
Severe and refractory solar urticaria treated with intravenous immunoglobulins: A phase II multicenter study

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Background: Retrospective data have suggested the effectiveness of intravenous immunoglobulins (IVIG) for solar urticaria (SU).

Objective: We sought to prospectively assess the efficacy of IVIG for SU.

Methods: We conducted a multicentric phase II study to test the efficacy of a single course of IVIG (2 g/kg) in patients with severe and refractory SU. The primary outcome was remission of SU on phototesting at 12 weeks after IVIG treatment. Secondary objectives included clinical remission, improved quality of life, and 50% improvement in disease intensity as measured on a visual analog scale.

Results: Of the 9 patients who received IVIG injection, 2 showed remission of SU on phototesting, corresponding to a response rate of 22.2% (95% confidence interval 2.8%-60.0%). In all, 6 patients (67%) showed at least 1 response criterion after 4 weeks and 5 (56%) after 12 weeks. Response was maintained after 24 weeks for 2 patients and after 48 weeks for 1 patient. About half of the patients (56%) had moderate to severe headache.

Limitations: Lack of control arm and small number of patients are limitations.

Conclusion: A single course of IVIG appears insufficient to obtain prolonged significant control of SU; future evaluation of different schedules of IVIG administration is warranted. (J Am Acad Dermatol 2014;71:948-53.)

Key words: adverse events; aseptic meningitis; headache; intravenous immunoglobulins; minimal urticarial dose; phototesting; side effects; solar urticaria.

Solar urticaria (SU) is a rare idiopathic photodermatosis in which wheals develop on skin areas within minutes after exposure to ultraviolet (UV) or visible radiation.¹⁻³ Photobiological investigations usually confirm the diagnosis,

showing the rapid appearance of wheals after exposure to UVB, UVA, or visible light.³ Severe cases of SU can be associated with extracutaneous manifestations, such as bronchospasm, malaise, and systemic collapse.³ Moreover, daily life can be

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considerably restricted, particularly when first-line treatment with oral H1 antihistamines and sun protection are ineffective.⁴ In these latter cases, photodesensitization can be proposed. Anecdotal cases have shown the efficacy of cyclosporine, plasma exchange, photopheresis, or omalizumab.⁵⁻⁹

We recently reported the efficacy of intravenous immunoglobulins (IVIg) in a retrospective series of 7 patients with SU, with marked improvement in 5 (71%).¹⁰ We aimed to prospectively confirm these data.

METHODS

We conducted a phase II multicenter clinical trial of patients with severe and refractory SU; patients gave their signed informed consent to be in the trial (Comité de Protection des Personnes Est-II no. 10/570; EudraCT 2010-022071-54; NCT01360658).

Patients

To be included, patients had to fulfill the following criteria:

- Age between 18 and 65 years.
- Appearance of wheals within 15 minutes after sun exposure and lasting less than 2 hours in the shade.
- Wheals reproducible with phototesting: appearance after exposure to UVB, UVA, or visible light less than 30 minutes after exposure and lasting less than 2 hours.
- Severity criteria:
 - Very large effect on quality of life, with Dermatology Life Quality Index (DLQI) score greater than 10, and
 - At least 1 of the following: involvement of the face, SU eruptions throughout the year, extension of wheals on the nonphotoexposed skin, SU triggered by artificial light, SU flares accompanied by bronchospasm or syncope.
- Refractory criteria:
 - Resistance to photoprotection with broad-spectrum sunscreen with sun-protection factor 50 or higher, and
 - Resistance to administration of an association of 2 different antihistamines for 3 months or to photodesensitization.

Patients with contraindications to IVIg were excluded.

Photobiological investigations

Phototesting was a provocative measure and a way to determine the eliciting action spectrum and the minimal urticarial dose (MUD) necessary to evoke lesions. Phototesting was performed in each center as previously described.¹⁰

IVIg treatment

Patients received a single dose of IVIg (Clairyg, 50 mg/mL, LFB Biomedicaments, ATC Code J06BA02 [LFB Biomedicaments, Les Ulis, France]), 1 g/kg/d over 2 days (total dose received: 2 g/kg), with an initial infusion rate of 1 mL/kg/h during 30 minutes progressively increased to a maximum of 4 mL/kg/h in steps of 1 mL/

kg/h every 30 minutes. The dosage was tapered by 20% in patients with body mass index greater than 30 kg/m² as recommended (Summary of Product Characteristics for Clairyg, <http://agence-prd.ansm.sante.fr/php/ecodex/rcp/R0224132.htm>).

