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Treatment of solar urticaria using antihistamine and leukotriene receptor antagonist combinations tailored to disease severity

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

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Abstract

Background: Solar urticarial (SU) is characterized by erythema, whealing and/or pruritus occurring minutes after sun exposure. Treatment is difficult and often unsatisfactory.

Objectives: To determine the action spectra and minimal urticaria dose (MUD) and to tailor a treatment regimen graded according to disease severity in a series of patients with SU.

Patients and methods: Eleven patients (7 females, 4 males, age range: 5-60 years) with a clinical history suggestive of SU, verified by photo-provocation tests to UVA, visible light and/or UVB were treated with various combinations of antihistamines and leukotriene receptor antagonist.

Results: All patients were sensitive to visible light (median MUD 50 J/cm²). Three patients were sensitive to UVA (median MUD 3.75 J/cm²) and one patient was sensitive to UVB (MUD of 0.03 J/cm²). Two patients experienced a spontaneous remission without treatment. One patient declined treatment. The remaining 8 patients were managed by a combination of antihistamines (desloratidine, fexofenadine, cetirizine HCl) and a leukotriene receptor antagonist (montelukast). Seven out of the 8 patients experienced a sustained remission of symptoms and signs following treatment.

Conclusions: Photo-provocation for SU with determination of action spectra and MUD enables specifically tailored treatment regimens consisting of combinations of antihistamines and leukotriene receptor antagonist.

INTRODUCTION

Solar urticaria (SU) is a photodermatosis characterized by sudden onset of transient erythema, whealing and/or pruritus on sun exposed areas occurring during or minutes after sun exposure (1). Though SU appears to be rare, the exact incidence is unknown (2-3). The action spectrum for SU includes ultraviolet A (UVA), visible light and infrequently UVB (4). Patients may be sensitive to one or more action spectra and the spectrum might change within a single individual during the course of illness (5). Treatment modalities include broad spectrum sunscreens (6), antihistamines (6), leukotriene receptor antagonists (7), cyclosporine (8), anti-malaria medications (9), anti-IgE antibody (Omalizumab) (10), intravenous immunoglobulins (11) and UV hardening (12).

We here present our treatment experience of 11 patients with SU using a treatment protocol consisting of combinations of antihistamines and leukotriene receptor antagonists graded according to the severity of the condition.

PATIENTS AND METHODS

Patients

All patients were referred to our clinic during March 2012 – December 2013 with a history of urticaria following sun exposure.

Inclusion criteria: Development of urticaria within 1 hour of supervised exposure to natural sunlight in the hospital garden. All patients had unsuccessfully tried broad-spectrum sunscreens and standard dosage of one antihistamine medication to control symptoms. Patient 2 took prednisone 40 mg daily for one month with no effect and patient 1 had tried UVA rush hardening (12) resulting in only short-lived relief of symptoms.

Diagnostic procedures

Photo-provocation: Photo-provocation with the purpose of inducing an urticarial lesion (figure 1) mimicking the clinical complaint was performed by exposing 2 x 2 cm² skin areas of the back to a single exposure to 20 J/cm² of UVA1, 0.03 J/cm² of broad-band UVB and 50 J/cm² of visible light. UVA1 was delivered using a Sellmeier SELLMED 2400 UVA1 unit (Ennepetal, Germany). Broad band UVB was delivered with a Waldman 800 K unit (Villingen, Schwenningen, Germany) equipped with Phillips TL12 tubes, and visible light was delivered using an Osram HXL 64634 Xenophot bulb (Ausborg, Germany).

Minimal Urticaria Dose: In patients with positive reactions to the above exposures, the Minimal Urticaria Dose (MUD) was determined by stepwise decreasing fluences until no urticaria was provoked.

Laboratory evaluation: It consisted of CBC, ESR, CRP, kidney and liver function tests, anti-nuclear antibodies, anti-RO, anti-LA, porphyrins level in blood, stool and in 24 hours urine and collection.

