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Evaluation of methotrexate and corticosteroids for the treatment of localized scleroderma (morphoea) in children

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Summary

Background Localized scleroderma (LS) or morphoea is often considered to be a benign self-limiting condition confined to the skin and subcutaneous tissue. However, the course of the disease is unpredictable and severe functional and cosmetic disability may result. Drug treatment with systemic corticosteroids in combination with methotrexate has been reported to be beneficial in LS, but data in children is limited.

Objectives To evaluate the efficacy and tolerability of systemic corticosteroids in combination with methotrexate in children with LS.

Methods Treatment and outcome of 34 patients with LS were retrospectively analysed. Pulsed intravenous methylprednisolone was given, followed by oral prednisolone on a reducing regimen and maintenance treatment with methotrexate. We assessed treatment outcome clinically and by thermography and monitored adverse events.

Results From the onset of treatment, the disease stopped progressing in 94% of the patients. All patients demonstrated significant clinical improvement within a mean time of 5·7 ± 3·9 months. Mean duration of follow-up over the treatment period and beyond was 2·9 ± 2·0 years. In 16 (47%) patients therapy was discontinued when the disease was considered to be inactive clinically; however, seven (44%) of the 16 developed a relapse, necessitating repeat treatment. At last follow-up (range 0·2–7·0 years), 24 (71%) of the 34 patients had completely inactive disease. Observed adverse events were moderate and transient and no patient had to stop therapy.

Conclusions These data suggest that systemic corticosteroids and methotrexate in combination are beneficial and well tolerated in the treatment of children with LS. Because of the risk of relapse after discontinuing therapy, long-term monitoring is mandatory.

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Conflicts of interest
None declared.

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Localized scleroderma (LS) or morphoea is a recognized connective tissue disorder characterized by hardening and thickening of the skin due to an increased density of collagen. The course of LS includes an early inflammatory stage with hyperaemia of the skin, followed by fibrosis, sclerosis and, finally, atrophy.[1] LS shows a great variety in its clinical presentation and has been classified into plaque or circumscribed, linear including scleroderma *en coup de sabre*, generalized, morphoea profunda (deep), pansclerotic and combined forms.[1,2] LS is usually considered to be a condition confined to the skin and subcutaneous tissue and of a benign, self-limiting nature. However, it often affects underlying muscle and bone and, importantly, extracutaneous manifestations of LS can be found in almost one-quarter of affected children.[3] At the more severe end of the spectrum, the disease can progress over years and cause significant atrophy, growth retardation, irreversible structural deformities, joint contractures and severe functional, cosmetic and psychological disabilities.

The aim of therapy is to arrest the disease early in its course in order to prevent the development of cosmetic and functional complications. The management and treatment of severe LS is challenging. There is no specific therapy

available. Drugs are usually directed towards suppressing inflammation and collagen alteration. Numerous treatments, such as penicillamine, antimalarial drugs, retinoids, calcitriol, calcipotriol, imiquimod, ciclosporin, interferon gamma and ultraviolet (UV) A irradiation, have been used for the treatment of LS, with varying degrees of success and often limited effects on linear and deep forms of LS.[4–8] Corticosteroids and low-dose methotrexate have repeatedly been reported to be beneficial in the treatment of LS and in children methotrexate has been the most frequently used drug within the last 5 years.[9–12] However, to date the evidence for the efficacy and safety of a systemic treatment with corticosteroids and methotrexate in children with LS is limited. We evaluated a treatment protocol using intravenous methylprednisolone (IVMP) in the acute phase and/or oral prednisolone in combination with long-term methotrexate in a cohort of paediatric patients with LS. The aim of the study was to determine whether this treatment protocol was effective and safe. We furthermore wanted to identify factors influencing treatment response and important monitoring measures for adverse events and to evaluate the role of thermography for monitoring disease progress.

