

DR IGOR SNAST (Orcid ID : 0000-0002-7126-2193)

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Real-life experience in the treatment of solar urticaria: retrospective cohort study

I. Snast^{1,2}, M. Lapidoth^{1,2}, V. Uvaidov^{1,2}, C.D. Enk³, S. Mazor⁴, E. Hodak^{1,2} and A. Levi^{1,2}

¹Photodermatosis Clinic, Department of Dermatology, Rabin Medical Center – Beilinson Hospital, Petach Tikva, Israel

²Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

³Department of Dermatology, Hadassah-Hebrew University Medical Center, Jerusalem, Israel

⁴Department of Community Dentistry, School of Dental Medicine, Hebrew University-Hadassah Medical Center, Jerusalem, Israel

Correspondence: Assi Levi, MD

E mail: docalevi@gmail.com

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Key words: antihistamines, leukotriene receptor antagonist, omalizumab, photoprovocation, solar urticaria

What is already known about this topic

- The treatment of solar urticaria, a rare inducible urticaria caused by light exposure, may be challenging.

What this study adds

- This study shows that complete remission of symptoms can be achieved in most patients with solar urticaria under treatment with antihistamines and a leukotriene receptor antagonist tailored to the degree of photosensitivity, followed by omalizumab in refractory cases.

ABSTRACT

Background: Solar urticaria (SU) is a rare photodermatosis causing a significant impact on patients' quality of life. Treatment is often challenging. This study presents our clinical experience with a tailored stepwise therapeutic approach.

Methods: A retrospective cohort design was used. Patients with suspected SU underwent laboratory work-up and photoprovocation. Those with a high minimal urticaria dose (MUD) were treated with a single antihistamine (protocol 1), and those with a lower MUD received three types of antihistamines (protocol 2); both protocols included a leukotriene receptor antagonist (LRA). In cases of failure, treatment was switched to omalizumab < 300 mg with incremental dosage increases as necessary (monthly dose range, 150-600 mg). Symptom relief and photoprovocation under treatment were evaluated.

Results: Thirty patients (10 men, 20 women) were included. Most (87%) were sensitive to visible light (1-70 J/cm²) with or without extension to UVA. Twenty-one patients opted for

our stepwise approach: 22 achieved complete remission on protocol 1/2 (n=17) or after switching to omalizumab (n=5), and 1 achieved partial remission under omalizumab. There were no treatment-related severe adverse effects.

Conclusions: Symptoms of SU can be well controlled by treatment with antihistamines and a LRA tailored to the degree of photosensitivity, followed by omalizumab in refractory cases. This has important implications for patients' quality of life.

INTRODUCTION

Solar urticaria (SU) is a rare type of physical urticaria characterized by the presence of typical urticaria lesions that appear within minutes after exposure to light and resolve over several hours.¹ Most commonly, the action spectrum of SU is within the visible light range (400-700 nm), sometimes with extension to UVA (320-400 nm) and infrequently to UVB (280-320 nm).²

Treatment recommendations are based on retrospective studies and small case series. They include broad-spectrum sunscreens, antihistamines, leukotriene receptor antagonist (LRA), UV phototherapy (hardening), azathioprine, ciclosporine, intravenous immunoglobulins, and omalizumab.³⁻⁸ Some patients have to completely avoid outdoor activities, severely impacting their quality of life and highlighting the importance of effective treatment.

In the present study we present our experience in treating patients with SU. A stepwise approach was used with the administration of antihistamines, a LRA, and omalizumab according to disease severity and treatment's response.

PATIENTS AND METHODS

A retrospective cohort design was used. We included patients with a history of SU that were seen at the photodermatosis clinic of a tertiary medical center between 2013 and 2018.

Inclusion criteria were the development of urticaria within 1 hour of sunlight exposure and a positive photoprovocation. None of the SU patients was excluded from the cohort.

Laboratory work-up

Baseline laboratory work-up in all cases consisted of complete blood count, kidney and liver function tests, erythrocyte sedimentation rate, C-reactive protein level, thyroid function tests, antinuclear antibodies, anti-RO, and anti-LA, and porphyrin levels in blood and stool and on 24 h urine collection.

