Topical Corticosteroids for Mycosis Fungoides

Experience in 79 Patients

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Objective: To determine the effectiveness of topical corticosteroids in the management of mycosis fungoides.

Design: Prospective study.

Setting: Academic referral center, Veterans Affairs Medical Center, and private practice.

Patients: Seventy-nine patients with patch or plaque stage of mycosis fungoides. Fifty-one were stage T1 (less than 10% of skin involved) and 28 were stage T2 (10% or more of skin involved). Seventy-five had patch-stage and 4 had plaque-stage disease as determined by histological examination.

Intervention: Patients were treated with topical class I to III corticosteroids. Of the stage T1 patients, all used class I corticosteroids, and 4 (8%) also used class II or III corticosteroids. Of the stage T2 patients, 19 (68%) used class I and 12 (43%) used class II or III compounds. Some patients used more than 1 class of corticosteroid. Applications were almost always twice daily. Three stage T1 and 2 stage T2 patients used plastic film occlusion. Baseline and monthly morning serum cortisol levels were obtained during treatment.

Main Outcome Measures: Response to treatment and side effects.

Results: The median follow-up period was 9 months. Thirty-two (63%) of stage T1 patients achieved complete remission and 16 (31%) achieved partial remission, for a total response rate of 48 (94%). The comparable figures for stage T2 patients were 7 (25%), 16 (57%), and 23 (82%), respectively. Responses were determined by clinical examination. Thirty-nine patients achieved clinical clearing. In 7 of these, posttreatment biopsy specimens were obtained, and all showed histological clearing. Reversible depression of serum cortisol levels occurred in 10 (13%). Minor skin irritation occurred in 2 patients and localized, reversible skin atrophy in 1.

Conclusion: Topical corticosteroids, especially class I compounds, are an effective treatment for patch-stage mycosis fungoides.

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Although topical corticosteroids (CSs) are commonly used for early-stage cutaneous T-cell lymphoma (CTCL), documentation is surprisingly limited. A MEDLARS search failed to reveal reports of any series since the early trials of the 1960s.1-3 There is a good rationale for using topical CSs in CTCL. Corticosteroids inhibit lymphocyte binding to endothelium and intercellular adhesion. They induce cell death of neoplastic lymphoid cells in acute lymphoblastic and chronic lymphocytic leukemia by means of apoptosis.5 Prednisone has an established role in the induction of remission in acute lymphoblastic leukemia of childhood, and it is usually included in combination drug therapy for Hodgkin and non-Hodgkin lymphoma.6

After we happened to observe that several patients responded better to topical class 1 CSs than to topical carmustine,7 we decided to conduct a prospective study of topical CSs in patients with early-stage CTCL.

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All patients were followed up for a minimum of 3 months. Fifty-one stage T1 patients were followed up for 3 to 36 months (median, 9 months). Twenty-eight stage T2 patients were followed up for 4 to 24 months (median, 8 months). The median follow-up for all 79 patients was 9 months.

Response to treatment is summarized in Table 2. The proportion of stage T1 patients achieving CR (63% [32]) was

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PATIENTS AND METHODS

PATIENTS

This study included 79 patients with mycosis fungoides (MF) treated at the Cutaneous Lymphoma Clinic at the University of California, San Francisco; the Veterans Affairs Medical Center, San Francisco; and in the private office of 1 of us (H.S.Z.). The patients included 43 men and 36 women, ranging in age from 14 to 84 years (median, 60 years). In 51 patients the MF was stage T1 (less than 10% of skin involved) and in 28 it was stage T2 (10% or more of skin involved). Seventy-five had disease in the patch stage (of which 5 were late patch) and 4, in the plaque stage as determined by histological examination according to published criteria. According to Timothy McCalmont, MD (written communication, November 13, 1997), "Late patch stage disease is defined microscopically by the presence of an expanded papillary dermis containing a moderate or dense infiltrate, with focal involvement of the reticular dermis as well." All histological diagnoses were made by Philip LeBoit, MD, Timothy McCalmont, MD, and Barbara Egbert, MD.

