Narrowband TL-01 Phototherapy for Patch-Stage Mycosis Fungoides

Colin Clark, MRCP; Robert S. Dawe, MRCP; Alan T. Evans, MRCPath; Graham Lowe, FRCP; James Ferguson, FRCP

**Background:** Although patch-stage mycosis fungoides (MF) has a generally good prognosis, and long-term survival rates with current therapies (UV-B, phototherapy, topical nitrogen mustards, electron-beam therapy) are similar, there is concern regarding their potential adverse effects. Narrowband or TL-01 UV-B phototherapy (311 nm), in use for more than 10 years, is more effective than broadband UV-B for the treatment of psoriasis, with an efficacy approaching that of psoralen UV-A. This open study assesses TL-01 as an alternative therapy for patch-stage MF.

**Observations:** Eight white patients (4 men, 4 women; age range, 66-83 years) with histologically proven patch-stage MF received TL-01 phototherapy 3 times weekly using a standard protocol. Complete clearance of MF was achieved in 6 cases in a mean of 9 weeks or 26 treatments (range, 20-37 weeks) and 4 patients have had prolonged remissions. Mean duration of clinical improvement has been 20 months (range, 11-40 months). Partial response to TL-01 or poor histologic improvement was associated with rapid relapse.

**Conclusions:** TL-01 is an effective, convenient therapy that may have less risk of long-term adverse effects than current alternatives. Although larger prospective studies are necessary, for some patients intermittent courses of TL-01 may offer effective long-term therapy.

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Mycosis fungoides (MF) is an uncommon T-cell lymphoma, initially confined to the skin, that can evolve from limited to widespread cutaneous disease. Progression from patch, plaque, and tumor stages may, in a few cases, culminate in disseminated lymphoma with visceral and lymphatic involvement. In patch-stage MF, the malignant clone of T helper cells demonstrates epidermotropism with abnormal cells evident in the epidermis and superficial dermis. The accessibility of this site for local treatment in conjunction with the failure of studies to demonstrate prolonged survival with more aggressive systemic therapy confirms topical therapeutic modalities as the treatment of choice for patch-stage MF.

Commonly used treatments for early MF include photochemotherapy (psoralen UV-A [PUVA]) and topical nitrogen mustard (mechlorethamine) or carmustine chemotherapy. Total-skin electron-beam radiation therapy is also used in some centers. All have been reported to have equal efficacy in stage 1 MF with a complete response to treatment in more than 70% of cases. Although the median duration of disease-free remissions reported for these therapies is variable, the long-term survival rates are not significantly different. Broadband UV-B has also been shown to have similar efficacy for skin clearance, with a 23% sustained disease-free remission on discontinuation of maintenance therapy in stage 1a disease (mainly patch-stage disease). Although several studies have suggested that narrowband TL-01 is more effective than broadband UV-B in the treatment of psoriasis, there is only 1 report of its use in MF.

**RESULTS**

Eight patients received a total of 11 TL-01 courses (Table 2). TL-01 was well tolerated, but toward the end of most courses dose increments were reduced to 10% when higher TL-01 doses were being used. All patients achieved a rapid and clinically significant improvement in their condition with abolition or reduction of pruritus. Six patients achieved complete clearance of the eruption (Figure 1), and the other 2 responded satisfactorily with partial clearance. For those patients who achieved complete clearing of the eruption, the median duration of disease-free remissions was 26 treatments (9 weeks) as required. While some of the residual areas were in sanctuary sites such as the gluteal cleft, others were not. One patient has had repeated prolonged clinical remissions without maintenance therapy (patient 1). Patient 2 relapsed soon after initial TL-01 clearance but has achieved prolonged re-
PATIENTS AND METHODS