Evaluation

Evaluation criteria included the MUD, DLQI, disease activity (appearance or not of at least 1 SU flare during the 7 days before the in-clinic evaluation), and intensity of SU measured by a visual analog scale score ranging from 0 (no SU) to 10 (maximal conceivable intensity of SU).

The primary objective was the proportion of patients with SU remission at 12 weeks after treatment under the following experimental conditions:

- For SU triggered with UVA, no triggering of SU with a dose greater than 10-fold the baseline MUD, with an upper limit of 50 J/cm² corresponding to the UVA dose received during a 3-hour exposure in Paris in June.¹¹
- For SU triggered with UVB, no triggering of SU with a dose greater than 10-fold the baseline MUD, with an upper limit of 1.5 J/cm², corresponding to the UVB dose received during a 3-hour exposure in Paris in June.¹¹
- For SU triggered with visible light and with baseline MUD less than 5 minutes, no triggering of SU with a dose 5-fold or greater than the baseline MUD.

CAPSULE SUMMARY

- A retrospective series showed marked improvement in 71% of patients with solar urticaria treated with intravenous immunoglobulins.
- A single course of 2 g/kg intravenous immunoglobulin leads to clinical benefit in half of the patients; severe adverse events (headache) are frequent.
- Future evaluation of repeated courses of intravenous immunoglobulins, with close monitoring of safety, is needed.

Abbreviations used:

DLQI:	Dermatology Life Quality Index
IVIG:	intravenous immunoglobulins
MUD:	minimal urticarial dose
SU:	solar urticaria
UV:	ultraviolet

- For SU triggered with visible light and with baseline MUD between 6 and 10 minutes, no triggering of SU with a dose 3-fold or greater than the baseline MUD.
- For SU triggered with visible light and with baseline MUD greater than 10 minutes, no triggering of SU with a dose 2-fold or greater than the baseline MUD.

The secondary objectives were the proportion of patients:

- With SU remission under experimental conditions at 4 weeks after treatment.
- With SU having a small effect on quality of life (DLQI score <6) at 4 and 12 weeks after treatment.
- Achieving 50% improvement in SU intensity (visual analog scale score) at 4 and 12 weeks after treatment.
- Achieving clinical remission of SU at 4 and 12 weeks after treatment.

Patients with clinical benefit at 12 weeks after treatment, defined as obtaining at least 1 response criterion (remission of SU on phototesting, clinical remission of SU, DLQI score <6, or 50% improvement in SU intensity), were retained in the study, did not receive any other specific treatment for SU, and were evaluated again at 24 and 48 weeks after treatment.

Statistical analysis

A 1-stage Fleming design with a 1-sided type I error of 2.5% and power of 90% was used to test the hypothesis that the true response rate was at most 10% versus the alternative hypothesis that the true response rate was at least 60%. A sample size of 9 evaluable patients was needed.¹² The response rate was estimated with its 95% confidence interval.

RESULTS

Patient baseline characteristics

We included 10 patients from May 2011 to February 2013 (Table I). The spectrum of light action for SU was predominantly UVA (Table II). All patients had received from 2 to 5 different antihistamines, up to 4-fold the usual daily dose, without control of SU.

Table I. Patient baseline characteristics

<i>n</i>	10 Patients
Sex ratio, M/F	3/7
Mean age, y (range)	39.4 (23-58)
Mean duration of SU, mo (range)	50 (5-150)
SU throughout the year	8/10 (80%)
SU with facial involvement	9/10 (90%)
SU with involvement of photoprotected skin	7/10 (70%)
SU with systemic symptoms	7/10 (70%)
SU triggered by artificial light	1/10 (10%)
Mean baseline DLQI score (range)	14.2 (9-23)
Mean baseline SU intensity/VAS score (range)	8.3 (6-10)

DLQI, Dermatology Life Quality Index; F, female; M, male; SU, solar urticaria; VAS, visual analog scale.

Two patients had received antimalarial drugs, without efficacy, and UVA desensitization was unsuccessful in 1 patient. One patient (patient 3) had previously received a single course of 2 g/kg IVIG (Tegeline) with complete remission of SU for 6 months.

Treatment received

Of the 10 patients included, 9 received a single course of IVIG and 1 patient was lost to follow-up before any IVIG treatment.

