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CLINICAL REPORT

Treatment of Chronic Urticaria with Narrowband Ultraviolet B Phototherapy: a Randomized Controlled Trial

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Data regarding narrowband ultraviolet B (NB-UVB) phototherapy in patients with chronic urticaria is limited. The aim of this open, controlled study was to determine whether NB-UVB is effective in treating urticaria in combination with antihistamin. A total of 81 patients with chronic urticaria were recruited, 48 of whom were randomized into the NB-UVB plus antihistamine group. The control group ($n=33$) received only antihistamine. Patients were assessed using the urticaria activity score and a visual analogue score (VAS). The 2 groups were evaluated at the same time-points: at treatment sessions 10 and 20 and at follow-up 3 months post-treatment. The reduction in urticaria activity score and VAS was statistically significant ($p<0.05$ for both groups). When comparing the groups, the mean urticaria activity score was significantly lower in the NB-UVB group at session 10 (22.6 vs. 27.3) and session 20 (17.4 vs. 20.7). Statistically significant differences were also noted in VAS between the 2 groups ($p<0.01$) at 3 months post-treatment. We conclude that NB-UVB may be an effective complementary treatment for patients with chronic urticaria. *Key words: chronic urticaria; narrowband; ultraviolet B phototherapy.*

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Chronic urticaria is a common skin disease, which lasts more than 6 weeks and can result in significant morbidity (1, 2). Antihistamines and systemic steroids form the basis of treatment, but response is often incomplete (3). Second-line therapies, such as cyclosporine (4) and intravenous immunoglobulin (5), have been shown to be effective in randomized controlled trials. However, there are concerns about safety and costs of this therapy.

A narrowband (311 nm) ultraviolet B (NB-UVB) fluorescent lamp (TL01) has been developed that is effective in the treatment of psoriasis (6). NB-UVB has increasingly been used in a variety of skin conditions other than psoriasis (7). Depending on the disease being treated, the mechanism of action includes anti-proliferative, anti-inflammatory and immunosuppressive effects. However, no controlled study of any form of UVB for urticaria has been conducted. The aim of this study was to evaluate whether NB-UVB could have a potential role in reducing the symptoms of urticaria.

PATIENTS AND METHODS

Patients

Patients aged 18–62 years attending our chronic urticaria assessment clinic between June 2006 and May 2007 were enrolled in the study. Patients were excluded if they had received phototherapy, used sun-beds, or had received systemic steroids, cyclosporine or immunosuppressive therapy during the preceding 3 months. Patients with a history of photosensitivity were excluded. Tests for physical urticaria were negative in all patients. Patients with urticaria caused by infection or food allergy were excluded. Patients with angioedema and symptomatic dermographism were also excluded. Baseline investigations in all patients included a full blood count, erythrocyte sedimentation rate and biochemical profile. Autologous serum skin testing (ASST) was performed on all patients. The study protocol was approved by the ethics committee of our university.

NB-UVB-levocetirizine and levocetirizine group

The patients were randomly assigned into 2 groups by rolling a dice without knowing the treatment options (numbers 1–3 = NB-UVB-levocetirizine group; numbers 4–6 = levocetirizine group). The NB-UVB-levocetirizine group received NB-UVB phototherapy 3 times weekly (Monday, Wednesday and Friday) combined with levocetirizine 10 mg daily. The levocetirizine group received the same antihistamine as the first group without phototherapy treatment. Because of the severity of urticaria, antihistamine was maintained throughout the study in the 2 groups in order to assess the effects of NB-UVB in patients with urticaria. All patients received 5 mg of levocetirizine during a 3-month follow-up period.

