Phase 1/2 Pilot Study of Methotrexate-Laurocapram Topical Gel for the Treatment of Patients With Early-Stage Mycosis Fungoides

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Objectives: To assess the safety and tolerability of a topical gel formulation combining methotrexate and laurocapram and to obtain preliminary information on the therapeutic potential of methotrexate-laurocapram in patients with early-stage mycosis fungoides (stage IA or IB).

Design: An open-label, phase 1/2 pilot study.

Setting: Two academic referral centers.

Patients: Ten patients 18 years or older with histologically confirmed stage IA or IB mycosis fungoides.

Intervention: The gel formulation of methotrexate-laurocapram was applied to the total body surface, excluding genital, perianal areas, nipples, face, and skin under the breasts, on an every-other-day basis for 24 consecutive weeks.

Main Outcome Measures: The safety of methotrexate-laurocapram was assessed in this study by reviewing adverse events and laboratory data. Efficacy outcomes included changes in lesion condition and severity assessments, reduction in area of sample lesions, and the investigator’s global evaluation.

Results: Adverse events consisted of skin reactions of mild severity. No clinically significant laboratory abnormalities were observed. Based on the investigator’s global evaluation at the end of the treatment phase (week 24), 7 (78%) of 9 patients demonstrated a slight-to-moderate response to treatment with methotrexate-laurocapram. Statistical significance (P = .049) was reached for induration and pruritus, a trend (P = .10) was observed for erythema, and no change was found for scaling (P = .37).

Conclusions: These findings indicate that the topical administration of methotrexate-laurocapram is safe and in general well tolerated. This treatment may represent a new therapeutic potential for patients with mycosis fungoides.

Arch Dermatol. 2003;139:624-628

Mycosis fungoides (MF) is the most common form of cutaneous T-cell lymphoma (CTCL). Mycosis fungoides is predominantly an indolent disease with 5-year disease-specific survival rates of 100% and 80%, respectively, for individuals with either limited skin involvement or skin tumors. To date, no therapies for MF have demonstrated a survival advantage. Thus, skin-directed therapies remain the first line of therapy in patients with early-stage MF (skin limited). Currently, these therapies include topical steroids, topical chemotherapy (topical carmustine and nitrogen mustard), topical retinoids, phototherapy, and local radiation.

Although oral or parenteral methotrexate is approved by the Food and Drug Administration for the treatment of advanced MF, this agent has shown efficacy in treating erythrodermic MF, and oral methotrexate has been used off-label for resistant patch or plaque MF and tumor stage MF. However, its systemic toxicity potential (gastrointestinal tract, bone marrow, lungs, kidneys, liver, and immune system) has precluded its use in patients with early-stage MF. No topical formulations of methotrexate are currently commercially available for clinical use. Topical therapy of early-stage MF with the existing oral or parenteral formulations of methotrexate is ineffective because of the inability of methotrexate to penetrate the stratum corneum from aqueous solutions. The development of a topical formulation of methotrexate with enhanced dermal penetration characteristics would hence provide an additional effective therapy for patients with early-stage MF, a population for whom oral or intravenous methotrexate is currently not indicated for treatment.
Methotrexate-laurocapram is a topical hydrophilic gel formulation of methotrexate (1% wt/wt) with the penetration enhancer laurocapram (Azone). Laurocapram is a lipophilic compound initially developed by Whitby Research (Richmond, Va) and now manufactured by Durham Pharmaceuticals (Durham, NC) that has been shown to enhance percutaneous absorption of a wide variety of pharmaceutical compounds. Results obtained in patients with psoriasis indicated that the topical application of methotrexate-laurocapram was safe, well tolerated, and led to an improvement of the disease status in a significant proportion of patients. Preliminary results from a pilot study in 4 patients with early-stage MF (stage IA or IB) indicated that methotrexate-laurocapram was both safe and well tolerated, and 2 patients had a moderate response with a 50% to 99% disappearance of measurable and assessable disease. We present the results of a phase 1/2 study in 10 patients with early-stage MF who were administered a topical formulation of methotrexate-laurocapram every second day for 24 consecutive weeks.

METHODS

The primary objective of this open-label, phase 1/2 study was to evaluate the safety and tolerability of the topical administration of methotrexate-laurocapram in patients with stages IA and IB plaque CTCL. The secondary objectives were to evaluate the efficacy of topical methotrexate-laurocapram in this patient population and to obtain preliminary information on the systemic absorption of methotrexate following topical administration of methotrexate-laurocapram.