Eight white patients (age range, 66-82 years) with histologically proven patch-stage MF received narrowband TL-01 phototherapy. All histologic analyses were done independently by 2 of us (J.G.L. and A.T.E.), and patients with preMF or doubtful histologic findings were excluded. Pretreatment and posttreatment skin biopsy specimens were taken from patches, residual areas, or treatment-cleared sites. All had normal full hematologic and biochemical profiles (full blood count, urea and electrolyte, and liver function tests) and urinalysis and chest radiograph findings. None had palpable lymphadenopathy or organomegaly, but 1 patient (case 3) had an atypical acute presentation underwent bone marrow examination and an abdominal computed tomographic scan, both of which produced normal results. Cutaneous involvement was classified by recognized TNMB and clinical staging protocols11 (Table 1 and Table 2). All of the patients had clinical stage 1 disease (T1 or T2, N0, M0), with cutaneous involvement consisting of patch-stage disease of limited extent in 4 cases (stage 1a) and more widespread in the others (stage 1b) (Table 3). Although a Sézary preparation was not available for all patients, the b classification does not affect the clinical staging. Patients were offered TL-01 treatment when prior therapy (topical steroids, PUVA) had either failed or produced adverse effects or if they were reluctant to have systemic medication. There was a minimum of 3 months between TL-01 treatment and previous phototherapy. Patients used emollients during treatment, and topical steroids were limited to use at sanctuary sites.

All treatments were carried out in a purpose-built cubicule constructed by the medical physics department of Ninewells Hospital, Dundee, Scotland, containing 50 100-W TL-01 fluorescent lamps (Philips Electronics, New York, NY). The irradiance within the cubicule changed from 3.33 mW/cm² to 2.22 mW/cm² during the study period, and exposure times were adjusted accordingly. Irradiance was measured monthly, by a standard protocol, with an international light meter (IL-4000; Able Instruments, Reading, England) calibrated using a spectroradiometer.

Patients received TL-01 phototherapy by our standard protocol.13 The minimum erythemal dose for each patient was determined prior to starting treatment by irradiation of a template of eight 1×1 cm² apertures on the upper back with a TL-01 source 20 cm from the patient. Two standard ranges of doses were administered: 25 to 390 ml/m² for phototypes 1 and 2 or 70 to 770 ml/m² for phototypes 3 and 4.14 Therapy commenced with 70% of the minimum erythemal dose. Treatment was administered 3 times weekly with 20% increment at each exposure unless modified by the erythemal response assessed at 48 hours after treatment. Phototherapy was continued until complete clinical clearance or minimal residual activity was achieved. Minimal residual activity and partial response were defined as a greater than 90% and 50% improvement, respectively, with persistent skin disease despite continuing treatment (ie, sanctuary sites). Relapse was defined as clinically significant disease requiring further therapy. A face shield and gloves were used to minimize UV-B exposure to areas habitually exposed to sunlight but unaffected by MF (cases 2, 3, 5, and 7).

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reduction of the inflammatory infiltrate (cases 1, 2, 3, 6, 7, and 8). Marked reduction of the inflammatory infiltrate with loss of epidermotropism and Pautrier microabcesses was found in those who achieved a prolonged remission (patients 1 and 2), but acanthosis and a mild chronic atypical dermal inflammatory infiltrate remained (Figure 2). In case 3, despite apparent clinical clearance, the atypical lymphocytic infiltrate was only moderately reduced after treatment, and the subsequent remission was short lived. Partial response (case 4) was associated with a persistent, atypical lymphoid cell infiltrate, epidermotropism, Pautrier microabcesses, and acanthosis.

**COMMENT**

The most important prognostic indicators for MF are the extent and type of skin involvement and whether extracutaneous spread has occurred. Failure to achieve complete remission following initial therapy is also a risk factor for progression. The outlook for most patients receiving treatment for limited patch MF (stage 1a) is good, with a life expectancy similar to the normal population (cases 1, 5, 6, and 8). More extensive patch/plaque disease (stage 1b) is associated with disease progression and mortality. One study reports disease progression in 24%

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**Table 3. Clinical Characteristics of Study Patients With Patch-Stage Mycosis Fungoides (MF)**