Treatment regimen

Prior to treatment, the NB-UVB-levocetirizine group was given an information sheet about treatment with NB-UVB, and informed written consent was obtained. They were given advice on the use of emollient therapy following phototherapy. The patients' skin types were defined according to the Fitzpatrick classification: skin type I/II vs. skin type III/IV. Whole-body phototherapy was administered 3 times a week for 20 exposures. No photo-testing was performed before the treatment. The initial dose was 200 mJ/cm^2, with percentage-based increments of 10–20% every session, up to a maximum dose of 1300 mJ/cm^2. The increment regimen was modulated following a standard protocol. All patients wore a face shield and male patients wore genital protection. All patients were monitored for an erythemal response by nursing staff after phototherapy. Adverse reactions were recorded. The follow-up to observe urticaria activity was made after 3 months.

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Irradiation cubicles

Phototherapy was performed in a Daavlin spectra 311 irradiation cubicle containing 100 W TL-01 (311 ± 2 nm) 24 fluorescent tubes. The cubicle had its own cooling fan and an additional air-conditioner was used in the unit. Test equipment is calibrated annually with the TL-01 emission spectrum by our hospital calibration service.

Assessment of treatment response

All patients in the 2 groups completed a daily record for the preceding 24 h of small (diameter < 3 cm) and large (diameter > 3 cm) wheal numbers and the severity of itch. The number of wheals was scored from 0 to 3: 0, < 10 small wheals; 1, 10–50 small wheals or < 10 large wheals; 2, > 50 small wheals or 10–50 large wheals; 3, almost covered. The severity of itch was also scored as 0, none; 1, mild; 2, moderate; 3, severe. Therefore, the urticaria activity score (UAS) ranged from 0 to 42 per week. Patients also completed a visual analogue score (VAS) at each visit, indicating the overall urticaria severity during the preceding 2 weeks. The score ranged from 0 to 10, 0 indicating no disease and 10 indicating very severe urticaria. The NB-UVB-levocetirizine group was assessed at baseline, and after 10 and 20 sessions, and 3 months after the 20th session. Assessments for the levocetirizine group were also made at the same time-points. One of our physicians (AB) helped to record the scores. He was unaware of treatment assignment of assessed patients. All assessments were made in a separate room under the control of another physician (İM). The mean reduction in UAS and VAS at every assessment point compared with baseline, in response to the NB-UVB plus antihistamine and antihistamine alone, were evaluated.

Statistical analysis

The results are presented as the mean change in outcome over 20 treatments for the NB-UVB-levocetirizine group and at the same time-points for the levocetirizine group, and the mean difference between groups with 95% confidence intervals (CIs). The Lilliefors test was used for normality testing. Mean score (UAS, VAS) changes within both groups at different time-points were compared using non-parametric Friedmann test and Bonferroni-adjusted Wilcoxon signed-ranks tests. The Mann-Whitney *U* test was used to compare inter-group differences at different time-points. $p < 0.05$ was considered statistically significant.

RESULTS

Fig. 1 shows the study profile. A total of 84 patients fulfilled the entry criteria and were allocated to a group. Three patients withdrew from the study before treatment began and were excluded from the analysis. Thus, 81 patients underwent study. Of the 48 patients who began phototherapy, 3 were excluded from the analysis because they were unable to attend the treatment. The majority of the patients had skin type III/IV ($n = 42$), followed by skin type I/II ($n = 3$).

Demographics and clinical characteristics

There were no significant differences in demographic characteristics or baseline UAS and VAS between the 2 groups (Table I). Of the 45 patients in the NB-UVB-levocetirizine and 33 patients in the levocetirizine group, 32 and 21, respectively, had a positive ASST. There was no difference in treatment response between the ASST-positive and ASST-negative patients.

