

Narrowband ultraviolet B phototherapy is a suitable treatment option for solar urticaria

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Background: Narrowband (NB) ultraviolet (UV) B lamps are widely used for treatment and prophylaxis of several skin diseases.

Objective: We sought to assess the efficacy of two protocols of NB-UVB therapy for the prophylaxis of UVB-sensitive and UVB-insensitive solar urticaria (SU).

Methods: Subjects affected by SU underwent phototesting for assessment of the minimal erythematous dose and minimal urticarial dose. Patients without urticarial response to UVB underwent a single daily exposure every other day for 4 weeks (group A). Patients with a urticarial test response to broadband UVB or NB-UVB (group B) received 3 daily exposures (on working days) for the first week. Afterward, they were treated as the patients of group A for 3 weeks. Follow-up visits took place after 1 and 3 months.

Results: A total of 39 patients completed the study. In groups A (29 patients) and B (10 patients), the median total number of exposures was 12 (interquartile range [IQR]: 12; 15) and 25.5 (IQR 24; 27), respectively. The median total NB-UVB dose was 10.3 J/cm² (IQR 9.9; 11) for group A and 9.1 J/cm² (IQR 8.5; 10.6) for group B. At follow-up visits, patients reported good tolerance to the sun.

Limitations: A direct comparison of NB-UVB with UVA or psoralen plus UVA for the photoprophylaxis of SU is still lacking.

Conclusion: NB-UVB phototherapy was well-tolerated and effectively prevented SU relapses. (J Am Acad Dermatol 10.1016/j.jaad.2011.01.030.)

Key words: clinical trial; minimal erythematous dose; minimal urticarial dose; narrowband ultraviolet B phototherapy; phototest; solar urticaria.

Idiopathic solar urticaria (SU) is an uncommon photodermatosis with a strong negative impact on the quality of life.¹

Many experimental and clinical findings seem to indicate that it is caused by an immediate-type antibody reaction to a cutaneous or circulating antigen that is produced in the skin from a precursor after the absorption of light energy.^{2,3}

The action spectra differ between subjects, with wavelength dependency extending from the ultraviolet (UV) B (280-320 nm) and UVA (320-400 nm) wavebands into the visible region

Abbreviations used:

BB:	broadband
IQR:	interquartile range
MED:	minimal erythematous dose
MUD:	minimal urticarial dose
NB:	narrowband
PUVA:	psoralen plus ultraviolet A
SU:	solar urticaria
UV:	ultraviolet

(400-700 nm). The individual threshold doses range widely as well and these differences can

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be attributed to the heterogeneous nature of the photoantigens.⁴

In milder cases, appropriate sunscreen photoprotection and patient-controlled desensitization may suffice. For unresponsive cases, nonsedative potent antihistamines (eg, loratadine, desloratadine, fexofenadine, and cetirizine)⁵ and photoprophylaxis with UVA (320–400 nm) phototherapy or psoralen plus UVA (PUVA) are largely used.

Narrowband (NB) UVB phototherapy is also described as a successful treatment option in many reviews but its use has been described in detail only in 1 anecdotal case report.⁶

This prompted us to investigate its tolerability and prophylactic efficacy for SU. Our study was also motivated by the fact that, in many dermatologic centers, only UVB lamps are used for phototherapy. In several countries, including Italy, where psoralens are no longer available, UVA lamps have been removed from offices.

METHODS

Patients

Patients had severe, generalized SU that had been poorly responsive to oral antihistamines and/or highly protective UVA and UVB sunscreens.

The study was approved by the local ethics committee and all subjects gave their written informed consent.

Exclusion criteria were: age younger than 18 years, poor compliance, pregnancy or lactation, any other active systemic or skin disease, and use of immunosuppressive or photosensitizing drugs.

