

Pharmacology and therapeutics

Narrowband ultraviolet B (311 nm, TL01) phototherapy in chronic ordinary urticariaKenan Aydogan¹, MD, Serap Koran Karadogan², MD, Sukran Tunali¹, MD, and Hayriye Saricaoglu¹, MD¹Department of Dermatology, Uludag University, Faculty of Medicine, Bursa, Turkey, and ²Esrefpasa Hospital, Izmir, Turkey**Correspondence**Assoc. Prof. Dr. Kenan Aydogan, MD
Department of Dermatology
Faculty of Medicine
University of Uludag
TR-16059 Görükle Bursa
Turkey
E-mail: aydogank@uludag.edu.tr**Abstract****Background** Chronic ordinary urticaria (COU) can severely reduce quality of life and be difficult to control. Ultraviolet (UV) A and UVB phototherapy has been reported to decrease the release of histamine from either mast cells and/or basophils. Previous small studies have suggested that UVB phototherapy is a good alternative treatment for COU.**Objectives** The purpose of this study was to assess the efficacy of narrow-band UVB (NB-UVB) phototherapy for COU.**Materials and methods** Twenty-two patients (three male, 19 female) received NB-UVB phototherapy. These patients had not responded to at least two H1 antihistamines, and most had been treated with a variety of antihistamine combinations. Clinical responses were assessed according to an outcome scoring scale. During both visits, patients were administered the following: the visual analogue scale (VAS) on present pruritus and/or whealing; chronic urticaria impact on patients' quality of life according to the interference with daily activities, quality of sleep, and flare-up rates.**Results** The median number of treatments was 31.4 (9–44), and the mean top dose was 9.46 J/cm² (1.1–16.4 J/cm²). NB-UVB treatment led to clearance in 10 patients (45%), marked improvement in five (22%), and moderate improvement in seven (31%) patients according to an outcome scoring scale. Mild side effects were observed in two patients. Six patients who cleared or observed marked improvement remained clear at follow-up for a period of six months to one year, and other patients had a few recurrent lesions that did not need retreatment. For VAS scores and total chronic urticaria impact on patients' quality of life scores, the differences between baseline and after treatment scores were significantly lower ($P < 0.001$, $P < 0.001$, respectively).**Conclusion** Narrow-band UVB (NB-UVB) therapy is an effective, well-tolerated treatment option in second-line therapy for COU. This therapy can lead to subjective relief of pruritus and whealing and objective reduction of whealing. Further larger studies with longer follow-up periods are necessary to determine the proper clinical response and long-term complications of this therapy in COU.**Introduction**

Chronic urticaria is characterized by widespread, transient, and itchy cutaneous swellings affecting patients for six weeks or longer with individual lesions lasting less than 24 hours.¹ The term chronic “ordinary” urticaria (COU) has been proposed to classify chronic urticaria by clinical presentation rather than etiology, as up to 40–50% of patients previously diagnosed as “chronic idiopathic urticaria” (CIU) have an autoimmune basis for their disorder.² The term “COU” can be used when predominantly physical, vasculitic, and contact urticarias have been excluded.²

The exact incidence and prevalence of COU are not known, although it occurs in at least 0.1% and possibly up to 3% of the population.² Severe COU is a disabling condition and may be distressing. It can greatly reduce quality of life and can be difficult to treat with little response to conventional antihistamine therapy.^{1–3}

In vitro tests showed that ultraviolet (UV) irradiation can inhibit the stimulated histamine release from human basophils and rat or human mast cells.^{4–8} It has also been shown that experimentally induced itching can be reduced by UVA, UVB, and psoralen UVA (PUVA).⁹ Although therapeutic guidelines for urticaria commented that the

evidence for phototherapy was unconvincing,^{10,11} the efficacy of broadband (BB)-UVB has been previously demonstrated in an open study.¹² Several studies recently suggested that narrow-band UVB (NB-UVB) phototherapy may be more promising for managing CIU.^{13,14}

The purpose of this study was to assess the efficacy of NB-UVB phototherapy in the management of COU.