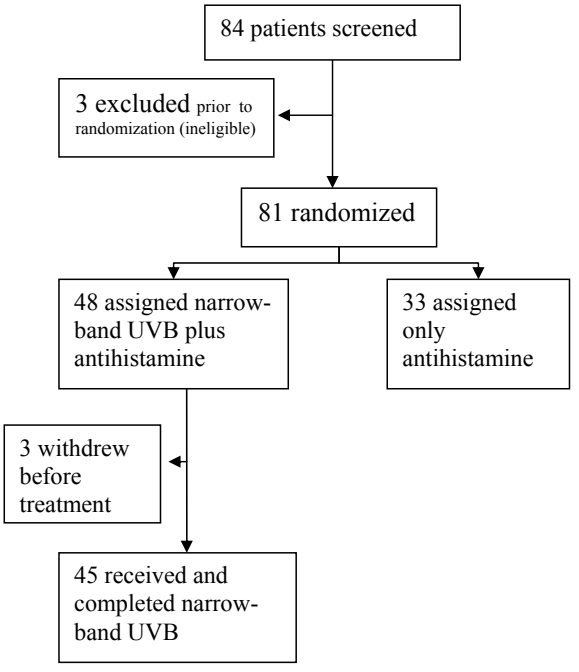

Fig. 1. Trial profile.

Response to treatment

The mean UAS and VAS in the NB-UVB-levocetirizine group were reduced from 34.2 and 6.1 (baseline) to 22.6 and 4.3 (after 10 treatment sessions) and to 17.4 and 3.0 (after 20 treatment sessions), respectively. In the levocetirizine group, the corresponding mean values were reduced from 33.4 and 6.4 (baseline) to 27.3 and 5.0 and to 20.7 and 4.2, respectively. The reduction in UAS and VAS within the 2 groups was statistically significant ($p < 0.05$ for both groups). Comparing the groups, the mean UAS was significantly lower in the NB-UVB-levocetirizine group at the 10th session (22.6 vs. 27.3) and 20th session (17.4 vs. 20.7) (Fig. 2). Ho-

Table I. *Characteristics of the patients in the narrow-band ultraviolet B (NB-UVB)-levocetirizine and levocetirizine groups*

Characteristics	NB-UVB-levocetirizine group $n = 45$	Levocetirizine group $n = 33$
Mean age (years)	34.2	32.6
Sex (*n*)		
Male	11	14
Female	34	19
Mean duration of disease (months)	14.2	12
Mean baseline UAS (maximum 42)	34.22	33.42
Mean baseline VAS (maximum 10)	6.07	6.42

UAS: urticaria activity score; VAS: visual analogue score.

wever, the mean VAS was similar at the 10th session (4.3 vs. 5.0) and 20th session (3.0 vs. 4.2) (Fig. 3).

The difference in mean UAS reduction between the 2 groups was significant at the 10th and 20th sessions (Table II).

Follow-up period

Follow-up data was obtained from all patients after 3 months (see Figs. 2 and 3). The mean UAS and VAS reduced significantly from 17.4 and 3.0 after 20 sessions to 15.7 and 2.5 at 3 months post-treatment in the NB-UVB-levocetirizine group. In the levocetirizine group, however, the corresponding values *increased* significantly from 20.7 and 4.2 to 31.2 and 6.2, respectively. Statistically significant differences were noted in the 3-month post-treatment mean UAS and VAS changes between the 2 groups ($p < 0.01$).

Exposure and cumulative dose

The number of treatments was 20 in all patients receiving phototherapy. The mean top dose was 1200 mJ/cm^2 (range 800–1300 mJ/cm^2) and the median cumulative dose was 15,090 mJ/cm^2 (range 10,224–16,540 mJ/cm^2).

Adverse reactions

The therapy was generally well tolerated, but type A adverse reactions were reported in 4 patients in the NB-UVB-levocetirizine group. Two patients experienced at least one episode of well-demarcated erythema. However, all of these patients continued to receive treatment once their erythema had settled, with their regimens modified according to our standard protocol.