Materials and methods

Patients

We retrospectively reviewed the case notes of children treated for LS at Great Ormond Street Hospital for Children between 1998 and 2005. All patients who received therapy in the form of a combination of systemic corticosteroids and methotrexate were included in the study. The diagnosis of LS was made clinically by a paediatric dermatologist (J.I.H.) and paediatric rheumatologist (P.W.). The subtype of LS, as well as the site and extent of the lesions, were noted with the help of clinical photographs where necessary. We evaluated baseline characteristics regarding demographic, clinical and laboratory features. Extracutaneous manifestations of the disease, including complications and autoimmune conditions, were noted. Laboratory findings at the start of treatment included erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), antinuclear antibodies and smooth-muscle antibodies.

Treatment protocol

Figure 1 provides an outline of the standard treatment protocol that was used in most patients. Induction therapy included two courses of high-dose IVMP, each containing three pulses, given on two consecutive weeks. Oral prednisolone was started after the first course of IVMP, stopped during the second course of IVMP and then continued on a reducing regimen. Maintenance treatment with weekly methotrexate was started 1 week after the second course of IVMP. Within the treatment regimen we noted dose, duration and route of administration of corticosteroids and methotrexate.

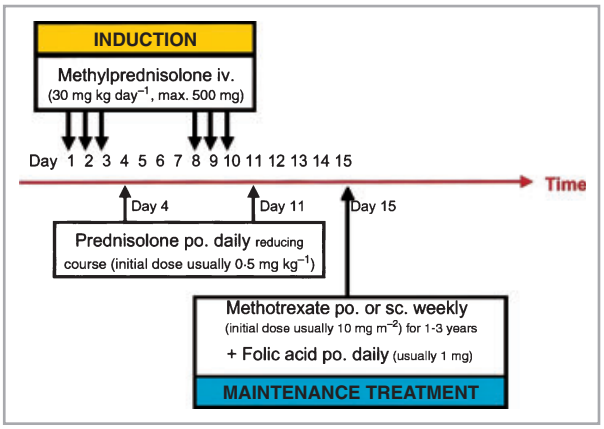

Fig 1 Treatment protocol for children with progressive localized scleroderma. po, orally; sc, subcutaneously.

Clinical outcome measures

We collected detailed information on treatment response and adverse events over the therapy period and beyond. To date there are no universally recognized criteria for clinical activity. Therefore we defined the disease as clinically 'active' if new lesions appeared; previous lesions increased in size; the lesions were erythematous or warm to touch; there was oedema with thickening of the skin and/or pain related to joints or muscles. Lesions described as having a pale or brownish colour, without thermal changes, of static size, with softening and/or atrophy of the skin and no related pain, were defined as clinically 'inactive'. 'Arrest of disease progression' was defined as no extension of the lesions and no further functional or cosmetic impairment. 'Clinical improvement' was defined as softening of the skin, fading signs of inflammation and improvement of previous joint impairment. During maintenance treatment the need for repeat administration of IVMP due to re-activation of disease was described as 'flare of disease' whereas the re-activation after discontinuing treatment was defined as 'relapse'.

Thermography

We and others have previously described the method of thermography to detect disease activity in LS.[13,14] All thermographs included in this study were performed at the Royal Free Hospital by the same thermographer (K.J.H.), using the same infrared camera from 1998 to 2000 (StarSight pyroelectric infrared imager; Insight Vision Systems, Great Malvern, Worcs, U.K.) and from 2001 to 2005 (FLIR SC 500 'Thermacam'; Flir Systems, West Malling, U.K.). Patients were assessed prior to treatment and again during follow-up. Lesions were considered 'active' on thermography when the affected area was more than 0·5 °C warmer than the matching opposite body area. For this study, a total of 130 thermal images were assessed. To evaluate the inter-observer reproducibility, two observers experienced in thermography independently reviewed the images blinded to both the clinical description

of activity and to the thermography report. Thermograms that were 'active' prior to treatment were reviewed over a follow-up period of at least 2 years.