Treatment schedule

Treatment consisted of a combination of antihistamines and leukotriene receptor antagonists.

Two protocols were used:

Protocol 1: desloratadine 5 mg twice daily + montelukast 10 mg once daily

Protocol 2: desloratidine 5 mg twice daily + fexofenadine 120 mg twice daily + cetirizine
Hcl 10 mg twice daily + montelukast 10 mg once daily

Patients with mild photosensitivity i.e. **patients who presented with high MUDs (visible light $> 30 \text{ J/cm}^2$ or UVA $> 5 \text{ J/cm}^2$)** were treated with Protocol 1. Patients with more severe photosensitivity, i.e. with low MUD (visible light $\leq 30 \text{ J/cm}^2$ or UVA $\leq 5 \text{ J/cm}^2$) were treated with Protocol 2 (Figure 2). Dose adjustments were made for pediatric patients in both protocols.

RESULTS

Eleven patients with SU were included (Table 1). Seven were females and 4 males. Median age was 21 years (range 5-60), and median duration of disease was 18 months (range 2-60 months). All laboratory workup was unremarkable except for elevated IgE in patient 1 (652 IU/ml) and patient 9 (2004 IU/ml). .

Minimal Urticaria Dose

All 11 patients were sensitive to visible light with a median MUD of 50 J/cm^2 (range $30\text{-}70 \text{ J/cm}^2$). Three patients were sensitive to UVA with a median MUD of 3.75 J/cm^2 (range $1\text{-}20 \text{ J/cm}^2$) and one patient was sensitive to UVB (MUD 0.03 J/cm^2). Patient 4 was sensitive to all 3 light spectra (UVA + visible light + UVB). Patients 1 and 2 were sensitive to 2 light spectra (UVA + visible light) and the rest of the patients were sensitive to only visible light.

Clinical outcome and repeated photo-provocations

Patients 2 and 8 improved spontaneously without treatment. Patient 7 declined treatment and was lost for follow-up. Eight patients were treated with combinations of antihistamines and leukotriene receptor antagonists. Three patients were treated with Protocol 1, and 5 patients with Protocol 2. Seven patients (patients 1, 3, 4, 5,6,10 and 11) experienced complete remission of symptoms and could return to normal outdoor activity in daylight, whereas one patient (patient 9) only showed subjective response. Photo-provocation was repeated in 6 patients (Table 1) verifying the clinical improvement by demonstrating increased MUDs for UVA, UVB and visible light.

Patients were followed for up to 30 months during which time treatment was continued and no disease relapse was encountered

DISCUSSION

Treatment of SU is highly challenging. Prior to enrollment, all of our patients had unsuccessfully tried broad-spectrum sunscreens and standard dosages of one antihistamine medication to control symptoms. Patient 2 took 40 mg of prednisone daily for one month with no effect and patient 1 had tried UVA rush hardening (12) resulting with only short-lived relief of symptoms. Patients with action spectra in the longer wavelengths often have to entirely avoid sun exposure with a major impact on their quality of life (13). **UV hardening with gradually increasing doses of light exposure is considered the first line of treatment in many countries. However, even when performed as "rush hardening" over 2-3 days (12), the procedure is extremely resource consuming and is not covered by The National Health Insurance in our country.**

We therefore decided on an alternative therapeutic approach consisting of a combination of antihistamines and leukotriene receptor antagonists.

In the present series of patients, all patients displayed sensitivity to visible light, 3 patients were also sensitive to UVA and one demonstrated sensitivity to all three spectra evaluated. Though sensitivity to visible light was more frequent than in other series (2,3,14), our finding of UVB sensitivity in only one patient is in accord with the infrequent occurrence of UVB induced SU reported by others.