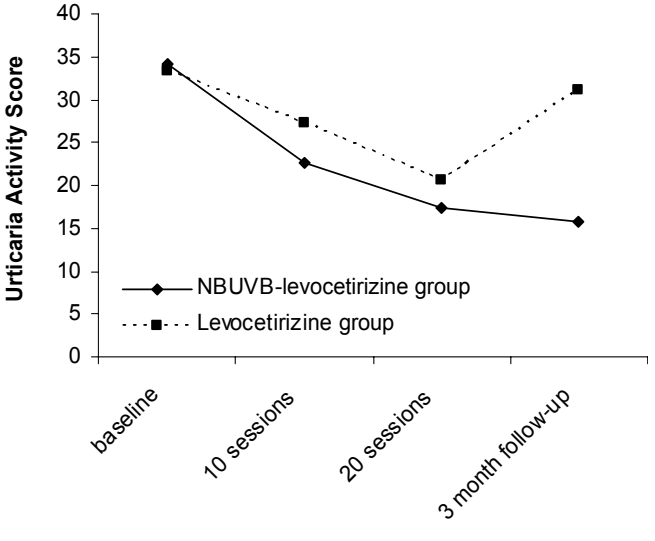

Fig. 2. Mean urticaria activity score (see Materials and Methods) during treatment and during follow-up (levocitrizine reduced to 5 mg/day in both groups). NBUVB: narrowband ultraviolet B.

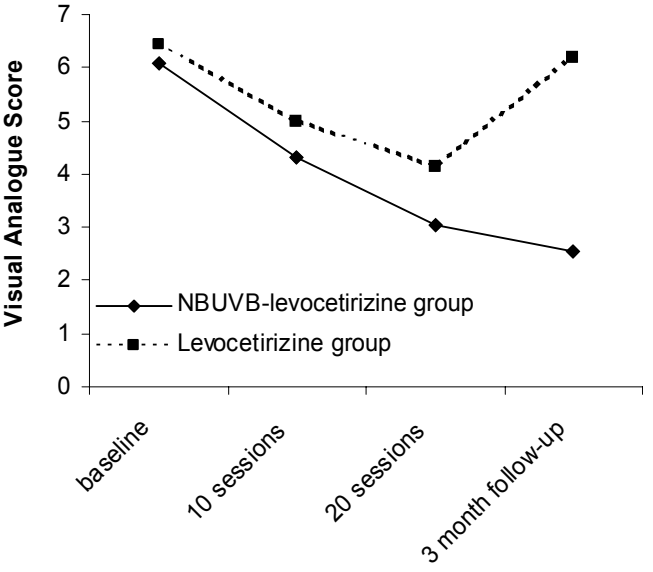

Fig. 3. Mean visual analogue score (see Materials and Methods) during treatment and during follow-up (levocitrizine reduced to 5 mg/day in both groups). NBUVB: narrowband ultraviolet B.

No patients experienced an episode of painful erythema. Two patients also had pruritus.

DISCUSSION

This prospective study represents the largest study of NB-UVB phototherapy for patients with chronic urticaria. Therapeutic guidelines for urticaria comment that the evidence for phototherapy is unconvincing (8, 9). However, a retrospective study (10) demonstrated promising results in patients with chronic urticaria who were resistant to standard therapies (e.g. antihistamines and diet). Our results indicate that NB-UVB phototherapy is an effective treatment in patients with chronic urticaria. NB-UVB phototherapy combined with antihistamine was better than antihistamine alone at reducing urticaria activity and patient's scoring of itch on a VAS. Moreover, improvements in UAS and VAS seen during treatment were maintained 3 months after phototherapy had been stopped. Conversely, a significant increase in disease activity was recorded after 3 month follow-up in the levocetirizine only group.

The mechanism of the long-term improvement in the NB-UVB group is unclear. It is possible that it is related to an immunoregulatory role of UVB that lasts longer. However, it is also possible that the long-lasting effect of NB-UVB is explained by a psychological effect.

In view of the design of this study (unblinded and concomitant therapy with antihistamine), the results may have some limitations. Of course the NB-UVB-levocetirizine group knew that they were receiving phototherapy and the levocetirizine group were not given placebo-phototherapy. And also no objective outcome measure was defined prior to the start of the study.