None of the patients had clinically significant adenopathy (1 node at least 2 cm in diameter, or 2 or more nodes larger than 1 cm). The blood of 3 stage T2 patients was examined for evidence of Sézary cells by 3 techniques: T-cell receptor gene rearrangement, CD4+CD7− phenotype, and CD4:CD8 ratio. The CD4:CD8 ratio was slightly elevated (5.3 (reference range at the University of California, San Francisco, 1-4.3) in 1 patient; otherwise no abnormalities were found.

Previous known treatments, according to the number of patients, included topical corticosteroids in 23 patients, topical (but poorly documented) CSs in 7, methotrexate in 4, psoralen–UV-A (PUVA) in 4, topical mechlorethamine hydrochloride in 2, total skin electron beam treatment in 2, and local electron beam, photopheresis, isotretinoin, and thioguanine in 1 each.

METHODS

Patients who had active MF were enrolled prospectively, mostly consecutively, in the study. These were of approximately equal proportions of previously untreated and treated patients (Table 1). Topical CSs were offered to those in whom previous therapies had failed or who had bothersome side effects. Patients who were doing well were usually not offered topical CSs.

Pretreatment workup included a complete blood cell count, broad-spectrum chemistry panel, morning serum cortisol level, and chest radiogram. No significant abnormalities that would have compromised treatment were noted. The serum cortisol determination was repeated at monthly intervals during treatment. Otherwise, blood cell counts, chemistry studies, and chest radiographs were not repeated during treatment unless there was some indication for doing so. There was some variation in the reference range of morning serum cortisol levels between different laboratories. These ranged from a low of 138 to 221 nmol/L (5-8 µg/dL) to a high of 552 to 690 nmol/L (20-25 µg/dL) in almost all cases, the same laboratory was used for sequential tests.

Topical CSs are ranked in decreasing order of potency based on the vasoconstrictor assay (the highest potency is class I). Predominantly class I compounds were prescribed (Table 1). The following were used according to number of patients (some patients used more than 1 preparation): stage T1: 0.05% clobetasol propionate (class I), 46 patients; 0.05% diflorasone diacetate (class I), 5; 0.05% halobetasol propionate (class I), 3; 0.1% triamcinolone acetonide (class III), 3; and 0.05% fluocinonide (class II), 1; and stage T2: clobetasol, 18; triamcinolone, 9; diflornesone, 3; 0.05% betamethasone valerate (class III), 2; halobetasol, 1; and fluocinonide, 1. In summary, all stage T1 patients used class I drugs at one time or another, whereas 75% of stage T2 patients did so. None of the patients used systemic agents while being treated with topical CSs.

Patients were instructed to apply the preparations vigorously twice daily to the lesions only. This was necessary because of the common practice of pharmacists to write "apply lightly" or "sparingly" on the label. They were told to treat for 2 to 3 months before assuming that the treatment was ineffective, and to continue treatment for an additional month after clearing. Occlusive therapy was used in 3 stage T1 patients. One with palmar involvement applied clobetasol ointment under plastic gloves at night, and 2 applied clobetasol cream twice daily under plastic film to individual plaques. Two stage T2 patients used 0.1% triamcinolone cream or ointment under a plastic suit for several hours, daily or on alternate days. Six stage T2 patients were treated for varying times with alternating periods of 2 weeks on and 2 weeks off treatment, but were changed to daily applications because of inadequate responses.