Grundmann et al (15) reported the successful management of 4 patients with solar urticaria using a combination of antihistamines and leukotriene receptor antagonists. **Whereas the series of Grundman et al (15) consisted of patients with rather severe photosensitivity exhibiting multiple spectra sensitivities with very low UVA MUDs, our series of patients displayed more diverse degrees of photosensitivity with varied MUDs mainly to only 1 or 2 action spectra(apart from one patient).** We therefore modified the regimen by adjusting the treatment to the severity of the light sensitivity. Patients with low MUDs were treated with three types of antihistamines twice daily (protocol 2), whereas patients with high MUDs were treated with only a single antihistamine (protocol 1) in addition to a leukotriene receptor antagonist.

The recently published European guidelines for the treatment of chronic urticaria (16) advocates a therapeutic ladder with a standard second generation antihistamine dosage as the first step. If the clinical response is insufficient, up-dosing up to four-fold of the same antihistamine is recommended. In our series, all patients had failed to respond to a

standard second generation antihistamine dosage even before enrolling into the study.

However, four-fold dosing of a single antihistamine was not possible due to lack of medical insurance coverage. We therefor chose to administer a combination of different types of antihistamines allowing a high therapeutic dose of antihistamines without exceeding the maximal recommended dose for each antihistamine. Seven out of 8 patients experienced a complete response a few days after initiation of the above therapy. Side-effects were mild. Thus that 6 out of the 8 patients reported drowsiness and tiredness following treatment. Theses side effects were short-lived resolving within 2 weeks in all patients.

Whereas the various treatment modalities may succeed in inducing considerable and sustained remission, guidelines are lacking. A randomized controlled approach is difficult to apply partly due to the paucity of the disease and partly due to the occurrence of spontaneous remission (2, 14) which was also observed in 2 of our patients. Future studies, exploring additional protocols, however, would definitely benefit from incorporating a systematic approach whenever possible.

In summary, we here describe an individualized regimen for treatment of SU consisting of antihistamine combinations and leukotriene receptor antagonists and governed by the **severity of the photosensitivity**. This regimen showed high efficacy with only minor transient side effects.

SUMMARY

Solar urticaria is characterized by erythema, whealing and/or pruritus occurring minutes after sun exposure. Patients with action spectra in the longer wavelengths often have to entirely avoid sun exposure with a major impact on their quality of life.

Treatment of solar urticaria is highly challenging, often unsatisfactory and specific guidelines are lacking.

We here describe an individualized regimen for treatment of solar urticaria consisting of antihistamine combinations and leukotriene receptor antagonist and governed by the actual minimal urticaria dose (disease's severity). This regimen showed high efficacy with only minor transient side effects.

REFERENCES

1. Dice JP. Physical urticaria. *Immunol Allergy Clin North Am*. 2004;24:225-46
2. Beattie PE, Dawe RS, Ibbotson SH, Ferguson J. Characteristics and prognosis of idiopathic solar urticaria: a cohort of 87 cases. *Arch Dermatol*. 2003; 39:1149-54.
3. Botto NC, Warshaw EM. Solar urticaria. *J Am Acad Dermatol*. 2008; 59:909-20.
4. Miyauchi H, Horio T. Detection of action, inhibition and augmentation spectra in solar urticaria. *Dermatology*. 1995;191(4):286-91
5. Ng JC, Foley PA, Crouch RH, Baker CS. Changes of photosensitivity and action spectrum with time in solar urticaria. *Photodermatol Photoimmunol Photomed*. 2002; 18:191- 195.