Efficacy of IVIG

The efficacy of IVIG was evaluated in all 9 patients who received treatment at 4 and 12 weeks after the single course of IVIG. Two of the 9 patients (patients 6 and 7) showed remission of SU on phototesting at 12 weeks after IVIG (primary objective) (Table II), for a response rate of 22.2% (95% confidence interval 2.8%-60.0%). The response rate at 4 weeks after IVIG was also 22.2% (Table II).

The mean DLQI score was 7.9 (range 0-22) at 4 weeks and 9.1 (range 0-22) at 12 weeks after treatment; the mean visual analog scale score was 5.4 (range 2.1-10) at 4 weeks and 6.0 (range 1.4-10) at 12 weeks after treatment (Fig 1). The other outcomes are reported in Table III and in Supplementary Table I.

Overall, 6 patients (67%) achieved at least 1 response criterion at 4 weeks after IVIG treatment and 5 (56%) at 12 weeks after treatment (Table III and Supplementary Table I [available at <http://www.jaad.org>]). Therefore, 5 patients were followed up, but only 3 were re-evaluated at 24 weeks after treatment: 2 (patients 2 and 7) maintained efficacy (Supplementary Table I; available at <http://www.jaad.org>). These 2 patients were re-evaluated at

Table II. Evolution of the minimal urticarial dose after intravenous immunoglobulin administration in each patient

Patient	Minimal urticarial dose				
	Before IVIG (action spectrum)	4 wk after IVIG	12 wk after IVIG	24 wk after IVIG	48 wk after IVIG
1	0.7 J/cm ² (UVA) 90 mJ/cm ² (UVB)	6 J/cm ² 240 mJ/cm ²	6 J/cm ² 150 mJ/cm ²	-	-
2	1 mJ/cm ² (polyC) 0.4 J/cm ² (UVA)	1.25 mJ/cm ² 0.12 J/cm ²	4.6 mJ/cm ² 0.12 J/cm ²	1.56 mJ/cm ² 0.12 J/cm ²	1.56 mJ/cm ² 0.48 J/cm ²
3	12 J/cm ² (UVA) 4 min (visible)	20 J/cm ² 9 min	>30 J/cm ² >10 min	6.5 J/cm ² 2 min	-
4	0.2 J/cm ² (UVA)	0.55 J/cm ²	0.8 J/cm ²	-	-
5	<0.5 J/cm ² (UVA) <30 mJ/cm ² (UVB)	<0.5 J/cm ² <30 mJ/cm ²	<0.5 J/cm ² <30 mJ/cm ²	-	-
6	12 min (visible)	>60 min (visible)	40 min (visible)	-	-
7	20 J/cm ² (UVA)	>50 J/cm ²	>50 J/cm ²	30 J/cm ²	50 J/cm ²
8	20 J/cm ² (UVA)	20 J/cm ²	20 J/cm ²	-	-
9	107 mJ/cm ² (polyC) 0.5 J/cm ² (UVA)	157 mJ/cm ² 2 J/cm ²	182 mJ/cm ² 2 J/cm ²	-	-

IVIG, Intravenous immunoglobulin; polyC, polychromatic solar spectrum including 95% UVA and 5% UVB; UV, ultraviolet.

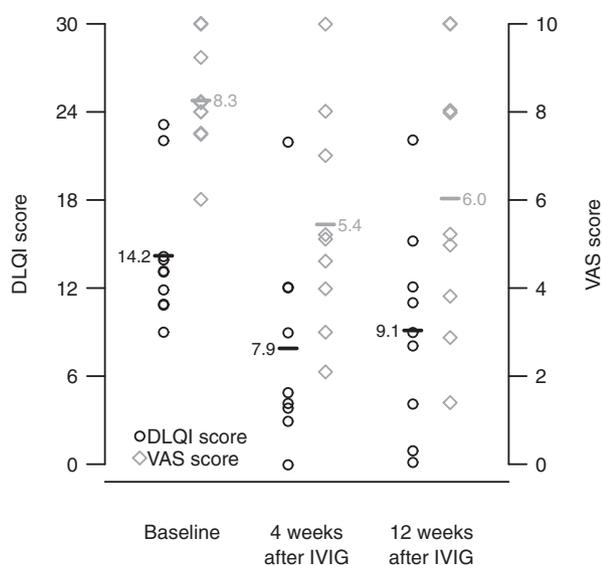


Fig 1. Evolution of quality of life (by the Dermatology Life Quality Index [DLQI]) and intensity of solar urticaria (by a visual analog scale [VAS]) at 4 and 12 weeks after intravenous immunoglobulin (IVIG) administration.