Routine blood chemistries, hematology, urinalysis, erythrocyte sedimentation rate, C3, C4, total complement activity, C-reactive protein, antinuclear antibodies, antidouble-stranded DNA, antibodies against extractable nuclear antigens, anti-Ro/SS-A antibodies, antineutrophil cytoplasm antibodies, and total serum IgE were assessed by routine methodology.

Levels of urinary and erythrocytic porphyrins⁷ were assessed in selected patients, if the need was suggested by clinical findings.

Phototesting

The minimal erythematous dose (MED) and minimal urticarial dose (MUD) of broadband (BB)-UVB and NB-UVB were assessed at baseline by exposing two series of six 2- × 2-cm² areas of untanned skin of the

back to increasing doses of BB-UVB and NB-UVB (ranging from 0.01–0.057 J/cm²) with each consecutive dose increased by the factor 1.414 ($\sqrt{2}$). UVA test doses ranged from 1.0 to 5.7 J/cm². If no threshold responses (MED or MUD) were elicited by these tests, a second series of BB-UVB and NB-UVB (dose range 0.08–0.45 J/cm²) and/or UVA (dose range 8.0–45.3 J/cm²) was delivered 2 to 7 days later.

The tested areas were observed during and soon after irradiation, and then after 10 and 30 minutes and 1, 2, 4, 8, 24, and 48 hours.

Urticarial response to visible light was investigated by exposing a single 2- × 2-cm² area for 20 minutes to visible light from a slide projector at a distance of 20 cm.

CAPSULE SUMMARY

- This study assessed the efficacy and tolerability of two protocols of narrowband UVB therapy for the prophylaxis of UVB-sensitive and UVB-insensitive solar urticaria.
- Narrowband UVB phototherapy proved effective and well tolerated in the prophylaxis of solar urticaria induced by either UVB or UVA exposure.

Treatment protocol

In group A, patients without urticarial response to NB-UVB and BB-UVB were treated according to the standard protocol that is used for the prophylaxis of polymorphic light eruption.⁸ The initial irradiation dose was approximately 70% of the MED to NB-UVB. If patients had an undetectable MED, the initial dose was 70% of the highest tested dose (0.45 J/cm²). At subsequent exposures, dose increments of 20% or 10% were delivered if an erythematous response was not seen or was barely perceptible after 48 hours. Conversely, if a well-defined painful erythematous response was observed the treatment was interrupted until recovery and then resumed with 50% of the last dose. If SU was precipitated, the following exposure was delivered with the penultimate dose.⁸ Patients were treated 3 times a week for 4 weeks.

In group B, patients who had a MUD elicited by UVB were treated 3 times daily (at 4-hour intervals), 5 days a week (on working days) for the first week. The initial dose of NB-UVB was 50% of the MUD and 10% increments were delivered at each exposure. Exposures were delivered first to the upper aspect of the trunk, face, and arms and then, if no wheal appeared, to the lower aspect of the trunk and legs. During the first week of treatment, an oral antihistamine (cetirizine 10 mg/d) was administered. Afterward, the treatment cycle continued with a single exposure per day, 3 days a week for 3 weeks following the same dose protocol that was used for group A.

If the treatment cycle had been interrupted because of episodes of marked phototoxic erythema

Table I. Results of minimal erythema dose and minimal urticarial dose phototesting

Treatment group	MUD BB-UVB	MUD NB-UVB	MUD UVA	MUD VIS	MED BB-UVB	MED NB-UVB
A (n = 29)	Negative	Negative	Positive (11.30 [4; 16.0] J/cm ²)	Positive (n = 9) Negative (n = 20)	Positive (0.23 [0.23; 0.45] J/cm ²)	Positive (0.32 [0.32; 0.45] J/cm ²)
B (n = 10)	Positive (0.09 [0.06; 0.21] J/cm ²)	Positive (0.11 [0.08; 0.16] J/cm ²)	Positive (8.00 [4; 13.6] J/cm ²) Negative	Positive (n = 5) Negative (2) Negative (3)	Undetectable	Undetectable

BB, Broadband; MED, minimal erythema dose; MUD, minimal urticarial dose; NB, narrowband; UV, ultraviolet; VIS, visible.

or SU relapse, the treatment cycle was prolonged for 1 or 2 additional weeks with either protocol.