Table II. Mean ± SD reduction of urticaria activity score (UAS) from baseline value in the two treatment groups

	NB-UVB-levocetirizine group	Levocetirizine group	Difference (95% CI)	*p*-value
After 10 sessions	11.58 ± 6.75	6.09 ± 4.68	5.49 (8.2–2.7)	<0.01
After 20 sessions	16.78 ± 7.91	12.76 ± 6.47	4.02 (7.3–0.6)	0.019
3 months post-treatment	18.51 ± 8.35	2.24 ± 4.98	16.27 (19.5–13.01)	<0.01

NB-UVB: narrowband ultraviolet B; CI: confidence interval; SD: standard deviation.

We chose a low starting dose of NB-UVB of 200 mJ/cm^2. Unlike psoriasis, in which UVB doses that approach the minimum erythema dose have been shown to be more effective than lower doses (11), for urticaria the correlation between dose and effectiveness is unclear. Berroeta et al. (10) reported that 68 phototherapy courses produced clearance in 40% of patients, whereas 27 courses were documented as unsuccessful. However, the median number of treatments was 22 in that study. It is also known that a typical course for psoriasis requires 18–24 treatments for disease clearance (12). In our study we designed a 20-session protocol of NB-UVB phototherapy. Our treatment schedule was based on our general phototherapy experience, yet improvement of urticaria with NB-UVB seemed to be continuing at 20 treatments. Therefore we need to identify the optimum therapeutic schedules of NB-UVB phototherapy in chronic urticaria and to ascertain whether particular subgroups of patients benefit more than others.

Several studies have confirmed the efficacy of the NB-UVB in the treatment of many dermatological diseases (7, 13). The exact mechanism of action of NB-UVB in urticaria is unknown, although UVB has been shown to induce a variety of immunosuppressive and anti-inflammatory cytokines (14, 15). Degranulation of mast cells with release of histamine is central to the pathogenesis of urticaria (1, 16, 17). A range of pro-inflammatory mediators and cytokines is released from mast cells at the time of degranulation (18). NB-UVB decreases the production of pro-inflammatory cytokines released by degranulation. UVB phototherapy is known to induce the production of the anti-inflammatory cytokine interleukin-10, which may be responsible for the immunosuppressive and anti-inflammatory effects of UVB (19). Whether mast cell numbers are increased in chronic urticaria is unknown (1), although their mediator content may be released more easily. NB-UVB probably induces apoptosis of dermal mast cells (20). However, there are controversial results regarding mast cell depletion (21).

We know that exposure of human skin to sub-erythemogenic doses of UVB can result in immunological effects including alterations in circulating CD4/CD8 T-lymphocyte ratio (22). Urticaria could be explained by an underlying autoimmune mechanism in up to 50% of patients. Primary abnormality in some patients might be cellular rather than humoral (16, 23, 24). Under certain circumstances, T cells can induce activation of mast cells, as well as histamine release (18). It was proposed that UVB primarily affects the T cells in lesional skin (19).

The acute side-effects of NB-UVB include erythema and pruritus. Pruritus, although also a common side-effect of phototherapy, was recorded in only 2 patients. We did not formally assess the development of pigmentation; however, we noted that approximately 12% of the NB-UVB group showed some increase in skin pigmentation. Induction of photodegenerative changes by UVB is well established (7, 15). It is recommended that NB-UVB phototherapy should be used in limited duration courses. In our series we used only 20 courses, as described.

We conclude that NB-UVB is a second-line therapy for chronic urticaria that is unresponsive to antihistamines. In particular, our study shows that NB-UVB therapy may result in lower urticaria activity for long durations.