Adverse events

Adverse events were noted during the entire treatment period. For the administration of IVMP, the children were admitted and monitored closely. During treatment with oral prednisolone, weekly blood pressure and urine analysis tests were performed. Laboratory monitoring during maintenance treatment included full blood count, electrolytes, urea, creatinine and liver function tests (which included serum alanine aminotransferase, ALT) every 4–6 weeks.

Statistical analysis

All data were collected from the patient charts and entered into a computerized spreadsheet. Mean, standard deviation (SD) or percentage were calculated for the overall sample and subgroups. Comparisons were made with the use of Student's t-test, Fisher's exact test or the χ^2 test, as appropriate. Linear correlations were described by the Pearson correlation coefficient (r). The null hypothesis was rejected with a two-sided P-value of $< 0{\cdot}05$. All analyses were performed with the use of SPSS 11·0 for Macintosh (Statistical Package for the Social Sciences, SPSS Inc., Chicago, IL, U.S.A.).

Results

Patients

Thirty-four patients with LS were included in the study. The relevant epidemiological, clinical and laboratory features of the patients are shown in Tables 1 and 2. All but three patients (91%) had linear morphoea or a combination with the linear subtype. Twenty (59%) children presented with a variety of deformities: tissue atrophy and/or muscle bulk reduction was found in 17 (50%) patients, joint restriction and growth impairment of the affected limb were present in six (18%) and five (15%) children, respectively.

Extracutaneous involvement affected 24 (71%) patients and the most frequent manifestations were articular, muscular and/or bone related, as found in 17 (50%) cases. Three (9%) children presented with vitiligo and two (6%) with ocular involvement. In 19 patients (56%) the disease affected more than 5% of the total body surface area.

Treatment

Twelve (35%) children had previously been treated with different agents, but without clinical improvement: topical corticosteroids, systemic therapy (ciclosporin, penicillamine, prednisolone and methotrexate) and UVA irradiation were used in 10 (29%), three (9%) and one (3%) patient, respectively. Twenty-eight (82%) children with acute progressive disease received the standard protocol as shown in Figure 1. In eight of these children with little sign of inflammation only one course of IVMP was administered. A group of six (18%) patients (nos 1, 6, 7, 10, 12 and 22) with milder disease (mainly limited to the skin and with minimal signs of acute inflammation) was treated with oral corticosteroids and methotrexate only.

In Table 1 the patients are listed in order of their time of follow-up from 0·2 to 7·0 years. The mean duration of follow-up was $2{\cdot}9 \pm 2{\cdot}0$ years. Nineteen (56%) patients (nos 16–34) had a follow-up time of over 2 years.

The mean initial dose of oral prednisolone was $0{\cdot}6 \pm 0{\cdot}34$ mg kg^{-1} daily. Of the total 34 patients, 28 (82%) had stopped prednisolone after a mean time of 13 ± 5 months.

Maintenance treatment with methotrexate was started at a mean initial dose of $10{\cdot}0 \pm 3{\cdot}5$ mg m^{-2} per week. This was increased when there were still signs of ongoing low-grade disease activity in 26 (76%) patients over the treatment period to a mean maximum dose of $12{\cdot}4 \pm 4{\cdot}3$ mg m^{-2} per week. Maintenance treatment with weekly methotrexate was started orally in all but two (94%) patients (nos 9 and 25), who received subcutaneous injections due to an extensive and aggressive disease for which increased drug bioavailability was required. Over the total treatment period 14 (41%) patients switched from oral to subcutaneous administration of methotrexate. This was because of gastric intolerance and the intention of increased bioavailability in nine and five patients, respectively.

Clinical outcome

The most relevant clinical outcome measures are listed in Table 3 and shown in Figure 2. No patients dropped out. From the onset of treatment, the disease stopped progressing in 32 (94%) of the 34 patients. The mean time to achieve a definite clinical improvement was $5{\cdot}7 \pm 3{\cdot}9$ months. There was no correlation found between the time of responding with clinical improvement and the time of disease duration ($r = -0{\cdot}061$, P-value 0·7). At the 2-year follow-up, which included 19 patients, 14 (74%) had completely inactive disease, four (21%) some ongoing low-grade activity and one (5%) clinically active disease. At last follow-up (between 0·2 and 7·0 years) for all 34 patients, 24 (71%) had completely inactive disease.