Patients and methods

Patients

This is a prospective analysis of all patients with COU treated in our institution with NB-UVB. The diagnosis of COU was based on typical clinical features and results of normal or negative routine investigations. Twenty-two patients (three male, 19 female) were enrolled in the study after giving informed consent. Their mean age was 39.2 years (range 19–64 years). Patients were excluded if they had received phototherapy, used sunbed, or had received systemic steroids, cyclosporin, or immunosuppressive therapy during the preceding three months. Patients with history of photosensitivity and angioedema were excluded. Tests for physical urticaria were negative in all patients. Patients with urticaria caused by infection or food allergy were excluded. None of the patients had features of vasculitic urticaria. Patients with clinical suspicion of urticarial vasculitis were excluded by histopathological examination of lesional skin biopsies. Patients' age, gender, skin type according to Fitzpatrick's classification, disease duration, and previous treatments were recorded. These patients had not responded to at least two H1 antihistamines, and most had experienced a variety of antihistamine combinations and a trial of a diet low in histamine-releasing foodstuffs. Their demographic data are listed in Table 1. The ethics committee of our university approved the study protocol.

Radiation source and irradiation protocol

Treatment with NB-UVB (311 ± 2 nm) was given three to four times weekly in a Daavlin cabinet (Daavlin, CA, USA) equipped with Philips TL-01/100 W fluorescent lamps (Philips Company,

Eindhoven, the Netherlands). Patients were treated with a starting dose of 50–70% of minimal erythmal dose and followed a percentage incremental regimen (20%/10%/0%) adjusted according to erythema (and others, such as heat-induced urticaria and polymorphic light eruption) responses. The dose was increased weekly by 20% if previous treatment had caused no or slight erythema. If previous treatment had produced marked erythema, the dose was not increased and if treatment had caused intense erythema, the dose was decreased by 10%. Two independent physicians (K.A. and S.K.K) evaluated patients every two weeks. All patients were monitored for an erythmal response by nursing staff after phototherapy. Adverse reactions were recorded. Follow-up to observe the urticaria activity was made after six months to a year. During the study and follow-up period, only emollients were permitted for topical skin care. NB-UVB phototherapy was given for a maximum of 30–45 sessions.

Evaluation of clinical response and follow-up period

Clinical responses were assessed according to an outcome scoring scale¹³ (Table 2). Patients were examined initially every 2–3 months and subsequently every year for any recurrent lesions after treatment.

Measures

The visual analogue scale (VAS) on present severity of pruritus and/or wheals ranged from “no” to the “maximum.” Scores ranged from 0 to 10. VAS was evaluated at baseline and after treatment.

Chronic urticaria impact on patients' quality of life according to interference with daily activities (such as outdoor activity, sports, work/study, leisure/social, and sexual activities, etc.), limiting and impairing sleeping function, and flare-up rates were assessed at baseline and after treatment. Scores ranged from 0 to 3 (0 = none; 1 = mild; 2 = moderate; 3 = severe). Therefore, total quality of life score ranged from 0 to 9.

Statistical analysis

Mann–Whitney *U*-test was used for the comparison scores between baseline and after treatment. The statistically

Table 1 Demographic data

Disease	Patients	Mean age	Gender M/F	Duration of disease (years)	Pretreatment	Skin type
COU	22	39.2 ± 12.1 (19–64)	3 : 19	4.7 ± 3.7 (7 months–16 years)	At least two H1	I: 1 antihistamines II: 19 III: 2

Table 2 Outcome scoring scale for narrowband ultraviolet B treatment of chronic ordinary urticaria

1	No change
2	Minimal improvement (no change in frequency or extent symptomatic improvement ±)
3	Moderate improvement (less frequent or extensive symptomatic improvement +)
4	Marked improvement (occasional episodes and less extensive symptomatic improvement ++ reduced antihistamine use)
5	Clearance with or without antihistamines

significant cut-off value was set at $P < 0.05$. The statistical analyses were implemented by using SPSS 14 for windows (SPSS Inc., Chicago, IL, USA).