Photoprovocation and minimal urticaria dose

Photoprovocation testing was performed as previously described.⁹ Briefly, 2*2 cm² of exposed skin on the back was exposed to 50 J/cm² of visible light, 20 J/cm² of UVA, and 0.03 J/cm² of broadband UVB in a single session. The minimal urticaria dose (MUD) was defined as the lowest dose that caused a minimally perceptible urticaria after irradiation. After establishment of the relevant action spectrum, MUD was determined by decreasing fluencies in a stepwise manner until a dose not provoking urticaria was reached (for instance: in case of visible light induced SU sequential photoprovocations at 40J/cm², 30J/cm², 20 J/cm² etc. took place until urticaria could not be induced).

Treatment regimens

Patients were assigned a therapeutic regimen consisting of a combination of antihistamine(s) and LRA tailored to their degree of photosensitivity.

Protocol 1: desloratadine 5 mg or fexofenadine 180 mg BID and montelukast 10 mg QD;

Protocol 2: desloratadine 5 mg BID, fexofenadine 180 mg BID, cetirizine HCl 10 mg BID, and montelukast 10 mg QD. All patients in protocol 2 used the three stated types of antihistamines.

Patients with a high MUD value on photoprovocation (visible light $>30 \text{ J/cm}^2$ or UVA $>5 \text{ J/cm}^2$) or isolated UVB sensitivity unresponsive to broad-spectrum sunscreens were categorized as having mild photosensitivity and received treatment with protocol 1. Patients with low MUD values (visible light $\leq 30 \text{ J/cm}^2$ or UVA $\leq 5 \text{ J/cm}^2$) indicating severe photosensitivity received treatment with protocol 2. Patients were followed approximately 4 weeks after initiation of treatment. Treatment not enabling patients to remain free or almost free of symptoms outdoors was defined as failure. Patients who failed to improve on protocol 1 were switched to protocol 2. Patients who failed to improve on protocol 2 were switched to omalizumab. The initial dose of omalizumab in children and adults ranged between 75 to 150 mg and 150 to 300 mg once every 4 weeks, respectively. Patients who failed to improve received incremental dosage increases. The monthly doses ranged from 150 to 600 mg. In patients with a complete remission, attempts were made to increase omalizumab treatment intervals without affecting efficacy. As sunscreens failed to control symptoms in all but one patient prior to arrival to our clinic (chemical sunscreens 21; physical sunscreens 16; both 7 patients), they were not part of the recommended therapeutic protocol.

Statistical analysis

To assess the influence of atopic background, initial protocol used and action spectrum to treatment's outcome, bivariate analysis was performed using the Fisher's exact test. Mann Whitney test was used to assess correlation between duration of urticaria and treatment success or spontaneous remission. Likelihood ratio was used to assess correlation between MUD or presence of UVA sensitivity and treatment success.

RESULTS

Seventy patients had a suspected diagnosis of SU. Following evaluation, the final diagnosis was photo-aggravated dermatosis in 21 patients, polymorphic light eruption in 6, allergic photo-contact dermatitis in 6, and erythropoietic protoporphyria in 1. Six patients failed to complete evaluation. The remaining 30 patients were diagnosed with SU and formed our cohort. One patient was also diagnosed with allergic photo-contact dermatitis. None of the patients had remarkable and/or significant changes in laboratory tests. The demographic and clinical data are shown in Table 1.

There were 20 women and 10 men of median age 20 years (range 4-72 years) at onset of SU, and the median duration of disease prior to diagnosis was 3 years (range 0.2-25 years). Six patients (20%) had a background of atopic disease. All patients but one had unsuccessfully tried to control the symptoms with standard-dose (81%) or high-dose (15%) antihistamines, followed by LRA (11%), systemic steroids (7%), rush UVA1 hardening (4%), and hydroxychloroquine (4%).