Definitions of response, based on clinical examination, were as follows: complete response (CR), no evidence of disease; partial response, 50% or more improvement; stable disease, less than 50% improvement and less than 25% worsening; and progressive disease, 25% or more worsening. All responses were required to last at least 4 weeks to be considered an event. Posttreatment biopsy specimens were obtained in 7 of 39 patients who achieved clinical CR. These confirmed CR in all but 1 patient who initially had a plaque-stage lesion on the base of the palm in which the posttreatment biopsy specimen showed patch-stage disease. Further treatment resulted in complete histological and clinical clearing.

more than twice that of the T2 patients (25% [7]); however, the total response rates (CR plus partial response) were not greatly different: 48 (94%) for stage T1 and 23 (82%) for stage T2. As expected, the percentage of patients in CR dropped from the maximum response to that when last seen: for stage T1 from 32 (63%) to 19 (37%), and for stage T2 from 7 (25%) to 5 (18%). However, the total response rate showed a lesser degree of change: for stage T1 from 48 (94%) to 41 (80%) and for stage T2 from 23 (82%) to 19 (68%).

Results were analyzed as to depth of infiltrate, ie, patch- vs plaque-stage disease. Our series consisted predominantly of patients with patch-stage disease. Only 3 of 51 stage T1 patients and 1 of 31 stage T2 patients had plaque-stage disease. Of our 3 patients with stage T1 plaque-stage disease, at their last visit 1 was in partial
remission, 1 was in stable disease, and 1 had progressive disease. The patient with progressive disease had developed a tumor-stage lesion outside of the areas of CS treatment. The stage T2 patient had more than 25% increase in extent of disease, and treatment was changed to methotrexate.

Only 5 (6%) of the 79 patients developed progressive disease. This included 2 (4%) of the 51 stage T1 patients and 3 (11%) of the 28 stage T2 patients. One of the previously noted stage T1 patients had plaque-stage disease and developed a tumor-stage lesion outside of the treated areas. The second stage T1 patient had marked involvement of the palms and soles and widespread small patches that became more extensive during treatment. Of the 3 stage T2 patients, 1 had extensive macular erythematous lesions that became more widespread. A second stage T2 patient with patch-stage disease developed a tumor-stage lesion. The third stage T2 patient had plaque-stage lesions that became more extensive.

Results were analyzed with regard to the possible influence of previous therapy (Table 3). Patients who had no previous therapy had a somewhat higher CR rate than those who had previous treatments. Therefore, the lack of a washout period did not create a bias in favor of previously treated patients.

Whereas other investigators have characterized patch- and plaque-stage lesions by clinical features, we believe that characterization by histological features is more objective and meaningful. We found that in 14 (18%) of our 79 patients, although clinically the patients were thought to have plaque-stage disease, the histological examinations showed patch-stage disease. In all other patients the clinical and histological features were concordant. This issue is discussed further in the “Comment” section.

Posttreatment biopsy specimens were obtained in 7 (18%) of 39 patients who achieved CR. There was no evidence of disease in any of those specimens.

A remarkable result was obtained in a 72-year-old man who originally had a plaque-stage lesion on the posterior part of the thigh. This had failed to clear despite treatment with unidentified topical CSs, maximum-strength carmustine solution and ointment, and local electron beam radiation, and persisted as an atrophic patch-stage lesion. The lesion cleared clinically and histologically with topical clobetasol under continuous occlusion (Figure 1 through Figure 5) and has remained clear for 29 months after clobetasol treatment was discontinued.

Ten patients (13%) experienced temporary depressions of the serum cortisol level below the lower limit of normal. Four of the patients were in stage T1 and 6 were in stage T2. However, 1 of the stage T1 patients had widely disseminated lesions requiring considerable amounts of topical CSs. Seven patients had 1, one had 2, and one had 3 occurrences of cortisol depression. In all patients, the cortisol level had returned to the normal range when checked 2 to 4 weeks after the CSs were discontinued, and all resumed topical use of CSs. No clinical side effects were noted as a result of the depressions. All but 1 of the patients experiencing cortisol depression had used class I CSs; that patient was in stage T2 and had used 0.1% triamcinolone without occlusion.

Two patients experienced temporary minor irritation from the CS preparations, but this was not severe.

