Narrowband UVB and psoralen-UVA in the treatment of early-stage mycosis fungoides: A retrospective study

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Background: Treatment of early-stage mycosis fungoides (MF) consists of topical steroids, phototherapy (UVB), photochemotherapy (psoralen plus UVA [PUVA]), topical nitrogen mustard, or total skin electron-beam irradiation. It has been reported that the same effective UVB dose is safer than PUVA regarding carcinogenicity and produces fewer side effects. Narrowband UVB (311 nm) results in less irritation and erythema and is more effective compared with broadband UVB.

Objective: Our purpose in this retrospective study was to analyze the response to treatment, relapse-free interval, and irradiation dose in 56 patients with early-stage MF (stage Ia and Ib). A total of 21 patients were treated with narrowband UVB (311 nm); 35 patients were treated with PUVA.

Results: Narrowband UVB treatment led to complete remission in 17 of 21 patients (81%), partial remission in 4 of 21 (19%), and none showed progressive disease. PUVA treatment led to complete remission in 25 of 35 patients (71%), partial remission in 10 of 35 (29%), and none showed progressive disease. The mean relapse-free interval for patients treated with UVB was 24.5 months (range, 2-66 months) and for patients treated with PUVA, 22.8 months (range, 1-43 months).

Conclusion: Narrowband UVB therapy for patients with early-stage MF is an effective treatment modality. It has several advantages over treatment with broadband UVB and PUVA. When treating patients with early-stage MF it may be beneficial to start with narrowband UVB therapy and, if there is progression or no response, switch to PUVA therapy. (J Am Acad Dermatol 2003;48:215-9.)
tive study of patients with clinical and histologically proven early-stage MF treated with narrowband UVB and PUVA.

**PATIENTS AND METHODS**

**Patients**

We analyzed retrospectively 56 patients with histologically proven early-stage MF treated with narrowband UVB and PUVA between 1982 and 1998. In the first period of the study most patients were assigned to PUVA; in the second period most patients were assigned to narrowband UVB. Selection was not made according to severity of disease. All patients had stage Ia and Ib disease. The stage of the disease was determined on the basis of the type and extent of skin involvement (without the presence of lymph node, visceral, or blood involvement) according to a modification of the classification scheme by Fuks et al,\textsuperscript{13} which can easily be translated into the TNM system.\textsuperscript{14–16} Stage Ia is MF confined to the skin with less than 10% patches and plaques covering the skin surface (ie, T1N0M0 in the TNM classification). Stage Ib is MF confined to the skin with equal or more than 10% patches and plaques covering the skin surface (T2N0M0). No obvious difference between the 2 groups were observed. A total of 21 patients (13 men, 8 women; mean age 45 years) were treated with narrowband UVB and 35 patients (20 men, 15 women; mean age 53 years) were treated with PUVA. We studied the response to treatment, the relapse-free interval, and irradiation dose. Biopsy specimen were taken before and after UV phototherapy (Fig 1).

**Methods**

Patients were exposed to UV radiation from fluorescent tubes of 2 different types in a square light cabinet with reflecting walls. The cabinet, measuring $1.3 \times 1.3$ m, contained 60 broadband narrowband UVB lamps (Philips TL100W/01, Eindhoven, The Netherlands) and 32 broadband lamps (Philips TL100W/09). These lamps emit mainly UVA and less than 0.5% UVB, and are of the same type as are used in many cabinets for PUVA therapy. The spectrum of the narrowband UVB lamps used in this study (TL-01, Philips) is dominated by a strong and narrow peak (bandwidth 2.5 nm) around 311 to 312 nm, with a second peak around 305 nm. Compared with currently used fluorescent UVB lamps, (eg, TL-12, Philips and FS sunlamps, Westinghouse, Bloomfield, Ind) the narrowband UVB lamp we used has a much smaller output at the most erythematogenous effective wavelengths of 300 nm or less. The spectral composition of the UV radiation in the light cabinet was selected by switching on the lamps of the desired type.

The spectral distribution (irradiance) measurements were performed with a calibrated spectroradiometer (model 742, Optronic Laboratories, Orlando, Fla). The irradiances were checked routinely with a UVA or UVB detector (Waldmann AG, Schwenningen, Germany). The irradiance for UVA was, on average, 5.8 mW/cm$^2$ and, for UVB, 4.1 mW/cm$^2$.