Minimal urticaria dose

The photoprovocation test yielded mild photosensitivity in 22 patients (73%) and severe sensitivity in 8 (27%). Twenty-six patients (87%) were sensitive to visible light (median MUD 50, range 1-70 J/cm²); 11 (37%) were sensitive to UVA (median MUD 10, range 1-20 J/cm²); and 4 (13%) were sensitive to UVB (median MUD 0.03; range 0.02-0.06 J/cm²). Seventeen patients (57%) had isolated visible light sensitivity, and the remainder had sensitivity to both visible light and UVA (27%), isolated UVA sensitivity (3%), isolated UVB sensitivity (7%), or sensitivity to all light spectra (3%).

Clinical outcomes

Two patients (case nos. 20 and 24) experienced complete remission without treatment. Four patients (case nos. 12, 14, 21, 28) declined treatment because the disease (isolated UVB

sensitivity) was appropriately controlled with sunscreen alone (1 patient) or a change in lifestyle was taken (night work, sunlight avoidance) that reduced sun exposure (3 patients).

One patient (case no. 6) was lost to follow-up.

The remaining 23 patients received stepwise treatment at our clinic. Thirteen patients were started on protocol 1 and 10 on protocol 2. Complete remission was achieved in 17 (74%) under a combination of antihistamine(s) and LRA (protocol 1, 12 patients; protocol 2, 4 patients; protocol 1 followed by protocol 2, 1 patient). We found no correlation between absence/presence of UVA sensitivity and response to treatment ($p=0.89$; results persisted when stratified by type of protocol). Likewise no correlation was found between VL MUD ≤ 30 or $> 30 \text{ J/cm}^2$ ($p=0.36$), or duration of SU ($p=0.38$) and treatment response. However, complete response to treatment was more likely in patients with less severe photosensitivity in whom protocol 1 was used rather than in patients with more severe photosensitivity on protocol 2 ($p<0.05$).

In the 6 patients who failed on protocol 2 treatment was switched to omalizumab. During a median follow-up period of 9 months (range, 2-39 months), 5 patients achieved complete remission and 1 patient achieved mild partial remission under omalizumab (monthly range 150-600 mg). The response to omalizumab at adequate dosage was prompt, and patients reported significant relief from symptoms within the first 2 months of treatment. Two patients (case nos. 5 and 11) required monthly doses $> 300 \text{ mg}$ to achieve complete clinical response. All patient continued omalizumab treatment to control symptoms, except patient 5 who experienced mild partial remission and declined incrementing dosage, and after 6 months of treatment ceased it altogether. No adverse effects were reported during omalizumab treatment. Of note, out of the 6 patients treated with omalizumab 5 had an atopic background (83% compared to 20% in the entire study population).

Follow-up photoprovocation, performed in 11 patients who achieved complete remission, yielded negative findings in 9 and an increase in MUD in 2.

Three patients in whom symptoms were successfully controlled with combined antihistamines and LRA discontinued treatment without disease relapse (case nos. 3, 8 and 9). Overall, during a median follow-up period of 17 months (range 7-72 months), 5 patients (17%) experienced disease resolution enabling treatment cessation. The median duration of SU in these 5 patients was 2.8 years (range 1-15.3) and no correlation between duration of SU and spontaneous remission was found ($p=0.49$).

DISCUSSION

Our study of 30 patients with SU shows that complete clinical remission with a return to normal outdoor activity can usually be achieved with a stepwise therapeutic approach based on a combination of antihistamine(s) and a LRA, followed by omalizumab in refractory cases.

Only 1 patient in our series had a concomitant photodermatosis (allergic photo-contact dermatitis). Additionally, none of the 40 excluded patients with other photodermatoses had SU. Although Beattie et al.¹⁰ found coexistent polymorphic light eruption in 23% of 87 patients with SU, others reported a low prevalence of concomitant photodermatoses in accordance with our findings.¹¹

The wavelength that triggers SU varies by geographic and ethnic background.¹² In our study, 87% of patients had sensitivity to visible light either alone or in association with UVA or UVB, and only 10% displayed UVB sensitivity. Although one study from France found that UVA was the most common action spectrum in SU,¹³ other studies from Europe and Asia reported that 70%-90% of patients were sensitive to visible light with or without UVA, similar to our findings.^{10,14} It is conceivable that patients with isolated UVB sensitivity were

less likely to seek treatment or to be referred to a tertiary center because their disease could be managed with broad-spectrum sunscreens (as was seen in patient 21). Thus, selection bias toward patients with recalcitrant disease may account for the low prevalence of UVB sensitivity seen in our cohort.

