Pulsed High-Dose Corticosteroids Combined With Low-Dose Methotrexate in Severe Localized Scleroderma

Alexander Kreuter, MD; Thilo Gambichler, MD; Frank Breuckmann, MD; Sebastian Rotterdam, MD; Marcus Freitag, MD; Markus Stuecker, MD; Klaus Hoffmann, MD; Peter Altmeyer, MD

Objective: To evaluate the efficacy of pulsed high-dose corticosteroids combined with orally administered low-dose methotrexate therapy in patients with severe localized scleroderma (LS).

Design: A prospective, nonrandomized, open pilot study.

Setting: Dermatology department at a university hospital in Bochum, Germany.

Patients: Fifteen patients with histologically confirmed severe LS.

Interventions: Oral methotrexate (15 mg/wk) combined with pulsed intravenous methylprednisolone (1000 mg for 3 days monthly) for at least 6 months.

Main Outcome Measures: Treatment outcome was evaluated by means of a clinical score, 20-MHz ultrasonography, and histopathologic analysis. Safety assessment included the monitoring of adverse effects and clinical laboratory parameters.

Results: One patient discontinued therapy. In most of the remaining 14 patients, significant elimination of all signs of active disease (inflammation) and remarkable softening of formerly affected sclerotic skin that resulted in a decrease of the mean ± SD clinical score from 10.9 ± 5.3 at the beginning to 5.5 ± 2.5 at the end of therapy was observed (P < .001). Clinical improvement was confirmed by histologic and ultrasonographic assessments. No serious adverse effects were noted.

Conclusions: These data suggest that pulsed high-dose corticosteroids combined with orally administered low-dose methotrexate therapy is beneficial and safe in the treatment of patients with LS. This treatment regimen should especially be considered for severe forms of LS in which conventional treatments have failed.

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Localized scleroderma (LS) or morphea denotes a spectrum of disorders characterized by hardening and thickening of different levels of the dermis, subcutis, and sometimes underlying soft tissue and bone. Localized scleroderma has been classified into plaque, generalized, bullous, linear including scleroderma en coup de sabre, and deep forms such as morphea profunda. Hence, the clinical spectrum of LS ranges from discrete, circumscribed sclerotic plaques of cosmetic importance only to more severe variants that may have devastating effects, such as growth retardation, muscle atrophy, flexion contractures, and psychological disability. The etiology of LS remains unknown, but autoimmune, genetic, infectious, and environmental factors have been implicated.

To date, no proven effective therapy for LS has been implemented. Numerous treatments, such as penicillamine, antimalarial drugs, retinoids, calcitriol, cyclosporine, and interferon gamma, have reportedly been used for the treatment of LS, with varying degrees of success.2-4 The first encouraging results in the treatment of LS were obtained with UV-A irradiation therapy (bath psoralen–UV-A and low-dose UV-A1 phototherapy) alone or in combination with calcipotriene ointment.5 However, the effects of UV-A are mainly restricted to the epidermis and dermis and may limit its use in deep generalized forms of LS. Both low-dose methotrexate and oral corticosteroid treatment are reportedly effective in severe forms of LS in adults and children.9,10 In the present study, we examined the effects of pulsed high-dose corticosteroids combined with orally administered low-dose...
methotrexate therapy (PCMT) in 15 consecutive patients with severe LS.

## METHODS

### PATIENTS

From 2000 to 2003, 15 consecutive patients (inpatient and outpatient settings) with severe LS were included in this open, prospective nonrandomized trial. The study followed the principles outlined in the Declaration of Helsinki. All patients gave informed oral consent. The presence of a severe form of LS had to be characterized by 1 of the following criteria: (1) generalized or deep morphea that involved more than 2 anatomical body sites, resulting in restricted mobility or constriction of the thorax with respiratory difficulties; (2) linear scleroderma lesions with the involvement of fat, fascia, muscle, or bone, resulting in flexion contractures of the joints; or (3) linear scleroderma, including disfiguring en coup de sabre lesions with ophthalmologic or neurologic changes. Additionally, inclusion criteria included signs of active disease manifested by growing of lesions, appearance of new lesions, or clinical signs of inflammation within the last 3 months. For each patient, a complete disease history was obtained before starting therapy, and signs of systemic involvement were ruled out. The initial laboratory evaluation was performed before starting therapy, and signs of systemic involvement were ruled out. The initial laboratory evaluation was performed before starting therapy, and signs of systemic involvement were ruled out. The initial laboratory evaluation was performed before starting therapy, and signs of systemic involvement were ruled out. The initial laboratory evaluation was performed before starting therapy, and signs of systemic involvement were ruled out. The initial laboratory evaluation was performed before starting therapy, and signs of systemic involvement were ruled out. The initial laboratory evaluation was performed before starting therapy, and signs of systemic involvement were ruled out. The initial laboratory evaluation was performed before starting therapy.