UVB therapy was conducted twice a week for 3 to 66 months (mean, 14 months). PUVA was administered twice a week for 2 to 37 months (mean, 11 months). The UVB doses were pending during the whole study and chosen with the aim to elicit a slight, but well-tolerable erythema after each exposure.\textsuperscript{5,7} The first exposure was 70% of the predetermined minimal erythema dose on the trunk. Successive doses were determined using the following

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*Fig 1. A, Patch-stage MF pretreatment showing papillary dermal mononuclear cell infiltrate containing abnormal lymphocytes that demonstrate epidermotropism. B, Marked reduction of atypical lymphocytic infiltrate in same patient after narrowband UVB phototherapy for 3 months. (Hematoxylin-eosin stain; original magnification ×166.)*
If the previous exposure had caused no perceptible effect, the next exposure time was increased by 40%; if the previous exposure induced just a slight erythema, the next exposure time was increased by 20%; and in case of a marked erythema, the same exposure time repeated.

The UVA radiation was administered 2 hours after the intake of 8-methoxypsoralen (8-MOP, Melodine, Galderma Belgilux, Paurs, Belgium). The doses of UVA were also chosen according to the guideline to cause a slight erythema after each exposure. The first exposure was 70% of the predetermined minimal phototoxic dose. Successive exposures were on the basis of skin reactions: if the previous exposure had not caused a noticeable effect, the next exposure time was increased by 40%; if the previous exposure induced a doubtful erythema, it was increased by 20%; and if it caused a slight erythema, the same exposure time was repeated. This practice was slightly different from that of UVB because 1 minimal phototoxic-dose exposure takes 3 days to develop, whereas 1 minimal erythema dose-UVB exposure develops within 1 day.

Clinical response was rated as follows: complete remission (no disease activity present); partial response (decrease of disease activity < 50%); and progressive disease (increase of disease activity > 25%). Before and after therapy, 4-mm punch biopsy specimens were taken from each patient at the site of a representative skin lesion for histologic examination. The specimens were processed routinely and stained with hematoxylin and eosin for light microscopic examination to study the histologic response.

RESULTS

The mean time interval from date of diagnosis to UVB therapy was 3 months, and, for PUVA, 7 months. The total UVB irradiation dose ranged from 21 to 62.8 J/cm² (mean: 31.8 J/cm²), and the total UVA dose ranged from 20 to 1760 J/cm² (mean: 283.2 J/cm²). The mean follow-up period for narrowband UVB therapy was 77 months, and, for PUVA, 45 months. UVB treatment lead to complete remission in 17 of 21 patients (81%) and partial remission in 4 of 21 (19%). PUVA treatment lead to complete remission in 25 of 35 patients (71%) and partial remission in 10 of 35 (29%). There were no patients with progressive disease in either treatment groups. The mean relapse-free interval for patients with MF treated with UVB was 24.5 months (range: 2-66 months) and, for patients treated with PUVA, 22.8 months (range: 1-43 months) (Table I). Patients who relapsed after treatment with narrowband UVB or PUVA were treated with topical steroids, topical nitrogen mustard, (narrowband) UVB, or PUVA.

Acute adverse effects from narrowband UVB reported were burning and pruritus in 1 patient. Two patients reported postinflammatory hyperpigmentation. Patients treated with PUVA reported nausea 3 times and headache twice after systemic psoralen intake; 2 patients reported burning and pain after treatment. All patients continued treatment. The follow-up period was too short to report chronic adverse effects like photoaging and photocarcinogenesis.

DISCUSSION

The results of phototherapy with broadband UVB (280-350 nm wavelength) in the treatment of MF have been reported previously. Ramsay et al reported results from a retrospective study of 32 patients with histologically proven MF and 5 patients with parapsoriasis who were treated with broadband UVB. Of these patients, 84% had patch-stage disease, and 13% had plaque-stage disease. Of these patients 71% achieved a complete remission. The median time to remission was 5 months. None of the patients with plaque-stage disease were responsive to UVB treatment. Of the patients with patch-stage disease, 20% relapsed while on or off therapy. Our results are in accordance with this study, although we did find a response to UVB therapy in patients with MF plaques (Table II).