The treatment of SU may be challenging. In the largest study to date of 224 patients, treatment consisted mostly of antihistamines and/or UV hardening, and only about one-fourth of the patients experienced complete symptom resolution.¹¹ UV hardening, though a popular option in the literature, is not covered by medical insurance in Israel, so it is not routinely available to patients, and medical personnel trained in the procedure are lacking. The present study is an expansion of our previous preliminary report describing a specifically tailored combination treatment of antihistamines and a leukotriene antagonist among 8 patients.¹⁵ The patients underwent photoprovocation to determine MUD values and were subsequently classified by degree of photosensitivity. Those with high MUD values (mild sensitivity) were initially treated with a single antihistamine, and those with lower MUD values (severe sensitivity) were treated with three types of antihistamines. The antihistamines were administered together with a LRA. Because of the Israeli regulatory restrictions, we were unable to adopt the European guidelines for the treatment of chronic spontaneous urticaria which recommend up to fourfold up-dosing of the same single antihistamine in severe cases.^{16,17} By using a combination of different types of antihistamines, we could administer a therapeutic dose that was sufficiently high while not exceeding the maximal recommended dose for each drug.

We found that patients with less severe photosensitivity compared to patients with more severe photosensitivity were significantly more likely to control disease with combination treatment with antihistamines and leukotriene antagonist. Thus, photoprovocation has not only diagnostic but also therapeutic significance. Additionally, although presence of UVA

sensitivity and MUD of VL were not significantly correlated with treatment success, larger studies may find these factors to have prognostic significance as well. Of note, two patients (case nos. 7 and 25) who experienced complete clinical response demonstrated only mild increment in MUD following treatment, suggesting that in some patients the relationship between MUD increment and the clinical response is not linear. Overall, 17 of the 23 (74%) patients treated by our protocols achieved a complete clinical response, supporting the efficacy of this approach. Importantly, none had severe adverse effects, although approximately 75% experienced short-lived (up to 7 days) drowsiness and tiredness.

The patients who failed to improve under treatment with antihistamines and a LRA were given omalizumab in incremental dosages, to a dosage above the standard (>300 mg) when necessary. In a recent systematic review by members of our group, of 48 patients with antihistamine-refractory SU, 38 (79%) achieved clinical improvement with omalizumab.¹⁸ Similarly, symptoms were completely alleviated, with no side effects, in 5 of the 6 omalizumab-treated patients in our cohort (83%), including 2 who received a higher-than-standard dosage.

In all, 22 of the 23 (96%) patients who underwent our stepwise therapeutic approach achieved complete remission. The outcome was objectively verified by increased MUDs or lack of photosensitivity on repeated photoprovocation.

Previous studies of SU reported a female predominance and highest rate of occurrence in the third and fourth decades of life.^{10,11} Accordingly, two-thirds of our cohort was female and the median patient age was 25 years. The reported prevalence of atopic disorders in patients with SU ranges widely among studies, from 0 to 48%.^{19,20} We found that 20% of patients had an atopic background, similar to other studies conducted in Mediterranean countries (Spain, Greece).^{11,21} Interestingly, we found that patients with atopic background were significantly less likely to respond to the combination of antihistamines and anti-

leukotriens irrespective of the initial protocol used. Thus, it is possible that atopic background predicts unfavorable response to antihistamines and LRA. Larger studies are required to validate this observation.

In the largest study of patients with SU, the probability of resolution after one year of follow-up was 23%.¹¹ In our cohort, 5 of 30 patients (17%) experienced complete resolution of symptoms and were able to discontinue treatment during a median follow-up period of 17 months.

Our study's main limitations include a retrospective design and due to the rarity of this condition a relatively small sample size.

In conclusion this study demonstrated that complete remission of symptoms can be achieved in most patients with SU under treatment with antihistamines and a LRA tailored to the degree of photosensitivity, followed by omalizumab in refractory cases.