After concluding the treatment cycle, patients were advised to expose themselves at noontime on sunny days for at least 20 to 30 minutes more than 2 to 3 times a week during spring and summer. Follow-up visits took place after 1 and 3 months.

Radiation sources

For phototesting, BB-UVB and UVA were delivered by a filtered metal halide lamp (Dermalight Vario, Dr Hönle AG, Martinsried, Germany) equipped with filter H1-UVB and filter H2-UVA.

For NB-UVB phototesting, we used a bank (Cosmedico GmbH, Stuttgart, Germany) with 6 TL01/20 W (Philips, Eindhoven, The Netherlands) fluorescent tubes.

Phototesting with visible light was done with a slide projector carousel equipped with a 300-W bulb (Kodak AG, Stuttgart, Germany).

NB-UVB phototherapy was delivered with a W7001k cabinet (Waldmann Lichttechnik GmbH, Schwenningen, Germany) equipped with 48 Waldmann TL01/100-W fluorescent tubes.

UV radiation was quantified with a SR9910 spectroradiometer (Macam Photometrics Ltd, Livingstone, United Kingdom). The irradiance and spectrum of the slide projector lamp were not measured.

Statistical analysis

All data are given as median (interquartile range [IQR]).

RESULTS

Baseline clinical characteristics

A total of 39 patients (11 male and 28 female; mean age 31.6 years; range 19-63 years) were enrolled. Two patients had skin phototype I, 11 phototype II, 23 phototype III, and 3 phototype IV. Twenty-four patients developed wheals upon sun exposure only on skin that is normally covered by

clothes. In 15 patients, their faces and the backs of their hands were involved as well. SU occurred even in skin covered by thin clothing in 5 patients. During SU episodes, 2 patients had also angioedema of the lips and eyelids and systemic symptoms were reported by 5 patients: dizziness (2), fever (2), and dyspnea (1). Antinuclear antibodies at low titer were detected in 6 patients.

Total IgE serum levels were elevated in 11 patients, who were affected by allergic rhinitis.

Other laboratory findings were normal in all patients.

Phototesting

In 29 patients (group A), MUD assessment was negative with both BB-UVB and NB-UVB. They developed a MUD with an irradiation of 11.30 (4; 12.48) J/cm² of UVA and 9 also with visible light. The median IQR MEDs to NB-UVB and BB-UVB were 0.32 (0.32-0.45) J/cm² and 0.23 (0.23-0.45) J/cm², respectively (Table I).

Ten patients (group B) had a MUD positive to BB-UVB (0.09 [0.06; 0.21] J/cm²). Seven of these showed also a MUD to UVA (8.00 [4; 13.65] J/cm²) and in 5 the sensitivity was extended to the visible waveband. Because of the low MUDs, the MEDs to UVB could not be assessed.

Treatment results

Patients of group A received a cumulative dose of 10.3 (9.9; 11.0) J/cm² of NB-UVB delivered over 12 (12; 15) exposures. In the last exposure, they received 1.9 (1.7; 2.0) J/cm². Nine (31.8%) patients developed SU during the treatment cycle, 25 (86.2%) had at least one episode of mild erythema and 5 (17.2%) had one or more episodes of painful marked erythema.