<table>
<thead>
<tr>
<th>Case No./Age,y/Sex</th>
<th>Phototype</th>
<th>Duration of Pre-MF Skin Eruption, y</th>
<th>Duration of MF, y</th>
<th>Stage, TNM</th>
<th>Previous Treatment</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/67/M II 29 3 1a</td>
<td>PUVA, topical steroid</td>
<td>PUVA pain</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2/77/M I 19 4 1b</td>
<td>PUVA, topical steroid</td>
<td>PUVA pain, basal cell carcinoma × 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3/82/M III 4 3 1b</td>
<td>PUVA, topical steroid</td>
<td>Basal cell carcinoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4/71/F I 5 1 1b</td>
<td>PUVA, topical steroid</td>
<td>basal cell carcinoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5/78/M II 1.5 1 1a</td>
<td>Topical/systemic steroid</td>
<td>solar keratoses, lentigines, basal cell carcinoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6/72/F II 70 1 1a</td>
<td>PUVA, topical steroid</td>
<td>Basal cell carcinoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7/71/F I 10 2 1b</td>
<td>Topical steroid</td>
<td>Basal cell carcinoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8/66/M III 19 1 1a</td>
<td>PUVA, topical steroid</td>
<td>Psoralen-associated nausea</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*PUVA indicates psoralen–UV-A. The psoralen used in all previous treatments was oral 8-methoxsalen.
of those with generalized patch/plaque MF, and 20% of patients ultimately died of their disease.\textsuperscript{16} However, clinical staging fails to differentiate between patch-stage MF and the more advanced plaque-stage disease. As a result, it is difficult to directly compare outcome and treatment efficacy between studies of stage 1 MF and those where only patch-stage disease has been included. Despite this, when controlled for the disease stage, the efficacy of currently available topical therapies is similar in respect to complete response and long-term survival rates, although the reported duration of disease-free remission is variable.

Although the ability of UV-B to clear patch-stage MF has been known since the 1950s, it seems to have been rarely studied.\textsuperscript{17} Two reports of broadband UV-B phototherapy for “early” MF have shown similar effectiveness. Most of these patients had limited patch-stage disease, and complete remission was achieved in more than 80% in a median of 5 months to clearance, results comparable with other topical therapies.\textsuperscript{2,3,10} Both studies used maintenance regimens following complete remission and noted high relapse rates when this treatment was stopped. Nevertheless, 23% of patients in 1 study had a long-term sustained remission (>58 months).\textsuperscript{4} Ultraviolet-B phototherapy was most effective with patch-stage or thin-plaque disease, and the authors concluded that this might be due to the limited ability of UV-B to penetrate thicker lesions. This may also be reflected in an Italian retrospective study where PUVA was reported to be more effective than broadband UV-B for stage 1 MF.\textsuperscript{20}

Narrowband phototherapy uses the Philips TL-01 lamp, which has an emission spectrum (311-313 nm) within the therapeutic action spectrum for psoriasis. In many centers it has replaced traditional broadband UV-B phototherapy as the treatment of choice for psoriasis and other dermatoses.

In this study, the response to TL-01 was best when there was a long history of premycotic eruption suggestive of an indolent and less aggressive disease more susceptible to this therapy. No correlation between skin phototype and therapeutic response was found (Table 3 and Table 4). Although persistent histologic abnormalities were demonstrated in all cases, similar findings have been reported with PUVA.\textsuperscript{21} Without maintenance therapy, 3 patients relapsed rapidly and required alternative therapy. One patient had extensive, indurated MF patches and her partial response to TL-01 and subsequent relapse was, perhaps, predictable (case 4).

Although current topical therapies are effective, they can have clinically significant adverse effects. High cumulative numbers of PUVA treatments in patients with psoriasis have been associated not only with an increased incidence of nonmelanoma cutaneous carcino-