PATIENT POPULATION

To be enrolled in the study, patients with histologically confirmed stage IA or IB CTCL had to be 18 years or older, be in good general health, and have liver transaminase levels less than twice the upper limit of the normal range, serum creatinine levels less than 2.0 mg/dL (176.8 µmol/L), hemoglobin level greater than 11 g/dL, a white blood cell count greater than 4000/µL, and platelet counts greater than 130,000/µL. Patients with stage II or higher CTCL, those with a history of intolerance to methotrexate or related drugs, or those currently undergoing treatment with sulfonamides and/or trimethoprim, phenytoin, sulfonylureas, phenylbutazone, or systemic steroids were excluded. Also excluded were patients with active hepatitis or active cytomegalovirus infection, systemic cutaneous bacterial infection or viral disease, or any other active malignant neoplastic disorder. Pregnant or lactating women or individuals of childbearing potential unwilling to practice adequate contraception were not eligible. A washout period was required before study entry as follows: 6 weeks for topically mechloethamine hydrochloride, topical steroids, topical carmustine, phototherapy, and oral methotrexate or 12 weeks for electron beam therapy. The study protocol was approved by the local institutional review boards, and informed consent was obtained for all patients before the initiation of the study.

TREATMENT PLAN

The gel formulation of methotrexate-laurocapram (provided in 2-oz jars containing 30 g of product) was applied at daily doses of either 12.5 or 25 g/m² to the total body surface, excluding genital, perianal areas, nipples, face, and skin under the breasts, on an every-other-day basis for 24 consecutive weeks. Based on the original design of this pilot study, the first patient, who was enrolled at the University of British Columbia, Vancouver, also received daily topical administration of nitrogen mustard on half the body, whereas the other half of the body was treated with 23 g/m² of methotrexate-laurocapram; the results obtained with nitrogen mustard in this particular patient will be the subject of a separate report. To comply with interactions with regulatory authorities, the protocol was then modified to include patients treated with methotrexate-laurocapram at Boston Medical Center only (Boston, Mass).

SAFETY ASSESSMENTS

The following safety assessments were conducted at screening, baseline, and every 4 weeks during the study: routine laboratory evaluations (hematologic and clinical chemical analyses) and pregnancy test. Urinalysis was performed at screening, baseline, weeks 12, and week 26. Adverse reporting and a physical examination were conducted every 2 weeks during the first month of the study and every 4 weeks thereafter.

EFFICACY ASSESSMENTS

The evaluation of therapeutic response to treatment included the body surface area involvement of lesions and the assessment of severity in 3 test lesions selected before the initiation of treatment; these outcomes were evaluated at baseline, weeks 12 and 24, and 2 weeks following the termination of treatment (week 26). Changes in severity outcomes (eg, induration, erythema, scaling, and pruritus) relative to baseline were graded as worsened (≤−2), no change (≥−1 and ≤1), or improved (≥2) for each test lesion and summed across the lesions for each patient. Photographic documentation was obtained at baseline, week 12, and week 24. Photographs were used to assess both the body surface area and severity (induration, erythema, scaling). Attempts were made to control both lighting and technical elements, but this was not possible for all patients. All photographs were evaluated by the site investigators (M.-F.D., V.H.) and were therefore not reviewed in a blinded fashion. At each enrolling site, the same investigator(s) scored the subjects throughout the study. Responses were defined as follows: progressive disease, defined as new lesions developing; no response, defined as stabilization of existing lesions with no new lesions developing; slight response, defined as less than 50% disappearance of measurable and evaluable lesions; moderate response, defined as 50% to 74% disappearance of measurable and evaluable lesions; marked response, defined as 75% to 99% disappearance of measurable and evaluable lesions; and complete response, defined as disease that is 100% clinically cleared.

METHOTREXATE SERUM LEVELS

Blood samples were drawn at screening, baseline, and 24 to 48 hours following the topical administration of methotrexate-laurocapram every 4 weeks during the study and the posttreatment follow-up visit (week 26). Samples were analyzed at the Department of Biochemistry of Maisonneuve-Rosemont Hospital, Montreal, Quebec, using the TDX Methotrexate system (Abbott Laboratories Ltd, Diagnostics Division, Mississauga, Ontario). The lowest limit of detection for the methotrexate assay was 0.05 µmol/L.

STATISTICAL ANALYSIS

SAS statistical software for Windows (SAS Institute Inc, Cary, NC) was used to performed the χ² and Maxwell-Stuart homogeneity tests.
RESULTS

Key demographic information on the study population is summarized in Table 1. Seven of these patients had previously received other treatment for MF, including topical therapies (steroids, carmustine, nitrogen mustard), psoralen–UV-A, oral methotrexate, and sunlight, with responses varying from progressive lesions to slight improvement.

