Pulsed High-Dose Corticosteroids Combined With Low-Dose Methotrexate Treatment in Patients With Refractory Generalized Extragenital Lichen Sclerosis

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Background: Lichen sclerosus (LS) is a rare, chronic inflammatory skin disease that predominantly affects the anogenital area. A few patients exhibit widespread extragenital disease that may lead to blister formation and superficial erosions. We evaluated the efficacy of pulsed high-dose corticosteroids combined with low-dose methotrexate treatment in patients with refractory generalized LS that had failed to respond to standard topical corticosteroid therapy.

Observation: Seven patients were included in this retrospective study, all of whom were treated with pulsed high-dose corticosteroids combined with low-dose methotrexate for at least 6 months. The outcome measure was an individual, nonvalidated clinical score. Overall, a significant decrease in the clinical score was observed, from a median score of 8 (range, 5 to 24) before treatment to 2 (range, 1 to 4) after treatment. Adverse effects observed during therapy were moderate and disappeared after the end of treatment. During the follow-up period of at least 3 months (mean, 4.7 [range, 3-8] months), none of the patients experienced a relapse of extragenital LS.

Conclusions: Patients with severe extragenital LS benefit from pulsed high-dose corticosteroids combined with low-dose methotrexate therapy. This combination therapy should be considered in generalized disease, especially disease that is refractory to conventional treatment.

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The coexistence of both conditions has been reported. We therefore speculated that PCMT might also be beneficial in patients with extragenital LS. The present report is a retrospective evaluation of PCMT in patients with generalized LS that failed to respond to conventional treatment.

**METHODS**

**PATIENTS**

Patients with extragenital LS were recruited from the outpatient clinic for connective tissue diseases at the Department of Dermatology and Allergology, Ruhr-University Bochum. Patients had to meet all of the following criteria to be eligible for the initiation of PCMT: biopsy-proved and clinically confirmed extragenital LS, the presence of generalized disease affecting more than 2 anatomic regions of the body, clinical signs of active disease manifested by growing lesions, the appearance of new lesions, clinical signs of inflammation within the past 3 months, and failure to respond to conventional treatment with a potent topical corticosteroid. The baseline examination consisted of a screening for other autoimmune diseases, as previously reported. The initial serologic examination included a complete blood cell count; measurement of antinuclear antibody, extractable nuclear antibody (including anti-Ro and anti-La antibodies), rheumatoid factor, circulating immune complex, and immunoglobulin (IgA, IgM, and IgG) levels; screening for *Borrelia burgdorferi* infection; and routine blood chemistry. We excluded patients younger than 18 years, those with concomitant severe chronic or malignant disease or with a contraindication for PCMT, and women with childbearing potential without acceptable means of contraception. A protocol on sclerotic skin diseases including LS was approved by the ethics review board of the Ruhr-University Bochum. Informed consent was obtained from every patient included.

**TREATMENT**

Pulsed intravenous high-dose corticosteroids combined with orally administered low-dose methotrexate therapy was administered according to a previously published treatment algorithm from our group. In brief, patients received an oral dose of methotrexate, 15 mg/wk. In addition, high-dose intravenous methylprednisolone sodium succinate, given as a 1000-mg single dose for 3 consecutive days monthly, was administered. Adjustments of the methotrexate dosage were allowed according to a previously published protocol. Treatment was administered to all patients for a duration of at least 6 months. Clinical examinations were performed every 4 weeks. At these visits, a complete blood cell count; serum chemical analysis, including measurement of glucose and electrolyte levels; and urinalysis were performed. Additional topical therapy was restricted to the use of emollients and hydrocolloid dressings (if erosions were present).
CLINICAL EVALUATION

For the clinical assessment of skin involvement before and after PCMT, an individual, nonvalidated clinical score was established on the basis of a modified skin score for localized scleroderma and a previously reported individual clinical score for extragenital LS.10,13 In brief, the body is divided into the 7 anatomic regions in which extragenital LS preferentially manifests: arms, shoulders, chest (including the submammary region), abdomen, back, inguinal area, and legs. Clinical severity of LS is assessed on a 4-point scale (a score of 0 indicates normal skin; 1, mild sclerosis/induration, atrophy, and/or depigmentation; 2, moderate sclerosis/induration, atrophy, and/or depigmentation with or without blister formation; and 3, severe sclerosis/induration, atrophy, and/or depigmentation with or without superficial erosions). Involvement of each body area is further assessed on a 4-point scale (a score of 0 indicates no involvement; 1, <33%; 2, 33%-67%; and 3, >67%). The sum of the numerical units for clinical severity and skin involvement of the affected anatomic areas represents the total clinical score.