<table>
<thead>
<tr>
<th>Case</th>
<th>TL-01 Courses</th>
<th>No. of Treatments</th>
<th>MED, mJ/cm²</th>
<th>PEAK TL-01 Dose, mJ/cm²</th>
<th>Clinical Response</th>
<th>Histologic Improvement</th>
<th>Time to Relapse, mo†</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>May 1992</td>
<td>20</td>
<td>140</td>
<td>673</td>
<td>Clear</td>
<td>...</td>
<td>40</td>
</tr>
<tr>
<td>2</td>
<td>November 1997</td>
<td>20</td>
<td>200</td>
<td>1192</td>
<td>Clear</td>
<td>Marked</td>
<td>24</td>
</tr>
<tr>
<td>2</td>
<td>February 1997</td>
<td>37</td>
<td>191</td>
<td>814</td>
<td>Clear</td>
<td>Marked</td>
<td>&lt;3</td>
</tr>
<tr>
<td>3</td>
<td>January 1996</td>
<td>28</td>
<td>2111</td>
<td>Clear</td>
<td>Moderate</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>May 1997</td>
<td>14</td>
<td>70</td>
<td>1083</td>
<td>Partial response</td>
<td>Minimal</td>
<td>...</td>
</tr>
<tr>
<td>5</td>
<td>June 1997</td>
<td>30</td>
<td>200</td>
<td>1919</td>
<td>Partial response</td>
<td>...</td>
<td>Remission</td>
</tr>
<tr>
<td>6</td>
<td>June 1998</td>
<td>37</td>
<td>285</td>
<td>Clear</td>
<td>Marked</td>
<td>Remission</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>July 1998</td>
<td>33</td>
<td>1442</td>
<td>Clear</td>
<td>Moderate</td>
<td>Remission</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>August 1998</td>
<td>38</td>
<td>195</td>
<td>1083</td>
<td>Clear</td>
<td>Marked</td>
<td>...</td>
</tr>
</tbody>
</table>

* MED indicates minimum erythemal dose; ellipses, not available; MRA, minimal residual activity; and NA, not applicable.
† Moderate improvement indicates residual mycosis fungoides; marked improvement is not diagnostic for mycosis fungoides.
‡ Relapse is defined as return of clinically significant disease.
mas, but also a small but important increase in malignant melanomas. Topical nitrogen mustard causes a high incidence of allergic contact dermatitis, an increased incidence of cutaneous and internal malignancies, and environmental contamination. Carmustine is associated with marrow suppression, intertrigo, and telangiectasia. Total-skin electron-beam radiation therapy can produce serious adverse effects including erythema, edema, desquamation, total alopecia and nail loss, blistering, pigmentation, telangiectasias, and chronic xerosis.

When compared with PUVA, TL-01 phototherapy has several advantages. As systemic psoralen is not required, related acute adverse effects (nausea, headaches, and light-headedness) and the need for protective glasses after treatment are avoided. TL-01 phototherapy usually has shorter irradiation times, which aids compliance since patients with MF are often elderly and infirm. It can also be used in the rare instance where therapy is required during pregnancy.

Although we have achieved sustained remissions in 50% of our patients (mean, 20 months), others have reported more transient remissions. Unlike PUVA, with which maintenance is effective, once-weekly treatment with TL-01, attempted for 1 patient (case 3), proved difficult because painful posttreatment erythema developed despite UV-B dose reduction.

Acute adverse effects from TL-01 phototherapy can include erythema and pruritus. The major chronic adverse effects are photoaging and photocarcinogenesis. Despite the absence of long-term prospective studies, the photocarcinogenic risk of TL-01 seems to be less than that associated with PUVA. Of concern is the recent discovery of p53 tumor suppressor gene mutations in some MF tumors (40%). These mutations were predominantly in C:T and CC:TT transitions, which are characteristic of UV-B–induced DNA damage and were not found in plaque-stage disease. This might suggest a role for UV radiation therapy in the progression of the later stages of MF. However, in the absence of epidemiological evidence for the association of UV radiation and MF progression, further work is necessary to determine the significance of these findings.

Narrowband phototherapy offers the potential for prolonged remission for some patients with patch-stage MF. Although our study cohort was small (8 patients), we believe TL-01 treatment should be included among the initial therapeutic options in view of its efficacy, convenience, and likelihood of fewer long-term adverse effects. Clearly, larger prospective, long-term follow-up studies are necessary to define the role of TL-01 in patch-stage MF. However, our experience has shown TL-01 to be effective when PUVA therapy has been unsatisfactory or curtailed because of adverse effects. The optimum therapeutic regimen for TL-01 therapy in MF is still to be determined, but a more prolonged induction phase or the use of maintenance therapy may improve its efficacy while retaining a favorable adverse-effect profile.

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REFERENCES