Of 10 patients with early-stage CTCL (stage IA or IB) who were enrolled in the study, 9 completed the study, and 1 discontinued participation at week 10 of the treatment phase. Five patients were administered only the dose of 12.5 g/m², 2 applied both 12.5 g/m² for 8 and 20 weeks, respectively, and 25 g/m², and 2 were treated only with the dose of 25 g/m² for the entire study.

A total of 22 adverse events were reported in 9 of the 10 patients enrolled in the study. These adverse events were grade 1 or 2 according to the National Cancer Institute’s Common Toxicity Criteria and involved the following body systems: skin and appendages (n=8), respiratory system (n=5), and hemic and lymphatic systems (n=2). Ten of these adverse events, reported by 7 patients (70%), were considered to be related to methotrexate-laurocapram according to the investigator (M.-F.D., V.H.). These adverse events included pruritus (n=6), rash (n=2), dry skin (n=1), and contact dermatitis (n=1). One patient who discontinued treatment at week 10 had experienced moderate pruritus and a skin eruption consistent with contact dermatitis. Among the 5 patients who applied 12.5 g/m² of methotrexate-laurocapram, 3 interrupted the gel application (1 patient for 4 days, 1 patient for 9 days, and 2 patients for 12 days) because of skin peeling and irritation, personal reasons, and skin eruption, respectively. Thereafter, 2 of these patients reapplied methotrexate-laurocapram on every third day instead of every second day.

Changes in clinical chemical and hematologic analysis results were reported in 9 and 8 patients, respectively. None of these changes were reported by the investigators (M.-F.D., V.H.) as being clinically significant in the context of the study.

According to the investigator’s global evaluation that was conducted at the end of the treatment phase (week 24), 3 patients (33%) had a moderate response, 4 (44%) had a slight response, and 2 (22%) had no response to treatment (Table 2), for a total of 7 (78%) who displayed a slight-to-moderate response to treatment of the 9 patients who completed the study. The Figure shows 1 patient’s lesion at baseline and 24 weeks. Two weeks following treatment termination (week 26), 1 patient (11%) had a moderate response to treatment with

### Table 1. Demographic Information and Previous Therapies

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<th>Variable</th>
<th>Men (n=7)</th>
<th>Women (n=3)</th>
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</thead>
<tbody>
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<td>Age, mean ± SD (range), y</td>
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<td>53 ± 18 (37-73)</td>
</tr>
<tr>
<td>Ethnicity</td>
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<tr>
<td>White</td>
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<td>2</td>
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<tr>
<td>African American</td>
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<td>Hispanic</td>
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<td>0</td>
</tr>
<tr>
<td>Previous therapies</td>
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<td></td>
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<tr>
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<tr>
<td>Nitrogen mustard</td>
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</tr>
<tr>
<td>Topical carmustine</td>
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</tr>
<tr>
<td>Psoralen–UV-A</td>
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<td>1</td>
</tr>
<tr>
<td>Oral methotrexate</td>
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<td>0</td>
</tr>
<tr>
<td>Sunlight</td>
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<td>0</td>
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</table>

### Table 2. Summary of Investigator’s Global Evaluation of Methotrexate-Laurocapram Therapy Relative to Baseline

<table>
<thead>
<tr>
<th>Visit</th>
<th>Patient’s Response to Therapy, No. (%)</th>
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</thead>
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<tr>
<td></td>
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<tr>
<td>Week 4 (n = 10)</td>
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<tr>
<td>Week 12 (n = 8)</td>
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<tr>
<td>Week 24 (n = 9)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Week 26 (n = 9)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

A

Erythematous plaque of patient 9 at baseline visit (A) and week 24 (B).
methotrexate-laurocapram, 7 (78%) had a slight response, and 1 (11%) had progressive disease, for a total of 8 (89%) who had a slight-to-moderate response.

Table 3 outlines the changes in severity outcomes of test lesions compared with baseline based on the collapsed categories derived from the sum of the lesion grading score. At the end of the treatment period, an improvement in induration, erythema, scaling, and pruritus was reported in 6, 7, 4, and 3 patients, respectively; these changes reached statistical significance for induration and pruritus, whereas a trend ($P = .10$) was observed for erythema. Two weeks following the completion of the treatment, the relative proportion of patients for whom an improvement was observed compared with baseline remained similar for both induration and erythema, whereas the number of patients for whom an improvement had been observed at week 24 decreased from 4 (44%) to 1 (13%) for scaling and from 3 (33%) to 1 (13%) for pruritus.