A treatment algorithm is provided in Figure 1. Patients who qualified for this trial received an oral dose of 15 mg/wk of methotrexate. Additionally, high-dose intravenous methylprednisolone sodium succinate, 1000 mg for 3 consecutive days monthly, was administered. Therapy was finished after 6 months in case of a reduction of the clinical score by one third. It was continued in case of insufficient response within this interval and finished if the primary end point (reduction of the clinical score by more than one third) was achieved. Methotrexate dosage adjustments were performed according to a protocol as reported previously.10 In case of leukopenia (<3000/µL), increase in levels of liver enzymes (3× the upper limit) or serum creatinine (>1.5 mg/dL), or clinical adverse events, methotrexate could be reduced to 7.5 mg/wk. Methotrexate could be increased to 25 mg/wk if softening of sclerosis was not sufficient after 3 months of therapy. In case of persistent signs of active inflammation, low-dose prednisolone, 5 mg/d, was added for a maximum of 2 months. Follow-up visits were performed every 4 weeks. On the initial and follow-up visits, a complete blood count, serum chemical analysis including glucose and electrolytes measurement, and urinalysis were performed. Additional therapy was restricted to the use of emollients. All patients were evaluated by 2 dermatologists at baseline and follow-up visits (A.K. and M.F.). In case of disagreement regarding the clinical score, a compromise was achieved.

## TREATMENT PROTOCOL

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## Table 1. Characteristics of Patients With Severe Localized Scleroderma Treated With PCMT

<table>
<thead>
<tr>
<th>No./Sex/Age, y</th>
<th>Type of Localized Scleroderma</th>
<th>Duration of Disease, y</th>
<th>Duration of Treatment, mo</th>
<th>Pretreatment</th>
<th>MSS Before Treatment</th>
<th>VAS Score for Tightness Before Treatment</th>
<th>VAS Score for Itching Before Treatment</th>
<th>VAS Score for Itching After Treatment</th>
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<td>3</td>
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<td>4</td>
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<tr>
<td>3/M/59</td>
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Mean ± SD: 8.7 ± 9.8 ± 10.9 ± 5.3 ± 5.5 ± 2.5 ± 65.3 ± 33.6 ± 27.5 ± 19.9 ± 52.3 ± 33.2 ± 14.4 ± 19.3

Abbreviations: CS, scleroderma en coup de sabre; GM, generalized morphea; LS, linear scleroderma; MSS, modified skin score; NA, not applicable; PCMT, pulsed high-dose corticosteroids combined with orally administered low-dose methotrexate therapy; PU, PUVA bath; SS, systemic steroids; TS, topical steroids; VAS, visual analog scale.
For assessment of skin involvement before and after treatment, a modified skin score (MSS) was used as described elsewhere.10,11 In brief, the body is divided into 7 regions (head and neck, trunk, arms, hands, fingers, legs, and feet); skin thickness is assessed on a 0- to 3-point scale (0, normal skin; 1, thickened skin; 2, decreased ability to pinch or move skin; and 3, unable to pinch or move skin); and involvement of each body area is assessed on a 0- to 3-point scale (0, no involvement; 1, <33%; 2, 33%-67%; and 3, >67%). The sum of numerical units for thickness and involvement equals the MSS with a maximum score of 42. Patients' estimates of pretherapeutic and posttherapeutic tightness and itching were evaluated by means of a visual analog scale (VAS) on a 100-mm scale with 0 as the absence and 100 as the maximum of symptoms.10

ULTRASONOGRAPHY

Initially and at study end, ultrasonography was performed with a digital 20-MHz ultrasound scanner (DUB 20, Taberna Pro Medicum, Lüneburg, Germany), measuring both structure and thickness of a representative area (total thickness, upper surface to the inner border of the subcutaneous tissue; usable depth of signal penetration, 8 mm). Additionally, pretherapeutic and posttherapeutic differences of mean cutaneous densiometric values were evaluated by the same investigator (S.R.).

HISTOPATHOLOGIC ANALYSIS

Skin biopsy specimens were obtained from a representative affected skin area to confirm the clinical diagnosis of LS by a different investigator (M.S.). Posttreatment specimens were obtained from previously affected areas next to the sides of the first specimen. Each biopsy specimen was stained with hematoxylin-eosin. To avoid sampling error, many sections were assessed by a blinded second investigator (P.A.).

STATISTICAL ANALYSIS

Data of clinical scores and values of biometrical assessment are given as mean±SD. After performing descriptive and explorative data analysis, pretherapeutic and posttherapeutic evaluations were performed using the t test for paired samples (normal distribution). P<.05 was considered statistically significant.