Patients of group B received 25.5 (24; 27) exposures and the cumulative NB-UVB dose was 9.1 (8.5; 10.6) J/cm². The dose of the last exposure was 1.2 (0.7; 1.4) J/cm². Five (50.0%) patients had at least one SU episode, 7 (70.0%) had one or more episodes

Table II. Treatment results of prophylactic narrowband ultraviolet B phototherapy

	Group A (UVB-insensitive patients) (n = 29)	Group B (UVB-sensitive patients) (n = 10)
No. of exposures	12 (12; 15)	25.5 (24; 27)
Cumulative NB-UVB dose	10.3 (9.9; 11.0) J/cm ²	9.1 (8.5; 10.6) J/cm ²
Last NB-UVB dose	1.9 (1.7; 2.0) J/cm ²	1.2 (0.7; 1.4) J/cm ²
Patients with ≥ 1 episode of SU relapses, n (% of their group)	9 (31.0%)	5 (50.0%)
Patients with ≥ 1 episode of mild erythema, n (% of their group)	25 (86.2%)	7 (70.0%)
Patients with ≥ 1 episode of painful marked erythema, n (% of their group)	5 (17.2%)	3 (30%)
Patients who reported SU relapses at follow-up visit after 1 mo, n (% of their group)	4 (13.8%)	2 (20.0%)
Patients who reported SU relapses at follow-up visit after 3 mo, n (% of their group)	6 (20.7%)	2 (20.0%)

NB, Narrowband; SU, solar urticaria; UV, ultraviolet.
Results are given as median (interquartile range).

of mild erythema and 3 (30%) had one or more episodes of painful marked erythema (Table II).

At the 1-month follow-up visit, 4 (13.8%) patients of group A and 2 (20.0%) of group B reported to have developed SU after sun exposure, although all patients reported that the light threshold was higher than in the previous years. The number of patients belonging to group A with SU relapses increased to 6 (20.7%) at the 3-month follow-up visit whereas no additional episode was reported by patients of group B. Patients who experienced SU relapses had not been regularly exposed to sunlight because of bad weather or various personal reasons. At the end of the summer, the follow-up period ended and we could not assess how long the protection lasted.

DISCUSSION

In this investigation, a short treatment cycle with NB-UVB phototherapy afforded an effective and well-tolerated prophylaxis for patients with severe generalized SU that previously had responded poorly or not at all to oral antihistamines and/or topical sunscreens. These results were obtained by individualizing the treatment protocol on the basis of MED and MUD assessments. Most of the patients enrolled had no response to UVB phototesting and responded to the same prophylactic phototherapy protocol used for polymorphous light eruption,⁸ whereas patients sensitive to UVB required a more cautious and time-consuming regimen.

The protection proved to be long lasting in most patients, provided that they exposed themselves regularly to sunlight.

UVA phototherapy is considered to be the standard treatment for UVA-sensitive SU but it is not effective for patients with UVB-sensitive SU, where any tolerance obtained usually lasts only a few days.⁹

The standard UVA protocol entails 2 to 4 exposures per week, a starting dose lower than the MUD, and 10% to 20% increments.⁸ A condensed protocol or “rush” hardening is also available with patients exposed to quarter- or half-body UVA irradiation at 50% of the determined MUD with hourly increases in body surface area, irradiation, and dose.¹⁰

The mechanisms of action of UVA photoprophylaxis for UVA-sensitive patients are still being debated. Experimental and clinical findings suggest direct destruction of photoallergen or its conversion back into precursors.¹¹⁻¹³ Competitive occupation by altered photoallergen of IgE binding sites on skin mast cells, as well as down-regulation of IgE production and blockage of IgE-mediated release of histamine from mast cells implicated in the therapeutic effect.¹⁴

UVA photoprophylaxis does not alter tissue histamine content or mast cell numbers.¹¹⁻¹³

PUVA therapy is another successful prophylactic modality. Possible mechanisms of action similar to those described for UVA therapy have been suggested and PUVA is claimed to induce a more lasting and effective tolerance than UVA phototherapy alone although the hazard of psoralen skin toxicity, including carcinogenesis, must be taken into account.¹⁵

The possible mechanisms of action of UVB phototherapy are only speculative. In the case of UVB-sensitive patients, UVB irradiations could work with the same above-mentioned mechanisms that have been demonstrated for UVA phototherapy of UVA-sensitive patients.