The mean total surface area of the test lesions varied from 5.6 to 165 cm$^2$ among the individual patients at baseline. On the whole, this outcome was not statistically different at the end of the treatment ($P = .38$). At the end of treatment, 5 patients displayed changes of less than 25% compared with baseline, 3 had decreases of 26%, 33%, and 37%, respectively, and 1 had a 32% increase. Similarly, the total body surface area involvement, which also varied substantially among the individual patients, was comparable at baseline (23%) and the end of the treatment (18%). On an individual basis, changes of less than 25% were observed during the study in 6 patients, whereas decreases of 40% and 50% were observed in 2 patients and an increase of 2% to 10% of BSA involvement was observed in 1 patient (data not shown). The serum concentration of methotrexate, as measured 24 to 48 hours following the topical application of methotrexate-laurocapram, was under the lowest limit of detection, ranging between 0.01 and 0.03 µmol/L in all samples analyzed, regardless of the dose received and the interval between dosing and sample collection.

The results of this phase 1/2 pilot study, conducted in 10 patients with early-stage MF disease, indicate that the topical application of 12.5 or 25 g/m$^2$ of methotrexate-laurocapram once every other day for 24 consecutive weeks led to minimal systemic exposure to methotrexate, was well-tolerated, did not generate changes in the safety assessments indicative of the toxicity usually associated with methotrexate, and produced a slight-to-moderate response in 7 (78%) of 9 patients, based on the investigator’s global evaluation. Except for unpublished data obtained in a pilot study of 4 patients, this is the first published study to our knowledge demonstrating that topical methotrexate is safe and could potentially be efficacious in treating patients with early-stage CTCL. Since the improvement in the severity of the lesions was accompanied with positive changes in either the surface area or body surface area involvement in some but not all patients, further investigation would be required to determine the optimal drug concentration, frequency of administration, and duration of treatment.

Most patients had grade 1 toxic effects, and only 1 patient discontinued the study because of contact dermatitis. Because this patient had also developed an allergic contact dermatitis to topical nitrogen mustard, the possibility that the patient had other topical allergies cannot be excluded.

Skin-directed therapies have been the first-line treatments for early-stage disease. Current topical options in-
clude highly potent topical steroids, topical carbustine or nitrogen mustard, and topical retinoids (1% bexarotene retinoid gel). High-potency steroids have been shown to be effective, with a response rate of 94% in stage T1 disease (complete response in 63%).20 Topical nitrogen mustard, which is the standard to which other therapies have been compared, displays response rates of approximately 88%, with a 51% complete response in stage T1 disease.20 However, its use has been limited by the frequency of allergic contact dermatitis, which ranges from 30% to 80%.21 Topical carbustine has comparable efficacy to topical nitrogen mustard and has a lower frequency of contact dermatitis.22 However, persistent telangiectasias at treated sites may be seen, and 3% to 5% can develop mild leukopenia with carbustine solution or ointment.23 Although 1% bexarotene gel has shown an overall response rate of 26% to 63% (complete response in 8%–21%) in patients with refractory stage IA-IIA CTCL, a skin eruption occurred in 56% of patients and pruritus in 18%.24,25

Methotrexate is known to be effective in CTCL, with a response rate in the range of 58%.26 Although methotrexate is widely available and the oral form is relatively inexpensive compared with other treatments for CTCL,26 it is widely available and the oral form is relatively expensive compared with other treatments for CTCL,26 trexate is widely available and the oral form is relatively expensive compared with other treatments for CTCL,26 demonstrating that aggressive therapy (combination chemotherapy and total skin electron beam therapy) did not offer a survival advantage over topical therapy in early-stage CTCL,3 emphasizing the critical role of topical therapies in early-stage CTCL. Thus, topical treatments will continue to be first line of therapy for those patients with early-stage CTCL. A topical formulation of methotrexate should be cost-effective and could have several indications in dermatology.

In conclusion, the primary objective of this phase 1/2 study was to assess the safety and tolerability of methotrexate-laurocapram, administered topically for 24 consecutive weeks in patients with early-stage CTCL. The results obtained are in agreement with previous findings in patients with psoriasis or MF, which indicate that methotrexate-laurocapram is safe and well tolerated and that there seems to be marginal systemic exposure to methotrexate using this formulation. Furthermore, despite the relatively low number of patients, positive results, some of which reached statistical significance, were obtained in the efficacy outcomes. Altogether, these findings indicate that methotrexate-laurocapram may represent a viable alternative treatment and route of administration for this patient population and warrant additional investigation aimed at further defining its efficacy profile.

Accepted for publication September 17, 2002.

This study was supported by grant FD-R-000843-02 from the Food and Drug Administration (Rockville, Md) Office of Orphan Products to Dr Leyland-Jones.

We thank Marsha Stevens, RN, BSN, Jasmin Abd-el-Baki, MD, Atul Taneja, MD, and Frank Pietrantonio, PhD, for their help with the study.

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