Resnik and Vonderheid reported similar results.
in their 15-year follow-up study of 31 patients with histologically proven cutaneous T-cell lymphoma who were treated with home UVB. In this study, 31 patients underwent home UVB phototherapy (280-350 nm). Of these patients, 21 were classified as having stage Ia disease, 9 had stage Ib disease, and 1 had stage Ila disease according to the TNM system adopted by the MF Cooperative Group. An objective clinical response was observed in 85% of the patients, with 74% achieving a complete clinical and histologic response to therapy. The maximum duration of the remission ranged from 5 months to more than 15 years (median, 51 months). The patients with plaque-stage disease tended to respond less favorably. After maintenance phototherapy was discontinued, 7 patients (23%) had a sustained disease-free interval lasting more than 58 months (median, >90 months).

Current study by Hofer et al and a study by Clark et al have reported treating early-stage MF with narrowband UVB. However, in the study by Hofer et al only 6 patients with early-stage (non-infiltrated patch) MF and 14 patients with small-plaque parapsoriasis were treated. Because there is ongoing controversy and inconsistent use of the terms “large-” and “small-plaque parapsoriasis,” it is perhaps better to abandon these terms and not to include these patients in a study.

In the study by Clark et al, 8 patients with histologically proven patch-stage MF were treated with narrowband UVB 3 times weekly using a standard protocol. Complete clearance of MF was achieved in 6 patients in a mean of 9 weeks or 26 treatments (range, 20-37 weeks) and 4 patients obtained prolonged remissions. Mean time to remission was 20 months (range, 11-40 months). Partial response to narrowband UVB or poor histologic improvement was associated with rapid relapse (Table II).

The mechanisms of action of (narrowband) UVB therapy in MF are still unknown. In vitro experiments show that UVB decreases the allo-activating and antigen-presenting capacity of Langerhans cells and increases interleukin 2 and interleukin 6 production by human keratinocytes. Increased tumor necrosis factor has also been detected after UVB irradiation. Possibly, UV light suppresses the function of the neoplastic population of clonal T cells in the skin and serves as an immune up-regulator. Also the overall effect of PUVA in MF may be a result of preferential mitotic inhibition, killing of neoplastic T cells, or both in the skin and superficial capillaries. Other PUVA effects in MF include psoralen adduct damage to cell organelles (eg, mitochondria) and alterations in the immune system. McGregor et al indicated p53 mutations in tumor-stage MF; a mutation spectrum strikingly similar to that reported in nonmelanoma skin cancer and characteristic of DNA damage caused by UVB radiation. Therefore, caution using UV therapy in patients with MF was advised.

In our retrospective study, we found that narrowband UVB therapy for patients with early-stage MF is an effective treatment. Among our patients, 81% achieved complete remission, 19% achieved partial remission, and none showed progressive disease. Mean relapse-free interval was 24.5 months. Considering the benefits of UVB therapy over PUVA, it may be advisable when treating early-stage MF to start with narrowband UVB therapy and, if there is progression during therapy or no response to therapy, switch to PUVA therapy.

Table II. Results of UVB treatment in early-stage mycosis fungoides compared with literature data

<table>
<thead>
<tr>
<th>Broadband UVB</th>
<th>No. patients</th>
<th>Stage of disease</th>
<th>Follow-up (mo)</th>
<th>CR (%)</th>
<th>PR (%)</th>
<th>Time to remission (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ramsay et al</td>
<td>32</td>
<td>Ia,b</td>
<td>84</td>
<td>71</td>
<td>3</td>
<td>22 (3-74)</td>
</tr>
<tr>
<td>Resnik and Vonderheid</td>
<td>31</td>
<td>Ia,b</td>
<td>36</td>
<td>74</td>
<td>11</td>
<td>51 (5-180)</td>
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<tr>
<td>Narrowband UVB (311 nm)</td>
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<tr>
<td>Hofer et al</td>
<td>6</td>
<td>Ia,b</td>
<td>unknown</td>
<td>83</td>
<td>17</td>
<td>6 (2-15)</td>
</tr>
<tr>
<td>Clark et al</td>
<td>8</td>
<td>Ia,b</td>
<td>75</td>
<td>75</td>
<td>25</td>
<td>20 (11-40)</td>
</tr>
<tr>
<td>Current study</td>
<td>21</td>
<td>Ia,b</td>
<td>77</td>
<td>81</td>
<td>19</td>
<td>25 (2-66)</td>
</tr>
</tbody>
</table>

CR, Complete response; PR, partial response.