6. Faurschou A, Wulf HC. Synergistic effect of broad-spectrum sunscreens and antihistamines in the control of idiopathic solar urticaria. *Arch Dermatol.* 2008;144:765-9.
7. Di Lorenzo G, D'Alcamo A, Rizzo M, Leto-Barone MS, Bianco CL, Ditta V, Politi D, Castello F, Pepe I, Di Fede G, Rini G. Leukotriene receptor antagonists in monotherapy or in combination with antihistamines in the treatment of chronic urticaria: a systematic review. *J Asthma Allergy.* 2008 9; 2:9-16.
8. Edström DW, Ros AM. Cyclosporin A therapy for severe solar urticaria. *Photodermatol Photoimmunol Photomed.* 1997; 13:61-3.
9. Koranda FC. Antimalarials. *J Am Acad Dermatol.* 1981; 4:650-5.
;63:1563-5.
10. Metz M, Altrichter S, Ardelean E, Kessler B, Krause K, Magerl M, Siebenhaar F, Weller K, Zuberbier T, Maurer M. Anti-immunoglobulin E treatment of patients with recalcitrant physical urticaria. *Int Arch Allergy Immunol.* 2011;154:177-80.
11. Correia I, Silva J, Filipe P, Gomes M. Solar urticaria treated successfully with intravenous high-dose immunoglobulin: a case report. *Photodermatol Photoimmunol Photomed.* 2008; 24:330-1.
12. Masuoka E, Fukunaga A, Kishigami K, Jimbo H, Nishioka M, Uchimura Y, Taguchi K, Ohgou N, Nishigori C. Successful and long-lasting treatment of solar urticaria with ultraviolet A rush hardening therapy. *Br J Dermatol.* 2012;167:198-201.
13. Jong CT, Finlay AY, Pearse AD, Kerr AC, Ferguson J, Benton EC, Hawk JL, Sarkany RP, McMullen E, Rhodes LE, Farr PM, Anstey AV. The quality of life of 790 patients with photodermatoses. *Br J Dermatol.* 2008; 159:192-7.

14. Du-Thanh A, Debu A, Lalheve P, Guillot B, Dereure O, Peyron JL. Solar urticaria: a time-extended retrospective series of 61 patients and review of the literature. *Eur J Dermatol* 2013; 23: 202-7.
15. Grundmann SA, Ständer S, Luger TA, Beissert S. Antihistamine combination treatment for solar urticaria. *Br J Dermatol*. 2008;158:1384-6.
16. Zuberbier T1, Aberer W, Asero R, Bindslev-Jensen C et al. **The EAACI/GA(2) LEN/EDF/WAO Guideline for the definition, classification, diagnosis, and management of urticaria: the 2013 revision and update. *Allergy*. 2014;69:868-87.**

FIGURE LEGEND

Figure 1: A positive photoprovocation for visible light and UVA in patient 4.

Figure 2: An algorithm for the evaluation and treatment of solar urticaria patients.

Table 1. Epidemiological, clinical and therapeutic data

Pre-treatment						Treatment			Post-treatment		
Patient	Gender / Age (years)	Disease Duration (months)	MUD (J/cm ²)			Treatment	Clinical Outcome	Follow up Period (months)	MUD (J/cm ²)		
			UV A	Visible Light	UV B				UV A	Visible Light	UV B
1	F/10	4	1	50	NR	Protocol 2	Full remission	12	20	NR	NR
2	M/60	60	20	50	NR	None	Full remission	6	-	-	-
3	F/24	11	NR	30	NR	Protocol 2	Full remission	12	NR	40	NR
4	M/16	6	3.75	50	0.03	Protocol 2	Full remission	30	12	NR	NR
5	F/25	60	NR	50	NR	Protocol 1	Full remission	24	NR	NR	NR
6	F/20	18	NR	30	NR	Protocol 2	Full remission	6	-	-	-
7	M/21	11	NR	50	NR	None	Lost to Follow up		-	-	-
8	F/34	2	NR	50	NR	None	Full remission	3	-	-	-
9	M/5	18	NR	30	NR	Protocol 2	Partial remission	16	NR	30	NR
10	F/32	36	NR	70	NR	Protocol 1	Full remission	12	-	-	-
11	F/7	30	NR	30	NR	Protocol 1	Full remission	13	NR	40	NR

NR: no response (> 20 J/cm² UVA, >70 J/cm² visible light, 0.03 J/cm² UVB)

Protocol 1: desloratidine 5 mg bid + montelukast 10 mg

Protocol 2: desloratidine 5 mg bid + fexofenadine HCl 120 mg bid + Cetrizine HCl 10 mg bid + montelukast 10 mg