Results

Phototherapeutic data

The median number of treatments was 31.4 (range 9–44) and the median top dose 9.46 J/cm² (range 1.1–16.46 J/cm²). NB-UVB treatment led to a good response with clearance in 45%, marked improvement in 22%, and moderate improvement in 31%, according to an outcome scoring scale. Mild side effects were observed in two patients. Six (40%) out of 15 patients who cleared or observed marked improvement remained clear at follow-up for six months to one year, other patients had a few recurrent lesions that did not necessitate retreatment. Patients who relapsed after treatment with NB-UVB were treated with antihistamines with complete response [Table 3(b)].

Measures

For VAS scores and chronic urticaria impact on patients' quality of life scores, the differences between baseline and after treatment scores were significantly lower ($P < 0.001$; for VAS score: 7.90 ± 1.44 vs. 2.72 ± 1.51 and $P < 0.001$; for total quality of life scores: 7.17 ± 1.65 vs. 2.57 ± 1.6) [Table 3(a)].

Discussion

Narrow-band UVB (NB-UVB) phototherapy seems to be an effective and well-tolerated treatment option for COU.

Chronic urticaria is a frequent skin disease persisting often for years with multifactorial trigger factors (autoreactivity, persistent infections, pseudoallergic intolerance reactions) and often exhibits a prolonged course with reduced quality of life and occupational problems. Therapy can be problematic and is not standardized. The recommended first-line treatments are nonsedating H₁ antihistamines. They should be administered in an adequate dose, up to fourfold the normal dose, while considering the side effects, according to many guidelines. However, for different urticaria subtypes and in view of individual variation in the course of the disease and response to treatment, additional or alternative therapies may be required. Besides antihistamines and the eradication or avoidance of identified trigger factors, many other drugs are administered (e.g., corticosteroids, cyclosporin A, antimalarial agents, intravenous immunoglobulins), most of which are not licensed for urticaria. The risk–benefit profile of each alternative (off-label use) should be carefully considered before treatment.^{1,2,10}

Psoralen photochemotherapy or UVA phototherapy for chronic urticaria have yielded inconsistent results,^{10,11} although BB-UVB and NB-UVB phototherapy may be more promising. There are few data to support the use of PUVA photochemotherapy or UVB phototherapy for chronic urticaria.¹¹ For the treatment of chronic urticaria, UVA and BB-UVB treatment for 1–3 months can be added to the antihistamine treatment.^{11,12} The efficacy of PUVA therapy was evaluated by Canadian dermatologists and allergists using a questionnaire, and it was ranked as neutral or ineffective.¹⁵ The report of a 15-patient open study suggested that BB-UVB treatment for 1–3 months might be effective for chronic urticaria, particularly the physical urticarias. However after follow-up, patients with CIU did not preserve the positive effects of treatment as well as patients with cold urticaria, cholinergic urticaria, or dermatographism.^{12,16} Similarly, in a study of 43 patients, UVB treatment induced remission or improvement in 39 patients, although 13 patients relapsed.¹⁷ Accordingly Berroeta *et al.*¹³ recently reported promising results of a large retrospective review in Dundee, Scotland. They treated 88 patients with CIU resistant to standard therapies (e.g., antihistamines and diet) with a less aggressive NB-UVB incremental protocol. The median number of treatments was 22 (median cumulative dose: 1.2 J/cm²). In all, 68 phototherapy courses (72% of evaluable courses) produced clearance (40%) or marked (15%) or moderate (45%) improvement, whereas 27 courses (28%) were documented as unsuccessful. Follow-up data were promising as well; follow-up data after least one year were available in 57 patients, 33% of whom were clear of symptoms, 46% felt that their condition had improved, and 21% felt that it was unchanged. In another study, according to urticaria activity score (UAS), and VAS, Engin *et al.*¹⁴ reported that the mean UAS and VAS were reduced from 34.2 and 6.1 (baseline) to 17.4 and 3.0 (after 20 treatments), respectively [Table 3(b)].