STATISTICAL ANALYSIS

Data analysis was performed using a commercially available statistical software package (MedCalc; MedCalc Software, Martelikkerke, Belgium). The distribution of data was graphically assessed. Nonnormally distributed data were expressed as medians, including the range. Pretherapeutic and posttherapeutic comparisons were performed using the Wilcoxon test for paired samples. The Spearman coefficient of rank correlation was evaluated for the clinical score and the duration of disease. *P* < .05 was considered significant.

RESULTS

PATIENT CHARACTERISTICS

A total of 7 patients (6 women and 1 man; mean age, 67.6 [range, 50-80] years) fulfilling the criteria of severe extragenital LS were included in this retrospective analysis. Patients’ relevant clinical characteristics are depicted in Table 1. Five of the 7 patients had concomitant genital LS, and 3 of them had other autoimmune diseases. None of them had clinical or histopathologic signs of morphea overlap. All of them had previously been treated with topical corticosteroids without substantive clinical benefit. Moreover, 6 of them had received insufficient pretreatment with different kinds of phototherapy. The mean duration of disease was 90.3 (range, 18-156) months.
TREATMENT RESPONSE

All of the 7 patients completed PCMT. Six patients were treated for a total of 6 months, and 1 (patient 1) was treated for 10 months because of a delayed response to PCMT. Dose reductions were not performed in any of the cases. The cumulative dose of methotrexate was 360 mg (except for patient 1, who received a cumulative methotrexate dose of 600 mg).

Overall, a significant decrease of the clinical score was observed from a median of 8 (range, 5 to 24) before treatment to 2 (range, 1 to 4) after PCMT ($P = .02$; Table 2). Representative clinical pictures of response to PCMT are provided in Figure 4. In most patients, the first signs of improvement were seen after the third month of treatment. We observed a significant inverse correlation between the baseline score and the duration of disease ($r = -0.81; \ P = .047$). However, there was no correlation between the duration of disease and the relative score reduction ($r = -0.54; \ P = .18$). Patients 6 and 7 experienced a notable reduction of lesional itching after the second and third months of PCMT, respectively. Adverse effects observed during PCMT (nausea in 3 patients, headache in 3, and a 2-fold increase of liver enzyme levels in 1) were moderate and disappeared after the end of treatment.

The follow-up period was at least 3 months (mean, 4.7 [range, 3-8] months). Patients 2 and 5 showed further improvement of skin lesions during follow-up (both had a reduction of the clinical score from 2 at the end of treatment to 1 at the end of follow-up). The other 5 patients had unchanged residual lesions (Table 2). Remarkably, none of the patients experienced a relapse of extragenital LS during the follow-up period.

This retrospective study demonstrated that PCMT is a safe and effective treatment option for patients with severe extragenital LS. Because this was a noncontrolled study design, bias owing to spontaneous remission cannot fully be excluded. However, all of our patients had active progressive disease that had been recalcitrant to several prior treatments. Thus, it appears very unlikely that the improvement of extragenital LS observed in this study was coincidental.

So far, most studies, including controlled clinical trials on the use of calcineurin inhibitors, have been performed in LS affecting the anogenital region.\textsuperscript{14,15} In contrast, only a few case reports exist on the management of extragenital disease. Genital LS frequently leads to distinct morbidity, whereas extragenital LS usually is asymptomatic and therefore often represents only a cosmetic problem for the patient. Nevertheless, a few patients have severe extragenital LS that requires intensive treatment.