Table 1. Corticosteroid Use Relative to Stage and Previous Therapy

<table>
<thead>
<tr>
<th>Stage</th>
<th>Class of CS Used</th>
<th>No.</th>
<th>CR</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
<th>TR</th>
</tr>
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<tbody>
<tr>
<td>T1</td>
<td>PA</td>
<td>23</td>
<td>1</td>
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<td>0</td>
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<tr>
<td></td>
<td>PL</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>T2</td>
<td>PA</td>
<td>17</td>
<td>1</td>
<td>0</td>
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<td>PL</td>
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<td>1</td>
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Table 2. Mycosis Fungoides Response to Topical Corticosteroids

<table>
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<tr>
<th>Stage</th>
<th>Maximum Response, No. (%)</th>
<th>CR</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
<th>TR</th>
</tr>
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<tbody>
<tr>
<td>T1</td>
<td>51</td>
<td>32 (63)</td>
<td>16 (31)</td>
<td>3 (6)</td>
<td>0 (0)</td>
<td>48 (94)</td>
</tr>
<tr>
<td>T2</td>
<td>28</td>
<td>7 (25)</td>
<td>16 (57)</td>
<td>5 (18)</td>
<td>0 (0)</td>
<td>23 (82)</td>
</tr>
</tbody>
</table>

Table 3. Response to Treatment With Regard to Previous Therapy

<table>
<thead>
<tr>
<th>Stage</th>
<th>No.</th>
<th>CR</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
<th>TR</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td></td>
<td></td>
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<tr>
<td>T2</td>
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</tbody>
</table>

*CR indicates complete remission; PR, partial remission; SD, stable disease; T1, less than 10% of skin involved; and T2, 10% or more of skin involved. For definitions of CR, PR, and SD, see the “Methods” subsection of the “Patients and Methods” section.

†Seven patients had received limited topical corticosteroids.
‡For an explanation of previous therapy, see the “Patients” subsection of the “Patients and Methods” section.

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Results of this study demonstrate that topical CSs, particularly the class I compounds, are an effective treatment for patch-stage MF. We cannot judge the effect of CSs in plaque stage because of the small number of such patients. This reflected our concern that penetration of topical CSs into the reticular dermis might not be adequate and the experience of Vonderheid et al and Ramsey et al that results with topical mechlorethamine are better in patch-stage than plaque-stage disease. Nevertheless, further experience in plaque stage is desirable.

Although the proportion of patients achieving CR (63% for stage T1 and 25% for stage T2) was less than desired, the high total response rate (CR plus partial response) (94% for stage T1 and 82% for stage T2) demonstrates a significant benefit. The higher response rate for stage T1 than for stage T2 patients is in accord with results obtained with other modalities.

The remarkable response of a 72-year-old patient to topical clobetasol after multiple therapies, including lo-
ical electron beam, has failed raises the intriguing possibility that some types of lymphoid cells may be more sensitive to Cs than to radiation.

We believe that classification as to patch or plaque stage should be based on well-defined histological features. As previously noted, there was discordance in 18% of our patients as to the clinical impression vs histology. According to Timothy McCalmont, MD (written communication, November 13, 1997), “Patch stage mycosis fungoides may give the false clinical impression of plaque stage disease if there is a dense papillary dermal infiltrate, striking papillary dermal fibrosis associated with a sparse infiltrate, or significant edema of the papillary dermis.”

We recognize that the proportion of patients who underwent posttreatment biopsy after achieving clinical CR (7 of 39) is low, and that a higher proportion would be desirable. However, the critical issue is long-term follow-up. The clinical significance of the presence of a few atypical cells in lesions that are clinically clear remains to be determined. In a review of 20 studies published since 1985 relating to treatment of CTCL, posttreatment biopsies were consistently performed in only 7. Additionally, the requirement that all responses persist for at least 4 weeks to be considered an event helps to avoid premature recognition of CRs.

Side effects were minor and did not cause treatment failure. The one instance of cutaneous atrophy resolved after treatment was discontinued. The few instances of cutaneous irritation were mild.