The exact mechanism of action of NB-UVB in urticaria is unknown, but the therapeutic activity could be at least partly related to the NB-UVB photophysical properties and photobiologic effects known so far. Whether mast cell numbers are increased in chronic urticaria is unknown, although their mediator content may be released more easily. Degranulation of mast cells with release of histamine is central to the pathogenesis of urticaria.^{1,2,10,18} Reducing skin mast cell reactivity is one possible explanation of UVB efficacy. In contrast to BB-UVB, NB-UVB has been demonstrated to deeply penetrate into the dermis. Approximately 5–14% of UVB applied to the skin can penetrate the epidermis, basal keratinocytes, and upper dermis.¹⁹ NB-UVB appears to have relatively more suppressive effects than BB-UVB on systemic immune responses.^{19,20} *In vitro* tests and *in vivo*

Table 3 (a) Results of visual analogue scale (VAS) scores and chronic urticaria impact on patients' quality of life scores for narrowband ultraviolet B treatment of chronic urticaria; (b) Results of UVB phototherapy in urticaria compared with literature

(a)		Before			After		P	
VAS pruritus/wheals		7.90 ± 1.44			2.72 ± 1.51		<0.001	
Total quality of life scores		7.17 ± 1.65			2.57 ± 1.6		<0.001	
(b)								
Study	Patients (n)	Duration of disease (years)	Skin phototypes	UVB phototherapy protocol	Mean exposure	Median top dose (mJ/cm ² or J/cm ²)	Results	Follow-up data
Hannuksela <i>et al.</i> ¹²	15 CU and physical urticarias	3.4 years (1–9 years)	NS	BB-UVB. During the first month: three times a week, subsequently once a week	22 (13–27)	0.4 J/cm ² (0.08–0.7 J/cm ²)	Excellent result: 47%; Clearly better: 27%; particularly effective in physical urticarias. No or slight response: 26%	After follow-up patients with idiopathic chronic urticaria did not preserve the positive effects of treatment as well as patients with physical urticarias
Johnson <i>et al.</i> ¹⁷	43 dermatographism	29 months–3 months–6 years)	Types II and III	BB-UVB. Five times a week	13 (6–21)	0.67 J/cm ² 0.14–1.8 J/cm ²	Free from symptoms : 25; Improved: 14; Unchanged: 4	After follow-up period (2 months–2 years); most of the patients (26 patients) had permanent effects, but 13 relapsed within 4–5 months
Berroeta <i>et al.</i> ¹³	88 CIU	3 months–20 years	Types I–III	NB-UVB. Less aggressive, incremental protocol such as 10% every third treatment. Three times a week	22 (2–37)	1238 mJ/cm ² (100–2111 mJ/cm ²)	68 courses (72% of valuable courses) produced in; clearance (40%), marked (15%) and moderate (45%) improvement, whereas 27 of courses (28%) produced unsuccessful response	58 courses (79%) produced a good response at follow-up with clearance in 30%, marked improvement in 29% and moderate improvement in 20%. After at least 1 year in 57 patients; clear of symptoms: 33%; felt that their condition had improved: 46% Unchanged: 21%
Engin <i>et al.</i> ¹⁴	45 CU	NS	Types I and II: 3; Types III and IV: 42	NB-UVB. Initial dose: 200 mJ/cm ² , incremental regimen 10–20%, three times a week	20	1.2 J/cm ² (8–13 J/cm ²)	According to the UAS, UAS reduced from 34.2 to 17.4 (improvement 49.1%)	After follow-up period (3 months) UAS reduced from 17.4 to 15.7 (overall improvement 54.1%)
Borzova <i>et al.</i> ¹⁶	8 symptomatic dermatographism	3 months	Type II: 4; Type III: 2; Type IV: 2	NB-UVB. Initial dose: 50% minimal erythema dose, incremental regimen 20–10–0%, three times a week	15–19	21.9 J/cm ² (14.2–39.4 J/cm ²)	According to the VAS, all patients showed significant improvement in itching (52.3%), and whealing (71%)	Relapse of the symptoms within 12–18 weeks after phototherapy
Aydogan <i>et al.</i> (present study)	22 COU	7 months–16 years	Type III: 2; Type II: 19; Type I: 1	NB-UVB. Standard incremental regimen 20/10/0%, three or four times a week	31.4 (9–44)	9.46 J/cm ² (1.1–16.4 J/cm ²)	Clearance: 45% Marked improvement: 22% Moderate improvement: 31%	Six out of patients (40%) who obtained good response remained clear at follow-up period (6 months–1 years)