48 weeks after treatment. Patient 2 no longer showed response for any criteria, and patient 7 showed maintained SU remission on phototesting (Table II).

Safety of IVIG

In all, 8 of the 9 patients (89%) receiving IVIG treatment reported 18 adverse events, related or potentially related to IVIG administration according to the investigators' opinion and occurring less than 12 weeks after IVIG administration (Supplementary Table II; available at <http://www.jaad.org>). Six

events were considered severe (33%), 7 moderate (39%), and 5 weak (28%). All events resolved, without sequelae.

The most frequent adverse events reported were headache, occurring during the second day or during the 24 hours after IVIG administration in 5 patients (56%), graded as severe in 4 (80%), with the protocol of IVIG administration adequately applied in all cases. In 1 patient, headache lasted for 13 days, with inability to work for 11 days. In 2 patients, prolonged hospitalization or re-hospitalization was required because of the intensity of headache and accompanied by vomiting. Another patient required hospitalization 24 hours after IVIG infusion because of aseptic meningitis that was confirmed by lumbar puncture.

Skin or mucosal reactions were frequent (44% of treated patients): 2 patients showed eczema, 1 and 4 days after IVIG administration; 1 patient had oral aphthous stomatitis flare 1 day after treatment; and 1 patient had dyshidrosis and psoriasiform eruption 8 days after treatment.

DISCUSSION

Because of its immunomodulatory properties, IVIG treatment has been used for several autoimmune or inflammatory dermatologic disorders, including idiopathic chronic urticaria or pressure-delayed urticaria, with 20% to 50% of patients achieving complete remission.^{13,14} Regarding SU, 12 patients have received IVIG: 7 were reported in our pivotal national retrospective survey¹⁰ and the remainder as small series of 2 patients or as isolated cases.¹⁵⁻¹⁷ The schedule of administration of IVIG

Table III. Response to intravenous immunoglobulins, 4 and 12 weeks after treatment

Response criteria	Wk 4	Wk 12
1. Remission of SU on phototesting	2/9 (22.2%)	2/9 (22.2%)
2. Clinical remission of SU	4/9 (44.4%)	2/9 (22.2%)
3. DLQI score <6	5/9 (55.6%)	3/9 (33.3%)
4. VAS 50	3/9 (33.3%)	4/9 (44.4%)
5. ≥ 1 of the above criteria	6/9 (66.6%)	5/9 (55.6%)

DLQI, Dermatology Life Quality Index; SU, solar urticaria; VAS 50, visual analog scale score of 50 (50% improvement in SU intensity).

varied. The median number of courses was 2 (range 1-6), with the median dose administered 2 g/kg (range 1.4-2.5 g/kg) and infused over a median of 3 days (range 2-5 days). Complete remission of SU was achieved in 8 of 12 patients (67%), lasting from at least 4 months to more than 4 years, with partial improvement of SU in 2 (17%).^{10,15,16} Finally, only 2 patients did not show any clinical and/or photobiological improvement (17%).¹⁷ The mechanism of action of IVIG in SU is unclear. SU could result from production, after UV radiation, of a skin chromophore, acting as a provocative allergen recognized by a specific IgE, and IVIG could act by blocking the fragment crystallizable (Fc) receptors of this IgE, thus preventing its fixation on mast cells and histamine release.¹⁰

We sought to confirm these results by conducting a multicenter prospective clinical trial, with a homogenous IVIG treatment schedule, to evaluate the benefit/risk balance of such treatment for SU. Because in our pivotal series,¹⁰ prolonged complete remission of SU, lasting for more than 12 weeks, was achieved with a single IVIG infusion in 3 of 7 patients, we tested the efficacy of a single course of 2 g/kg IVIG. For an evaluation not biased by the variability of the natural UV exposure inherent to the season or the weather, we chose the rate of patients with SU remission on photobiological explorations as the primary objective. The photobiological objectives were stringent, corresponding to a UV exposure without SU flare equivalent to a 3-hour exposure to sun.

The primary outcome was not achieved because we observed remission of SU on phototesting in only 2 patients. Nevertheless, we observed clinical benefits, consisting mostly in improved quality of life and decreased severity of SU, in two thirds of the patients at 1 month and in more than half at 3 months, with 2 patients still benefiting from the treatment at 6 months and 1 benefiting after 1 year.