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TABLE 1 Epidemiological, clinical and therapeutic response

Pt. no.	Sex/age	Duration prior diagnosis (yrs)	Photo-provocation, MUD prior treatment (J/cm2)			Protocol (months)	Clinical outcome	Spontaneous remission (months after diagnosis)	Follow-up period (months)	Photo-provocation, MUD after treatment (J/cm2)		
			UVA	VL	UVB					UVA	VL	UVB
1*	F/10	0.3	No response	50	No response	2 then Oma (19)	Complete remission	No	29	-	No response (50) [£]	-
2	F/29	0.6	10	30	No response	2 then Oma (9)	Complete remission	No	26	-	No response (50) [£]	-
3*	M/36	14	No response	50	No response	1	Complete remission	Yes (3)	16	-	-	-
4	F/18	10	No response	50	No response	1	Complete remission	No	27	-	-	-
5	F/30	0.2	2	1	No response	2 then Oma (6)	Partial remission	No	13	-	-	-
6	F/40	4	No response	50	No response	1	LTF	LTF	LTF	-	-	-
7*	M/40	7 ^y	No response	50	No response	Oma (9)	Complete remission	No	15	-	No response (50) ^{£†}	-
8	F/72	0.5	10	50 [†]	No response	1	Complete remission	Yes (18)	28	-	-	-
9	M/20	0.8	No response	50	No response	1	Complete remission	Yes (3)	13	-	No response (50) [£]	-
10	F/31	3	No response	50	No response	1	Complete remission	No	17	-	-	-
11	M/6	1.5	No response	30	No response	2 then Oma (39)	Almost complete remission	No	48	-	No response (50) [£]	-
12	M/18	3	No response	No response	0.06	Declined (only sunscreen)	No remission (good control)	No	44	-	-	-
13	F/28	4 ^y	10	50	No response	Oma (2)	Complete remission	No	8	-	-	-
14	F/59	25	10	50	No response	Declined	No remission	No	48	-	-	-
15	F/22	6	No response	No response	0.02	1	Almost complete remission	No	49	-	-	-
16	F/18	4	10	No response	No response	1	Complete remission	No	43	-	-	-
17	F/61	2	No response	50	No response	1 then 2	Complete remission	No	16			

18	F/7	3	No response	30	No response	1	Complete remission	No	7	-	40	-
19	F/32	3	No response	70	No response	1	Complete remission	No	12	-	No response (70) [£]	-
20	M/60	5	20	50	No response	None	Complete remission	Yes (6)	12	-	-	-
21	M/21	0.9	No response	50	No response	Declined	No remission	No	72	-	-	-
22	F/10	0.9	1	50	No response	2	Complete remission	No	18	20	No response (50) [£]	No response
23	F/20	1.5	No response	30	No response	2	Complete remission	No	12	-	-	-
24	F/34	0.2	No response	50	No response	None	Complete remission	Yes (3)	9	-	-	-
25	F/24	0.9	No response	30	No response	2	Complete remission	No	18	No response	40	No response
26	F/25	5	No response	50	No response	1	Complete remission	No	30	No response	No response (50) [£]	No response
27	M/16	0.5	3.8	50	0.03	2	Complete remission	No	36	12	No response (50) [£]	No response
28	M/13	3	No response	50	No response	Declined	No remission	No	9	-	-	-
29	M/41	31	10	50	No response	1	Complete remission	No	11	-	-	-
30	F/17	3	10	No response	0.03	1	Complete remission	No	11	-	-	-

AL, antileukotriene; CS, systemic corticosteroids; HAH, high-dose antihistamine; LTF, lost to follow-up; MUD, minimal urticarial dose; Oma, omalizumab; NA, not available;

NR, no response; SAH, standard-dose antihistamine; Tx, treatment; UV, ultraviolet; VL, visible light

*Patient underwent photo-provocation while being treated with AH.

