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LETTERS TO THE EDITOR

UVA1 Phototherapy of Netherton Syndrome

Rossana Capezzera[1], Marina Venturini[1], Denise Bianchi[2], Cristina Zane[1] and Piergiacomo Calzavara-Pinton[1]
[1]Department of Dermatology and [2]Institute of Pathology, Azienda Spedali Civili, P.le Spedali Civili 1, IT-25123 Brescia, Italy.
E-mail: calzavar@bshosp.osp.unibs.it
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Sir,

Netherton syndrome (NS) is a rare autosomal recessive disorder of keratinization. It is caused by a mutation of the SPINK5 gene that encodes a multidomain serine protease inhibitor (LEKTI) predominantly expressed in epithelial and lymphoid tissues (1). Clinical presentation is characterized by the triad of (i) ichthyosis, i.e. ichthyosis linearis circumflexa (ILC) and/or congenital ichthyosiform erythroderma (CIE), (ii) hair shaft abnormalities, i.e. trichorrhexis invaginata, pili torti and/or trichorrhexis nodosa, and (iii) atopic manifestations, mainly atopic dermatitis, eczema-like rashes and hay fever. The clinical course is chronic, with recurrent exacerbations of atopic and ichthyosiform lesions.

Several treatment approaches, including topical as well as systemic corticosteroids, antibiotics and retinoids, have been investigated with varying, often disappointing, results. UVB phototherapy and topical psoralen plus UVA (PUVA) photochemotherapy are effective, but treatment is accompanied by acute adverse effects and long-term toxicity. As UVA1 (340–400 nm) phototherapy has been found to be an effective and well-tolerated treatment for psoriasis in immunosuppressed patients (2) and atopic dermatitis (3), we investigated its use in the treatment of NS.

MATERIALS AND METHODS

A 36-year-old woman affected by NS was examined at the Dermatology department because of severe itching and cosmetic disfigurement. Topical and systemic steroids had provided partial amelioration of eczematous changes, with a mild relief of itching, but relapse was prompted at any attempt at dose reduction.

At dermatologic examination, skin was erythrodermic and finely desquamating with several crusted linear erosions caused by scratching. In addition, polycyclic and serpiginous hyperkeratotic plaques with a migratory, double-edged scaling at the margins were seen. The hairs of the scalp, eyebrows and eyelashes were sparse, short and brittle. The rest of the physical examination was normal. Results of routine haematology, blood chemistry and urinalysis were within normal values. Total IgE serum level was increased (2873 IU/ml).

A punch biopsy specimen of an ichthyosiform lesion revealed psoriasiform acanthosis with focal parakeratosis and mild spongiosis. No accumulation of eosinophilic, PAS-positive material was detected in the granular layer. Mononuclear inflammatory cells were seen with perivascular distribution. Scalp hair had the characteristic "bamboo" shape under light microscopic examination. In addition, irregularly spaced twists were seen.

Fixed daily exposures of 50 J/cm^2 UVA1 radiation were delivered three times weekly by a Dermalight UltrA1-24 KW irradiation unit (Hönle GmbH, Martinsried, D). Irradiance was measured with a SR 9910 spectroradiometer (Macam Photometrics Ltd, Livingston, UK) and found to be 80 mW/cm^2 at skin level. Treatments were continued until complete clearing was obtained. Unexposed lesions of the armpits and internal clefts served as control lesions. The patient was allowed to use an emollient cream as needed.

RESULTS

Complete remission of both eczematous and ichthyosiform lesions was obtained after 24 exposures. Unexposed control lesions showed no improvement. Similarly, no improvement of the hairs was observed. The treatment was well tolerated and no acute adverse effects to UVA1 exposures were registered. At follow-up, remission was maintained for up to 2 months. Afterwards, lesions progressively relapsed but could be controlled with emollient creams. After 11 months, eczematous and ichthyosiform skin lesions were as severe as at baseline. The patient was amenable to another UVA1 treatment cycle and responded again completely after 20 exposures.

DISCUSSION

Medium dose UVA1 therapy is an effective and well-tolerated treatment option for erythroderma, ILC and the atopic-like rash of NS. The mechanisms through which UVA1 radiation acts on NS abnormalities of keratinization and skin atopic reactions are unknown. UVA1 radiation could enhance the synthesis of other serine protease inhibitors that compensate activity of the defective LEKTI function. The LEKTI deficiency leads to abnormal keratinization of skin and hairs. In addition, protease inhibitors play a pivotal role in a widevariety of immune and inflammatory processes, including T- and B-cell differentiation, activation of cytokines and complement and recruitment of inflammatory cells (4).

Other immunomodulatory effects of UVA1 could be additionally helpful. UVA1 radiation can modulate the immunological function of several cell lines, e.g. keratinocytes, epidermal and dermal dendritic cells and CD4+ T cells as well as dermal mast cells. UVA1 radiation can influence the transcription of soluble mediators with anti-inflammatory activity, e.g. IL-10, α-MSH and PGE_2; the expression of cell-surface associated molecules, such as ICAM-1 and ELAM-1, and the induction of early and late apoptosis in pathogenetically relevant cells. The lack of efficacy in hair abnormalities could be explained by the location of hair bulbs in the deep dermis and subcutis, where UVA1 penetrates poorly.

Both broadband UVB (290–320 nm) phototherapy (5)

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and PUVA (320–400 nm) photochemotherapy (6, 7) have been reported as effective treatments for NS. However, UVA1 phototherapy is preferable, because the overall tolerability is better without episodes of oral drug intolerance or excessive phototoxic reactions.

Skin carcinogenesis is the most important hazard of all phototherapies, particularly if prolonged and protracted treatment cycles with high cumulative UV dosages are delivered for the treatment of a lifelong disease. However, the overall risk of UVA1 radiation seems lower than the potential of PUVA (8) and UVB (9). In addition, "medium dose" UVA1 phototherapy is delivered at doses much below the erythematous thresholds of all phototypes, whereas UVB and PUVA regimens are usually based on near-erythemogenic doses. Therefore, since the action spectra of erythemogenicity and carcinogenicity substantially overlap, the risk of "medium dose" UVA1 therapy may be reasonably lower.

In conclusion, medium dose UVA1 phototherapy seems an effective and well-tolerated treatment option for NS skin lesions. In addition, UVA1 therapy allowed prolonged periods of remission and a sustained efficacy for relapses. However, in order to limit its carcinogenic activity, its use should be restricted to the treatment of acute and disfiguring exacerbations.

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