar urticaria; *UV*, ultraviolet.
*The following antihistamines were given alone or in combination and were inefficient: terfenadine, astemizole, fexofenadine, cetirizine, levocetirizine, loratadine, and desloratadine.

Fig 1. Patient 2 before intravenous immunoglobulin treatment. Widespread erythematous, papular, and pruriginous lesions on trunk through thin clothing and on arms appeared after sun exposure during short walk.

Patients 2 and 3 who were previously unable to work returned to their employment. As far as the patients who did not improve with IVIG are concerned, patient 5 declined further infusion after a single course and was not followed up. Patient 4 received 3 courses of 2 g/kg of IVIG repeated every 2 months without clinical improvement and without any modification of the MUD. He did not benefit either from plasmapheresis prescribed later. Regarding the side effects observed during IVIG administration, minor symptoms occurred such as transient headache (patients 2 and 5) and eczema (patient 2). Patient 6 experienced meningeal syndrome during the IVIG infusion and finally received 70% of the 2-g/kg initial planned dosage.

DISCUSSION

The pathogenesis of SU is still obscure. SU lesions are most frequently triggered by UVA or visible light and less commonly by UVB.[4] It is hypothesized that a provocative allergen derived from a chromophore localized in the skin is produced after an appropriate wavelength radiation, allowing recognition by specific IgE. The histamine-releasing activity could be secondary to the cross-linking of these IgE on mast cells IgE receptors.[9,10]

First-intention treatment of SU including H1-blocking antihistamines and sun avoidance may be sufficient in the majority of cases. Repeated phototherapeutic exposure with an UV artificial source could represent another therapeutic option when antihistamines are ineffective. Different types of desensitization phototherapy have been used such as broadband UVB, narrowband UVB, psoralen plus UVA, or UVA alone. The starting dose should be inferior to the MUD to avoid flare or syncope.[4] In very debilitating SU, systemic treatments have been

Table II. Intravenous immunoglobulin administration modalities and outcome in patients with solar urticaria

Patient	IVIG modalities administration	MUD before IVIG in J/cm^2 (action spectrum)	MUD after IVIG in J/cm^2 (action spectrum)	Clinical outcome	Treatment after IVIG
1	Sandoglobuline 2 g/kg (over 5 d) 3 courses: months 1, 3, 5	0.025 (UVA)	27 (UVA)	Complete remission; no relapse 1 y after third course	Antihistamines
2	Tegeline 2.5 g/kg (over 3 d) 3 courses: months 1, 5, 12	1 (UVA) 0.1 (polyC)	15.6 (UVA) 1.6 (polyC)	Complete remission; no relapse 1 y after third course	Antihistamines, PUVA after first course
3	Tegeline 2 g/kg (over 4 d) 1 course	0.9 (UVA) 2.13 (polyC)	13 (UVA) 10 (polyC)	Complete remission; no relapse after 1 y	Antihistamines
4	Sandoglobuline 2 g/kg (over 2 d) 3 courses: months 1, 2, 4	0.02 (UVA) 0.01 (UVB) <0.05 (polyC)	0.03 (UVA) 0.01 (UVB) <0.05 (polyC)	Unchanged	Plasmapheresis (inefficient), antihistamines
5	Tegeline 2 g/kg (over 3 d) 1 course	1 (UVA) 0.5 (polyC)	1 (UVA) 0.5 (polyC)	Unchanged after 1 mo: declined further infusion	Lost to follow-up
6	Tegeline 1.4 g/kg (over 3 d) 1 course	0.3 (UVA)	20 (UVA)	Complete remission; no relapse after 6 mo	Antihistamines
7	Tegeline 2 g/kg (over 3 d) 1 course	2 (UVA)	20 (UVA)	Complete remission; no relapse after 4 mo	Antihistamines

IVIG, Intravenous immunoglobulin; *MUD*, minimal urticarial dose; *polyC*, polychromatic solar spectrum including 95% ultraviolet A and 5% ultraviolet B; *PUVA*, psoralen plus ultraviolet A; *UV*, ultraviolet.

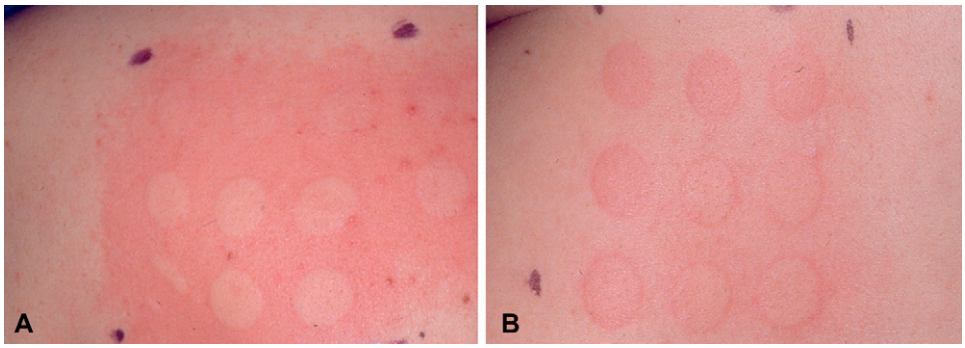

Fig 2. Polychromatic solar spectrum minimal urticarial dose (MUD) evaluations in patient 2 before and after treatment. **A,** Before intravenous immunoglobulin (IVIG) treatment, MUD value was decreased to 0.1 J/cm^2 with important urticarial reaction spreading out test area. **B**, One day after first course of IVIG, MUD value dramatically increased to 1.6 J/cm^2 with minimal urticarial reaction.

tested such as plasmapheresis,[11] extracorporeal photochimiotherapy,[12] or cyclosporine.[13]

IVIG are increasingly used to treat dysfunctional immune dermatosis.[5] Studies performed on patients with chronic urticaria[5] or delayed pressure urticaria[14] showed 20% to 50% of complete response. Sporadic cases of refractory SU successfully treated with IVIG have been previously reported,[6-8,15] including 3 of our patients.[6-8] Our report shows that of 7 patients affected with severe SU who have been treated with IVIG in France, 5 experienced a considerable improvement after 1 to 3 courses (71% complete remission rate) and remission has been maintained for more than 1 year in 60% of the responsive patients. A single infusion of IVIG afforded two patients a dramatic response. In two cases, IVIG were ineffective. The first patient did not respond to additional IVIG infusions, and the second one did not experience any improvement after a single course but did not receive any further treatment.

IVIG were usually well tolerated except in one patient who presented aseptic meningitis. The mechanisms of the action of IVIG in SU are not fully identified. The immunomodulatory activities of IVIG in SU could be similar to that in autoantibody IgG-mediated idiopathic thrombocytopenic purpura treated with IVIG and be based on a functional blockade of immunoglobulin Fc receptors secondary to saturation of Fc receptors by anti-idiotypic antibodies contained in IVIG.[5] In SU, immunoglobulin Fc saturation could avoid the fixation of the autoreactive IgE, specific for the provocative photoallergen, on mastocytes and prevent a consequent histamine release.[5]

The retrospective character of our series, the questionnaire-based study, the variations in the schedule of IVIG administration, and the small number of patients included in this study do not allow to draw out definitive conclusions regarding the effectiveness of IVIG in SU. Moreover, IVIG are expensive (average price €50/g). Nevertheless, the use of IVIG in SU can be considered when antihistamines are ineffective and quality of life is impaired. Additional prospective trials involving larger number of patient are required to demonstrate the effectiveness of IVIG in SU and to specify the optimal modalities of administration for this disease.

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