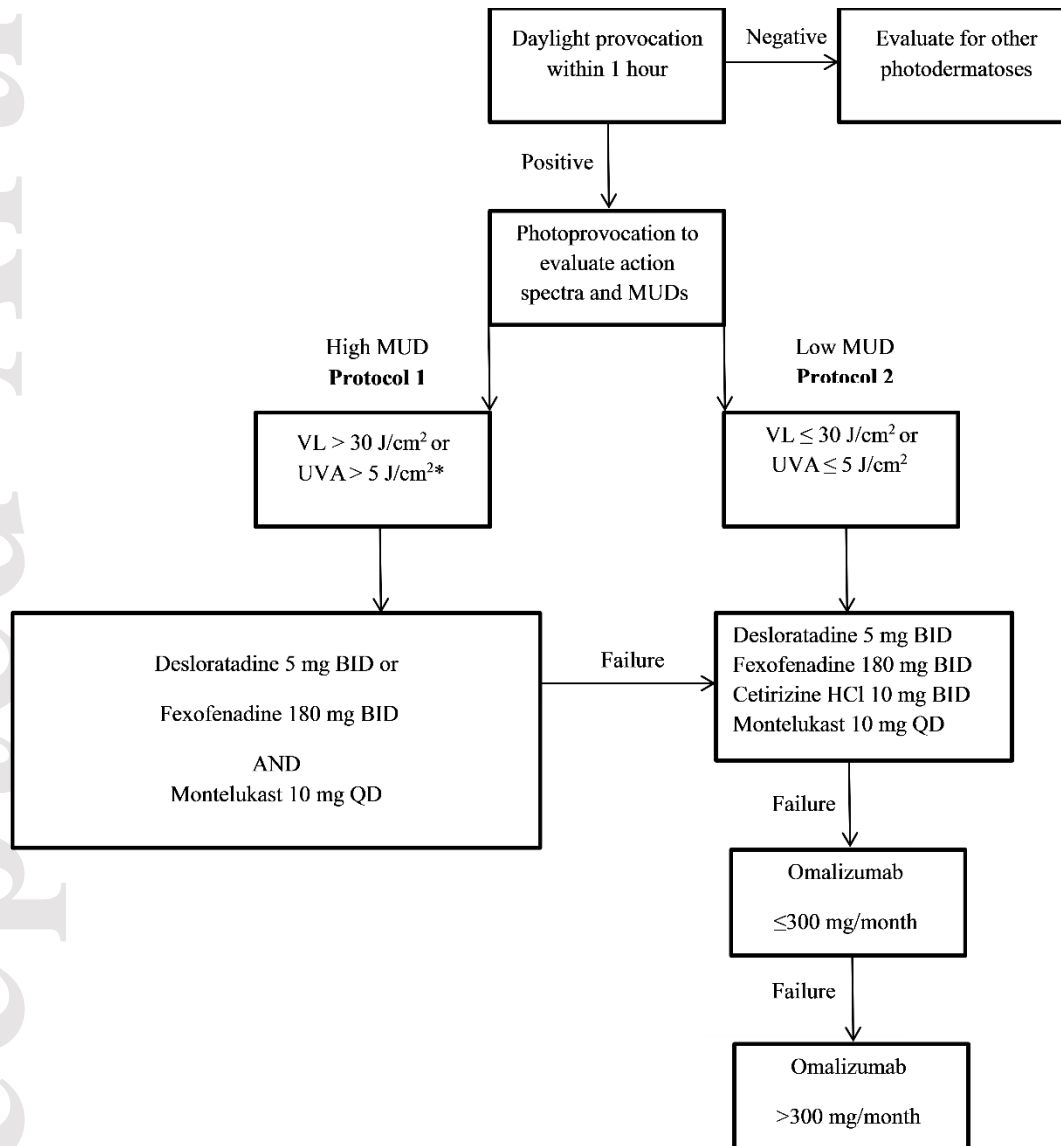
†Mild erythema.

‡Prior diagnosis patient was treated unsuccessfully with high-dose antihistamine and antileukotriene equivalent to protocol 2.

£Number in bracket refers to the maximum dose tested.

Legend to Figure

Fig. 1 Algorithm for the evaluation and treatment of patients with SU



*Patients with isolated UVB sensitivity receive treatment with protocol 1