Different mechanisms of action could explain the efficacy of UVB irradiation of patients whose disease is precipitated by the UVA or visible light. Here the strategy is to avoid the activating spectrum to

increase the UV-filtering properties of the patients' skin by means of increased melanin production, stratum corneum thickening, and epidermal hyperplasia.

UVB-induced immunomodulation^{16,17} must also be taken into account.

The main limitation to the use of NB-UVB in the prophylaxis of SU could be the danger of adverse effects. However, with our treatment protocols, episodes of sunburns and/or severe SU episodes were uncommon and the cumulative UVB dosage was very low.

In conclusion, in this investigation NB-UVB phototherapy proved effective in the prophylaxis of SU induced by either UVB and UVA. A direct comparison with UVA or PUVA is still lacking but NB-UVB may become widely used because UVA lamps and oral psoralens are no longer available in many European dermatologic centers.

REFERENCES

1. Jong CT, Finlay AY, Pearse AD, Kerr AC, Ferguson J, Benton EC, et al. The quality of life of 790 patients with photodermatoses. *Br J Dermatol* 2008;159:192-7.
2. Torinuki W, Tagami H. Solar urticaria without inhibitory spectrum: demonstration of both circulating photoallergen and reagenic antibodies. *Dermatologica* 1986;173:116-9.
3. Leenutaphong V, Hölzle E, Plewig G. Evidence for an epidermal photoallergen in solar urticaria. *J Invest Dermatol* 1988; 91:408.
4. Aoki T. Action spectrum and molecular weight of photoantigens in solar urticaria. *J Invest Dermatol* 1985;84:344-5.
5. Beattie PE, Dawe RS, Ibbotson SH, Ferguson J. Characteristics and prognosis of idiopathic solar urticaria: a cohort of 87 cases. *Arch Dermatol* 2003;139:1149-54.
6. Collins P, Ferguson J. Narrow-band UVB (TL-01) phototherapy: an effective preventative treatment for the photodermatoses. *Br J Dermatol* 1995;132:956-63.
7. Blake D, Poulos V, Rossi R. Diagnosis of porphyria—recommended methods for peripheral laboratories. *Clin Biochem Rev* 1999;13:S1-24.
8. Tanew A, Ferguson J. Phototherapy and photochemotherapy of the idiopathic photodermatosis. In: Krutmann J, Honigsmann H, Elmetts CA, editors. *Dermatological phototherapy and photodiagnosis methods*. 2nd ed. Berlin: Springer Verlag; 2009. pp. 119-33.
9. Roelandts R. Diagnosis and treatment of solar urticaria. *Dermatol Ther* 2003;16:52-6.
10. Beissert S, Stander H, Schwarz T. UVA rush hardening for the treatment of solar urticaria. *J Am Acad Dermatol* 2000;42: 1030-2.
11. Hasei K, Ichihashi M. Solar urticaria: determinations of action and inhibition spectra. *Arch Dermatol* 1982;118:346-50.
12. Horio T, Yoshioka A, Okamoto H. Production and inhibition of solar urticaria by visible light exposure. *J Am Acad Dermatol* 1984;11:1094-9.
13. Torinuki W, Kumai N, Miura T. Solar urticaria inhibited by visible light. *Dermatologica* 1983;166:151-5.
14. Leenutaphong V, Hölzle E, Plewig G. Solar urticaria: studies on mechanisms of tolerance. *Br J Dermatol* 1990;122:601-6.
15. Honigsmann H. Mechanisms of phototherapy and photochemotherapy for photodermatoses. *Dermatol Ther* 2003;16:23-7.
16. Beissert S, Schwarz T. Role of immunomodulation in diseases responsive to phototherapy. *Methods* 2002;28:138-44.
17. Sigmundsdottir H, Johnston A, Gudjonsson JE, Valdimarsson H. Narrowband—UVB irradiation decreases the production of pro-inflammatory cytokines by stimulated T cells. *Arch Dermatol Res* 2005;297:39-42.