A principal concern is possible depression of the hypothalamic-pituitary-adrenal axis from percutaneous absorption of topical Cs. As recommended by Walsh et al., status of the hypothalamic-pituitary-adrenal axis was monitored by morning serum cortisol levels. Approximately 13% of the patients experienced temporary depression of the hypothalamic-pituitary-adrenal axis. There were no associated clinical side effects. These occurred predominantly in stage T2 patients and in stage T1 patients whose lesions were widely scattered. The depressions did not cause treatment failure.

In this regard, the observation of Walsh et al that in patients with psoriasis recovery from hypothalamic-pituitary-adrenal axis suppression was rapid despite continued application of superpotent Cs is of interest. Additionally, Bromberg questions the value of biochemical tests for adrenal function in patients receiving exogenous Cs:

My data suggest that the adrenal function of such patients need not be tested except when there are clear-cut clinical indications, since in such patients the physiologic value of the biochemical tests is poor and clinical adrenal insufficiency is rare.

In Table 4 we compare response rates obtained with other topical modalities with those obtained with Cs in stage T1 and T2 patients. Such comparisons must be made with reservation because the relative proportion of patients with patch- or plaque-stage MF can vary greatly, and investigators may use different criteria for judging degrees of remission. Regardless, the data are the best available. In summary, CR rates for Cs are somewhat lower than those for other modalities except mechlorethamine, but the total response rates are not markedly different.

It should also be noted that all of the other modalities may cause significant side effects and/or lower the quality of life. A high proportion of patients treated with mechlorethamine develop allergic contact dermatitis, which is usually difficult to control. Both PUVA and UV-B require frequent outpatient visits, and PUVA requires the wearing of goggles during the day of treatment and monitoring for the possible development of cataracts. Treatment with UV-B may cause sunburn reactions. Mechlorethamine and PUVA increase the risk of skin cancer, especially squamous cell carcinomas. In addition, PUVA has been shown to increase the risk of developing malignant melanoma, and malignant melanoma occurring during PUVA therapy for MF has recently been reported. Although an increased risk of skin cancer in patients with MF treated with UV-B is not well documented, this may reflect lack of long-term follow-up in adequate numbers of patients. Carmustine does not increase the risk of skin cancer but commonly causes erythematous reactions that may be followed by telangiectasia and can cause bone marrow depression. Total skin electron beam treatment usually causes multiple side effects, including erythema, alopecia, xerosis, nail dystrophy, edema, and bullae.

Topical Cs have the advantage of ready availability and ease of application. Side effects are few. Although depression of serum cortisol levels may occur, these are readily reversible and have not been accompanies.

<table>
<thead>
<tr>
<th>Table 4. Response Rates of Topical Therapies for Mycosis Fungoides*</th>
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<tr>
<td>Stage</td>
</tr>
<tr>
<td>T1</td>
</tr>
<tr>
<td>T2</td>
</tr>
</tbody>
</table>

* All numbers, except for numbers of patients (N), are percentages. TSEB indicates total skin electron beam; CR, complete remission; PR, partial remission; TR, total response (CR + PR); T1, less than 10% of skin involved; and T2, 10% or more of skin involved. For definitions of CR and PR, see the “Methods” subsection of the “Patients and Methods” section.

† Present study.
‡ Taken from Hoppe et al.
§ Taken from Zackheim et al.
¶ Taken from Hermann et al.
¶¶ Taken from Ramsay et al.
# Taken from Hoppe.
nied by clinical symptoms. Additionally, the significance of such depressions in the absence of clinical manifestations is controversial.

Whether CTCL is curable is controversial.25 The data of Kim et al26 and our own findings (unpublished data, March 1998) demonstrate that treated patients with stage IA (T1 without adenopathy) disease have a life expectancy similar to that of an age-, sex-, and race-matched control population. Thus, in a statistical sense, at least, early-stage MF may be regarded as “curable.” Whether stage IA patients treated topically with CSs will also achieve statistical “cure” obviously requires a much larger series and longer follow-up.

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REFERENCES