BB-UVB, broadband UVB; CIU, chronic idiopathic urticaria; COU, chronic ordinary urticaria; CU, chronic urticaria; NB-UVB, narrowband UVB; NS, not stated; UAS, urticaria activity score; VAS, visual analogue score.

studies showed that UV irradiation can inhibit the stimulated histamine release from unpurified human basophils and human and rat mast cells.^{4-7,21-23} BB-UVA and UVA1 have been reported to decrease the release of histamine from both mast cells and basophils, but UVB only inhibited release from mast cells.²³ An altered membrane function and changes of the intracellular Ca⁺ content are thought to be involved in this mechanism.²³ Alternatively, Danno *et al.*⁴ showed that within an adequate irradiation dose, UVB suppresses histamine release from mast cells, probably by causing noncytotoxic damage to the membrane phospholipid metabolism (e.g. decreased diacylglycerol formation), which is tied to the degranulation mechanism. Some of the positive effects of phototherapy, like the suppression of itch, are due to inhibition on the histamine-releasing cells.²³ BB-UVB, BB-UVA, and PUVA given two to three times a week for four weeks decreased the itch response of the skin when histamine was injected, or when a mast cell degranulator, compound (48/80), was injected.⁹ According to Gollhausen *et al.*,²⁴ pretreatment of the skin with UV (and particularly with UVB) reduced the wheal but not the flare response after intradermal injection of codeine phosphate. NB-UVB probably induces apoptosis of dermal mast cells.²⁵ However, there are controversial results regarding mast cell depletion.²⁶

Ultraviolet B (UVB) has been shown to induce a variety of immunosuppressive and anti-inflammatory cytokines.²⁷ A range of proinflammatory mediators and cytokines are released from mast cells at the time of degranulation.^{1,2,10,18} NB-UVB decreases the production of proinflammatory cytokines released by degranulation. UVB phototherapy is known to induce the production of the anti-inflammatory cytokine interleukin (IL)-10, which may be responsible for the immunosuppressive and anti-inflammatory effects of UVB.²⁸ Intercellular adhesion molecule 1 (ICAM-1) is observed in cells in inflammatory skin diseases (including chronic urticaria) that can cause pruritus.²⁹ UVB irradiation has been found to suppress the expression of ICAM-1 in cultured human keratinocytes.^{30,31} An increased expression for IL-4, IL-5, and interferon (IFN) gamma has been reported in lesional skin of patients with chronic urticaria.^{29,32} BB-UVB increased IL-10 is known to decrease T-helper 1 cell's production of IFN-gamma in keratinocytes.³³ NB-UVB lowers the amount of messenger RNA for IL-12, which is known to decrease B-cell's production of IgE and IFN-gamma in serum.²⁷ *In vitro* tests showed low-dose UVB could inhibit cytokine production (e.g. IL-2, IL-4, IFN-gamma, and tumor necrosis factor alpha).³⁴ We know that suberythemogenic doses of UVB can result in immunological effects, including alterations in circulating CD4/CD8 T-lymphocyte ratio.³⁵ 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.³⁶ Under certain circumstances, T cells can induce activation of mast cells, as well as histamine release.^{36,37} It was proposed that UVB primarily affects the T cells in lesional skin.²⁸

Mild side effects, including erythema and pruritus, were observed in two patients. Six patients (40%) cleared or observed marked improvement and remained clear at follow up for a period of six months to one year, while other patients had a few recurrent lesions that did not need retreatment. Patients who relapsed after treatment with NB-UVB were treated with antihistamines with complete response.

Although not fully assessed and standardized, NB-UVB appears to be effective for the management of COU. This therapy can lead to subjective relief of pruritus and whealing and objective reduction of whealing. NB-UVB phototherapy may restore symptom control with antihistamines in some patients. The promising result of the present study should prompt further controlled clinical trials. Further investigations are needed to clarify the mode of action of NB-UVB phototherapy for chronic urticaria. In view of the efficacy, benefit/risk profile, and costs, NB-UVB may be considered a second-line therapy for COU.

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