The different IVIG treatment schedule may explain the disagreement between our results and previous retrospective studies.¹⁰ As well, our primary outcome

was stringent and not clinically relevant and the response rates for secondary objectives were much higher and relevant in terms of clinical efficiency. We observed a loss of efficacy starting at 4 weeks after the IVIG course, which reintroduces the question of the optimal therapeutic schedule and suggests that a single IVIG infusion could be insufficient to obtain an important and durable control of SU. Thus, repeated IVIG administrations every 3 to 4 weeks, as prescribed for other autoimmune diseases, deserve further consideration for severe SU.

These results must also be examined in view of the poor tolerance we observed. Indeed, about half of the patients had severe headache, including aseptic meningitis in 1 case, usually starting the second day of IVIG infusion or the day after. Headache is considered a frequent side effect of IVIG, occurring in more than 1 patient treated among 10 (Summary of Product Characteristics for Clairyg, <http://agence-prd.ansm.sante.fr/php/ecodex/rcp/R0224132.htm>) and the frequency of aseptic meningitis has been estimated to affect up to 11% of patients in a series of 54 patients with various autoimmune disorders treated with IVIG.¹⁸ Nevertheless, we were surprised by the high frequency of headache in our limited series, because the rate of infusion and the dosage of IVIG strictly followed the recommendations of the French national health authority. Because the manufacturing process and the final composition may differ among IVIG products, the high frequency of severe adverse events may be linked to the Clairyg (LFB Biomedicaments, Les Ulis, France) product itself, because not all IVIG preparations are equally tolerated.¹⁹ Nevertheless, recent studies of in vitro and in vivo properties of different IVIG preparations have suggested a favorable profile of Clairyg (LFB Biomedicaments, Les Ulis, France) as compared with other products, with, for example, a low concentration of prothrombotic factors XI and XII.²⁰ Moreover, a previous study suggested that aseptic meningitis developed independently of the type of commercial preparation or the infusion rate and that the only risk factor identified so far was migraine,¹⁸ which was indeed present in the history of 1 of our patients who showed severe headache. Finally, we cannot exclude that patients with SU may be susceptible to severe headache and aseptic meningitis induced by IVIG. Indeed, in the retrospective series of 7 patients with SU treated with IVIG, 1 patient showed aseptic meningitis and 2 patients showed headache.¹⁰

Altogether, a single course of IVIG was followed by clinical benefit during 3 months in more than half

of the patients with severe and refractory SU but seemed insufficient for complete and prolonged remission, which suggests the need to further test the efficacy of repeated courses of IVIG, while keeping in mind a potential poor tolerance to IVIG in these patients.

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Supplementary Table I. Detailed response criteria achieved at weeks 4 and 12 weeks after intravenous immunoglobulin administration in patients

Patient	Wk 4				Wk 12			
	Remission of SU on phototesting	Clinical SU remission*	VAS 50	DLQI score <6	Remission of SU on phototesting	Clinical SU remission*	VAS 50	DLQI score <6
1	No	Yes	No	No	No	No	No	No
2	No	No	No	No	No	No	Yes	No
3	No	Yes	Yes	Yes	No	Yes	No	Yes
4	No	No	No	No	No	No	No	No
5	No	No	No	No	No	No	No	No
6	Yes	No	Yes	Yes	Yes	No	Yes	Yes
7	Yes	No	No	Yes	Yes	Yes	Yes	Yes
8	No	Yes	No	Yes	No	No	No	No
9	No	Yes	Yes	Yes	No	No	Yes	No

DLQI, Dermatology Life Quality Index; SU, solar urticaria; VAS 50, visual analog scale score of 50 (50% improvement in SU intensity).

*During the previous 7 d.

Supplementary Table II. Adverse events related or potentially related to intravenous immunoglobulins, according to the investigators' opinion, with corresponding grading severity

Adverse event	Grade 1 (weak)	Grade 2 (moderate)	Grade 3 (severe)	No. of patients
Headache	0	1	4	5
Skin or mucosal reaction*	2	2	0	4
Nausea/vomiting	0	1	1	2
Fever	0	2	0	2
Aseptic meningitis	0	0	1	1
Hypotension	1	0	0	1
Vertigo	1	0	0	1
Chills	0	1	0	1
Fatigue	1	0	0	1

*Eczema, dyshidrosis, psoriasiform eruption, or aphthous.