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Table 2. Clinical Score Before and After PCMT and at the End of the Follow-up Period\textsuperscript{a}

<table>
<thead>
<tr>
<th>Patient No./Sex/Age, y</th>
<th>Arms</th>
<th>Shoulders</th>
<th>Chest</th>
<th>Abdomen</th>
<th>Back</th>
<th>Inguinal Area</th>
<th>Legs</th>
<th>Total Clinical Score</th>
</tr>
</thead>
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<tr>
<td></td>
<td>PT</td>
<td>PST</td>
<td>FU</td>
<td>PT</td>
<td>PST</td>
<td>FU</td>
<td>PT</td>
<td>PST</td>
</tr>
<tr>
<td>1/M/50</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>2/F/65</td>
<td>4</td>
<td>1</td>
<td>1</td>
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<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>3/F/74</td>
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<td>0</td>
<td>0</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
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<td>0</td>
</tr>
<tr>
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<td>NA</td>
<td>NA</td>
<td>2</td>
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<td>7/F/66</td>
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<td>NA</td>
</tr>
</tbody>
</table>

Abbreviations: FU, follow-up; NA, not affected; PCMT, pulsed intravenous high-dose corticosteroids combined with orally administered low-dose methotrexate treatment; PST, posttreatment; PT, pretreatment.

\textsuperscript{a}The scoring method is explained in the “Clinical Evaluation” subsection of the “Methods” section.

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Figure 4. Pulsed intravenous high-dose corticosteroids combined with orally administered low-dose methotrexate treatment (PCMT) in generalized and refractory extragenital lichen sclerosus (LS) (patient 1). A, Clinical aspects of widespread disease. B, Marked improvement of former skin lesions 6 months after the end of treatment. These clinical pictures are representative of the whole outcome of the study and demonstrate that the combination of PCMT is effective in patients with extensive extragenital LS.

COMMENT

This retrospective study demonstrated that PCMT is a safe and effective treatment option for patients with severe extragenital LS. Because this was a noncontrolled study design, bias owing to spontaneous remission cannot fully be excluded. However, all of our patients had active progressive disease that had been recalcitrant to several prior treatments. Thus, it appears very unlikely that the improvement of extragenital LS observed in this study was coincidental.
In recent years, combining methotrexate with corticosteroids has become an increasingly reported treatment strategy for localized scleroderma. Uziel et al were the first to report on the beneficial effects of PCMT in a case series of 10 children with localized scleroderma. These results were later confirmed by Weibel et al in a larger retrospective study of PCMT that included 34 patients with juvenile localized scleroderma. Our group’s previous experiences with PCMT in 15 adult patients with severe localized scleroderma encouraged us to investigate PCMT in a well-selected patient population with extragenital LS.

The exact mechanism of action of PCMT in sclerotic skin diseases is still unknown. It seems that PCMT combines the early anti-inflammatory effects of corticosteroids with the prolonged antifibrotic effects of methotrexate. Methotrexate inhibits several cytokines that play a central role in sclerotic skin diseases, such as interleukins 2, 4, and 6. Interleukin 6 has been shown to be upregulated in LS and localized scleroderma and seems to parallel with the extent of disease and response to treatment.

Although orally administered low-dose methotrexate causes adverse effects in the gastrointestinal tract (eg, nausea or vomiting), liver (elevations in liver enzyme levels), and central nervous system (eg, dizziness or headache) in about one-third of patients, clinically relevant complications, fortunately, are rare. In clinical trials of methotrexate therapy for rheumatoid arthritis, life-threatening pancytopenia and methotrexate-induced lung disease have been observed in 1.4% and in 2.1% to 6.8% of patients, respectively. Although the typical long-term adverse effects of corticosteroids usually do not occur with high-dose treatment, physicians should be aware of rare severe adverse events such as aseptic bone necrosis, anaphylaxis, or even sudden death in patients with renal insufficiency and/or imbalances in electrolyte levels. Therefore, patients should be carefully monitored while receiving PCMT, especially those with a history of cardiac and/or renal disease.

The results reported herein should be viewed in light of the limitations of the study. We performed an unblinded, uncontrolled retrospective analysis of a relatively small number of patients with a short follow-up period. Moreover, we evaluated treatment outcome by using an individual, nonvalidated clinical score, and secondary outcome measures such as ultrasonographic or histopathologic evaluation are missing. Finally, a severely affected patient population as described in the present study is rare in general practice and thus might predominantly be seen in an academic specialty clinic with a focus on sclerotic skin diseases.