RESULTS

Fifteen consecutive patients with severe LS were treated with PCMT. Ten had generalized morphea and 5 had linear scleroderma, including 1 with disfiguring scleroderma en coup de sabre. The relevant clinical and biological characteristics of the patients are summarized in Table 1. Most of them had previously been treated with a variety of agents without clinical benefit. All except 1 (patient 14 discontinued therapy because of personal reasons) completed this study. The PCMT was given for at least 6 months. However, the clinical improvement was not sufficient in 6 patients and therapy was continued. Mean duration of treatment was 9.8 months. The methotrexate dose was increased to 25 mg/wk in 1 patient (patient 3) to improve clinical outcome. In patients 4 and 8, oral methylprednisolone sodium succinate, 5 mg/d, was added for 2 months because of persistent inflammation.

Reduction of dosage was not performed in any case. Clinically, the results obtained were satisfactory for both the patients and the physicians. In all patients except 1 (patient 10, with scleroderma en coup de sabre; no change was observed) who completed PCMT, palpation and inspection showed an elimination of all signs of active disease (inflammation) and remarkable softening of formerly affected sclerotic skin that resulted in a decrease in the MSS from 10.9±5.3 at the beginning to 5.5±2.5 at the end of therapy (Figure 2A and Table 2). This difference was statistically significant (P<.001). In most patients, early signs of improvement were noted after the first 2 months of PCMT. No correlation existed between duration of disease and response to treatment.

The VAS score for tightness improved in 12 patients. Two patients had no sensation of tightness, and their score was 0. In general, the VAS score for tightness significantly decreased from 65.3±33.6 to 27.5±19.9 (P<.001). Similar results could be obtained for the VAS for itching, in which 10 patients reported a decrease in itching after PCMT, 1 patient recognized no improvement, and 3 patients had no itching before therapy. A statistically significant (P<.001) change in VAS score for itching from 52.3±33.2 to 14.4±19.3 could be evaluated.

The clinical improvement was confirmed by 20-MHz ultrasonographic examination. Corium thickness was increased before and significantly decreased toward an almost normal range after PCMT (Figure 3A and Table 3) (P<.001). Additionally, there was a significant increase in dermal density after PCMT (P<.001). Similar results were obtained by the histologic assessment of posttreatment biopsy specimens. The structure of the dermal collagen returned to normal or almost normal human skin architecture.
Adverse effects of PCMT were moderate. Three patients reported mild nausea and headache the day after methotrexate administration. Two patients developed diabetes mellitus (patients 3 and 4), and 1 had an increase in weight (10 kg; patient 4) most likely related to methylprednisolone. These effects returned to normal after the end of treatment. Apart from serum glucose level elevation in 2 patients, no significant laboratory abnormali-
ties have been detected during therapy. During follow-up for at least half a year, none of the patients experienced a relapse of LS.

**COMMENT**

Clinical and ultrasonographic evaluation revealed that most patients markedly improved during PCMT. Because no universally effective causative treatment exists, management of LS varies in its different subtypes. In the treatment of mild singular en plaque lesions, topical steroids, calcipotriene ointment, or even observation might be considered because of a tendency toward spontaneous resolution. Many systemic treatments, including some with potentially severe adverse effects such as penicillamine, calcitriol, cyclosporine, and interferon gamma, have been reported, but none of them have become generally accepted.

Recently, pulsed high-dose corticosteroid therapy has been shown to be effective even in patients with long-standing LS and therefore has been added to the therapeutic armamentarium. According to our experience, bath psoralen–UV-A is indicated for the early inflammatory stage, whereas UV-A1 appears to be more beneficial in the fibrotic stage of LS. The optimal dose of UV-A1 phototherapy in LS remains unclear, but a low-dose regimen (20-30 J/cm²) seems to be sufficient. However, UV-A1 phototherapy usually fails in rapid, severe courses of disease that involve the subcutaneous tissue and muscle, which generally require systemic therapy.

In the last decade, methotrexate has gained attention as a new approach for sclerotic skin diseases. The beneficial effects of methotrexate have been reported in a double-blind, placebo-controlled study of 29 patients with systemic sclerosis. Seyger et al reported their experience with 9 patients with widespread morphea treated with 15 mg/wk of methotrexate. All of them responded, resulting in a significant decrease of MSS and durometer score. Methotrexate’s mechanism of action seems to be based on an inhibition of various cytokines (eg, interleukins 2, 4, 6, and 8) that were shown to be increased in LS and parallel with the degree of skin sclerosis.

Beneficial effects of oral corticosteroids were reported by Joly et al in a follow-up study that included 17 patients with severe LS. Although mean duration of treatment was 18 months (0.5-1 mg/kg of oral prednisone per day, followed by a decrease in dose), 6 patients experienced a relapse after discontinuation of therapy.