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REFERENCES

1. Grattan CEH, Sabroe RA, Greaves MW. Chronic urticaria. J Am Acad Dermatol 2002; 46: 645–657.
2. Greaves MW. Chronic urticaria. N Engl J Med 1995; 332: 1767–1772.
3. Greaves MW. Antihistamine treatment: a patient self-assessment method in chronic urticaria. BMJ 1981; 283: 1435–1436.
4. Grattan CE, O'Donnell BF, Francis DM, Niimi N, Barlow RJ, Seed PT, et al. Randomized double-blind study of cyclosporin in chronic 'idiopathic' urticaria. Br J Dermatol 2000; 143: 365–372.
5. O'Donnell BF, Barr RM, Black AK, Francis DM, Kermani F, Niimi N, et al. Intravenous immunoglobulin in autoimmune chronic urticaria. Br J Dermatol 1998; 138: 101–106.
6. van Weelden H, Baart de la Faille H, Young E, van der Leun JC. A new development in UVB phototherapy of psoriasis. Br J Dermatol 1988; 119: 11–19.
7. Gambichler T, Breuckmann F, Boms S, Altmeyer P, Kreuter A. Narrowband UVB phototherapy in skin conditions beyond psoriasis. J Am Acad Dermatol 2005; 52: 660–670.
8. Hannuksela M, Kokkonen EL. Ultraviolet light therapy in chronic urticaria. Acta Derm Venereol 1985; 65: 449–450.
9. Grattan C, Powell S, Humphreys F. Management and diagnostic guidelines for urticaria and angio-oedema. Br J Dermatol 2001; 144: 708–714.
10. Berroeta I, Clark C, Ibbotson SH, Ferguson J, Dawe RS. Narrow-band (TL-01) ultraviolet B phototherapy for chronic urticaria. Clin Exp Dermatol 2004; 29: 97–99.

11. Fischer T. UV-light treatment of psoriasis. Acta Derm Venereol 1976; 56: 473–479.
12. Picot E, Picot-Debeze MC, Meunier L, Peyron JL, Meynadier J. Narrow-band UVB phototherapy (Philips TL01 lamps) in psoriasis. Ann Dermatol Venereol 1992; 119: 639–642.
13. Asawanonda P, Taylor CR. Narrowband (TL-01) UVB phototherapy beyond psoriasis. J Dermatol Treat 1999; 10: 53–57.
14. Walters IB, Ozawa M, Cardinale I, Gilleaudeau P, Trepicchio WL, Bliss J, Krueger JG. Narrowband (312 nm) UV-B suppresses interferon gamma and interleukin (IL) 12 and increases IL-4 transcripts: differential regulation of cytokines at the single-cell level. Arch Dermatol 2003; 139: 155–161.
15. Ibbotson SH, Bilsland D, Cox NH, Dawe RS, Diffey B, Edwards C, et al. An update and guidance on narrowband ultraviolet B phototherapy: a British Photodermatology Group Workshop Report. Br J Dermatol 2004; 151: 283–297.
16. Sabroe RA, Greaves MW. Chronic idiopathic urticaria with functional autoantibodies: 12 years on. Br J Dermatol 2006; 154: 813–819.
17. Kaplan AP. Chronic urticaria: pathogenesis and treatment. J Allergy Clin Immunol 2004; 114: 465–474.
18. Hennino A, Berard F, Guillot I, Saad N, Rozieres A, Nicolas JF. Pathophysiology of urticaria. Clin Rev Allergy Immunol 2006; 30: 3–11.
19. 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.
20. Szepietowski JC, Morita A, Tsuji T. Ultraviolet B induces mast cell apoptosis: a hypothetical mechanism of ultraviolet B treatment for uraemic pruritus. Med Hypotheses 2002; 58: 167–170.
21. Learn DB, Moloney SJ. Numbers of murine dermal mast cells remain unchanged during chronic ultraviolet B irradiation. Photodermatol Photoimmunol Photomed 1991; 8: 195–199.
22. Morison WL, Parrish JA, Bloch KJ, Krugler JI. In vivo effect of UV-B on lymphocyte function. Br J Dermatol 1979; 101: 513–519.
23. Barlow RJ, Ross EL, MacDonald DM, Kobza Black A, Greaves MW. Mast cells and T lymphocytes in chronic urticaria. Clin Exp Allergy 1995; 25: 317–322.
24. Rosenstreich DL. Chronic urticaria, activated T cells, and mast cell releasability. J Allergy Clin Immunol 1986; 78: 1099–1102.