Further studies on extragenital LS, gathered under more rigorous, prospective conditions with the aid of a standardized instrument to measure treatment response, would be ideal. However, such conditions are difficult to create given the rarity of this particular disease.

In conclusion, our experience suggests that patients with severe extragenital LS benefit from PCMT. This combination therapy should be considered in generalized disease, especially disease that is refractory to conventional treatment.

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Author Contributions: Dr Kreuter had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Kreuter. Acquisition of data: Kreuter, Tigges, Gaifullina, and Kirschke. Analysis and interpretation of data: Kreuter, Altmeyer, and Gambichler. Drafting of the manuscript: Kreuter and Gambichler. Critical revision of the manuscript for important intellectual content: Tigges, Gaifullina, Kirschke, Altmeyer, and Gambichler. Statistical analysis: Gambichler. Administrative, technical, and material support: Kreuter, Tigges, Gaifullina, and Kirschke. Study supervision: Kreuter and Altmeyer.

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REFERENCES

The Balm of Gilead

“Is there—is there balm in Gilead?—tell me,—tell me, I implore!” Quoth the raven, “Nevermore!”

Readers will recognize this verse as coming from Edgar Allan Poe’s beloved poem “The Raven,” which was published in 1845. There is much to enjoy in “The Raven,” and the poetic words “balm in Gilead” caught my attention. What exactly was the balm of Gilead?

This verse is directly paraphrased from the Book of Jeremiah (8:22): “Is there no balm in Gilead? Is there no physician there? Why then, has the health of the daughter of my people not been restored?”¹ The Biblical Hebraic word for “balm” in Gilead is tzori, which is also the term for one of the ingredients of the incense that was used thousands of years ago in the Temple in Jerusalem, as explained in the Talmud.² The tzori used in the incense appears to have been “the sap that drips from balsam trees.”² Maimonides, a renowned 12th century rabbi and physician, also identifies tzori as balsam sap, although he holds that it was the balsam wood itself that was used in the Temple incense.³

The balsam mentioned in the Bible is an oleoresin that is derived from the tree Commiphora opobalsamum, which is native to southern Arabia and was used in antiquity in perfumes.⁴ Apparently, during Biblical times, there was a large commercial trade in balsam, originating from the district of Gilead, which was situated east of the Jordan River. This balsam trade is also mentioned in the Book of Genesis (37:25) in connection with the sale of Joseph, where a caravan of Ishmaelites is seen bearing balsam and spices from Gilead to Egypt.

By the time of the prophet Jeremiah, the balm of Gilead became prized for its medicinal value, although it is unclear whether this balm was simply balsam or balsam that was compounded with other ingredients to form a unique salve, perhaps a forerunner to the Greek theriac.⁵ It appears to have been used to treat snake bites and other such serious ailments.⁶ In contemporary folk medicine, C opobalsamum is used topically, combined with oil to treat bruises, swellings, wounds, and rheumatic pains.⁷ As a tincture, balsam has been used in the treatment of cough, laryngitis, and chronic bronchitis as well as various kidney and stomach ailments.⁸ There is insufficient reliable information available about the effectiveness of balsam in these illnesses, although recent scientific studies are investigating its clinical properties.⁹

In the verse from Jeremiah cited above, the prophet speaks in metaphors by referring to a spiritual balm of Gilead and not to an actual medication. Jeremiah’s spiritual medication alludes to the qualities of repentance and performing good deeds, which are antidotes to sinful behavior. Jeremiah is asking why, if people can repent and if God is the ultimate healer, can’t Israel be saved and be restored to its proper spiritual health? Likewise, Poe, in “The Raven,” metaphorically refers to a spiritual balm of Gilead. In the poem, a bereaved lover mourns the death of a beautiful woman, and he desperately asks whether there is any succor or balm to alleviate his emotional grief. The raven answers “Nevermore!”

The original balm of Gilead salve, whatever it was, has been lost to antiquity. Its legend, however, lives on in the words of prophets and poets who have given it a spiritual meaning. This legacy also continues to endure in the hopes and hearts of all those who suffer from illness, grief, and pain as they search for that special balm to comfort their bodies and souls.

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