Recently, pulsed high-dose corticosteroid therapy has been considered an effective treatment regimen in different skin diseases, including pemphigus vulgaris and pyoderma gangrenosum. Administering pulsed high-dose corticosteroids fully exhibits anti-inflammatory and immunomodulatory effects without occurrence of well-known adverse effects associated with long-term corticosteroid treatment. To combine the early anti-inflammatory effects of corticosteroids and the antifibrotic action of methotrexate, Uziel et al initiated a combined methotrexate (0.3-0.6 mg/kg weekly) and pulsed intravenous high-dose methylprednisolone (3 consecutive days monthly for 3 months) therapy in 10 children with LS. All patients improved with this combination therapy. Unfortunately, the authors did not use a clinical scoring system or biometrical measurements to confirm the clinical improvement observed. Therefore, comparison with other studies might be difficult.

Because of its favorable profile of safety and tolerability, methotrexate is the most frequent choice of disease-modifying antirheumatic therapy for rheumatoid arthritis. The moderate and reversible adverse effects observed in our study correspond to the frequently occurring adverse reactions of low-dose methotrexate and/or pulsed high-dose corticosteroids that have previously been reported in the literature. Nevertheless, sudden death after high-dose intravenous methylprednisolone therapy has rarely been observed in patients with renal insufficiency, electrolyte imbalances, or diuretic application. Therefore, it is recommended that patients with a history of cardiac and/or renal diseases should be monitored carefully during therapy. Uncommon but more severe adverse effects of pulsed high-dose corticosteroid therapy may also include aseptic bone necrosis, osteoporosis, anaphylaxis, and exacerbation of preexisting diseases such as gastric ulcer. However, similar to low-dose methotrexate treatment, pulsed high-dose corticosteroid therapy is characterized by a markedly favorable risk-benefit ratio in the treatment of otherwise healthy patients.

Serologically, assessment of the therapeutic efficacy in LS remains a problem. Various immunologic phenoma and abnormalities such as antinuclear antibodies, antithrombine, and anti-single-stranded DNA antibodies, eosinophilia, hypergammaglobulinemia, and rheumatoid factor have been detected in up to 80% of patients with severe generalized or linear LS, and a correlation with the clinical activity of disease has been hypothesized. Elevated levels of IgG and IgM have been reported in up to 50% of patients with severe LS. In this context, Falanga et al demonstrated higher

**Table 3. Results of 20-MHz Ultrasonographic Measurements Before and After Treatment**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Skin Thickness, µm</th>
<th>Skin Density</th>
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<tr>
<td></td>
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<tr>
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Mean ± SD 1847 ± 545 1432 ± 479 26 ± 15 46 ± 24
levels of IgG in patients with LS and joint contractures. Sequential studies are necessary to assess the relative use of these markers over time. Serum aminoterminal propeptide of type III procollagen (PIIINP), a marker for type III collagen synthesis, has been recommended for monitoring the extent of sclerosis in patients with systemic sclerosis and LS. Because no significant change in PIIINP was observed with therapy in 2 recent trials, we refrained from determination of PIIINP in our patients.

In conclusion, most patients included in this trial showed excellent response to PCMT without any major adverse effects. Response was sustained in all cases, except for one, and resulted in a significant decrease of MSS, VAS score, and 20-MHz ultrasonographic measurement. Important limitations of trials such as this include the small numbers of patients, absence of any serologic disease activity markers, and a study design that is not double blinded and placebo controlled. Taking our data into account, patients with widespread lesions of LS, especially therapy-resistant, severe, and persistent active forms, should be selected for PCMT and have to be carefully monitored. Nevertheless, because we assessed only minimal adverse effects, PCMT application in less severe cases might also be considered. Even though placebo-controlled trials are difficult to perform in rare diseases, further studies are now needed to evaluate the optimal effective dosage and safety of PCMT in severe LS.

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REFERENCES

Losler. Drafting of the manuscript: Kruse-Lösler. Critical revision of the manuscript for important intellectual content: Kruse-Lösler, Presser, Metze, and Joos. Statistical analysis: Kruse-Lösler. Obtained funding: Kruse-Lösler. Administrative, technical, and material support: Kruse-Lösler and Metze. Study supervision: Joos. Financial Disclosure: None.

REFERENCES


Correction

Error in Reference List. In the Study by Kreuter et al titled “Pulsed High-Dose Corticosteroids Combined With Low-Dose Methotrexate in Severe Localized Scleroderma,” published in the July issue of the ARCHIVES (2005; 141:847-852), the following references were omitted from the reference list. This correction was made previously to online versions of this article.


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