For the four patients with a flare of disease during maintenance treatment all responded well to a repeat administration of IVMP.

In the 16 children in whom treatment with methotrexate was stopped, the disease remained inactive for a mean time of 20 ± 12 months prior to stopping treatment. Seven (44%) of the 16 patients had a relapse that occurred between 5 and 32 months after discontinuing maintenance treatment (mean time to relapse 16 ± 12 months). In comparing those patients who relapsed with those who did not, no significant difference was found in the duration of maintenance treatment, nor

Table 1 Clinical baseline features of 34 patients with morphoea

Patient	Type of morphoea	Site of lesions	Age at start of treatment (years)	Autoantibodies	Extracutaneous involvement
1	Linear: trunk, limbs	Right leg	13·9	Negative	Glucose impairment
2	Linear: trunk, limbs	Right abdomen, leg	8·9	Sm-ab	Muscle bulk reduction
3	Generalized	Trunk, legs, arms	6·2	Negative	Joint restriction and deformity
4	ECDS	Right forehead, cheek	15·2	Negative	Vitiligo, facial hemi-atrophy
5	Linear: trunk, limbs	Right lower leg	10·8	ANA 1 : 320 (s), sm-ab	None
6	ECDS	Right forehead, eye, scalp	9·1	Sm-ab	None
7	ECDS	Left forehead	7·6	Negative	None
8	Linear: trunk, limbs	Left leg	11·8	ANA 1 : 1280 (h)	None
9	Linear + plaque	Trunk, legs, face, right arm	5·6	Negative	Joint restriction and deformity
10	Linear: trunk, limbs	Left buttock, leg	14·8	NM	Calcinosis cutis with discharge
11	Linear: trunk, limbs	Right trunk, buttock, leg	5·3	Negative	Muscle bulk reduction
12	ECDS	Right forehead, nose	13·9	Sm-ab	Nose and forehead deformity
13	Linear: trunk, limbs	Right arm	5·5	Sm-ab	Joint restriction and deformity
14	Linear: trunk, limbs	Right trunk, arm	13·9	ANA 1 : 80 (h), sm-ab	Joint restriction and deformity, limb length discrepancy, muscle bulk reduction, Bell's palsy
15	ECDS	Left forehead, mouth, chin	3·7	Negative	None
16	Linear: trunk, limbs	Right trunk	12·8	Negative	None
17	ECDS	Left forehead, scalp	7·0	ANA 1 : 80 (s), sm-ab	Conjunctivitis, astigmatism
18	Linear: trunk, limbs	Left groin	7·7	ANA 1 : 40	Pyostomatitis vegetans
19	Linear: trunk, limbs	Left leg, buttock	8·3	NM	Limb length discrepancy, muscle bulk reduction
20	ECDS	Right forehead, eye, scalp	7·7	ANA 1 : 80 (s)	None
21	ECDS	Right nose, mouth, tongue, neck	4·1	Negative	Jaw and nose deformity
22	Profunda	Right lower arm, hand	6·9	Sm-ab	Limb length discrepancy, muscle bulk reduction
23	Linear: trunk, limbs	Right groin, leg	6·0	Negative	Muscle bulk reduction
24	Linear: trunk, limbs + ECDS	Right trunk, leg, arm, left forehead	8·4	Negative	Vitiligo, strabism, muscle spasms, muscle bulk reduction
25	Generalized	Right trunk, face, both legs, arms	7·4	ANA 1 : 5120 (h), anticardiolipin-ab	Weight loss, fatigue, muscle bulk reduction, joint restriction and deformity
26	ECDS	Left forehead, scalp	10·1	NM	None
27	Linear: trunk, limbs	Left trunk, back	7·0	ANA 1 : 80 (s), sm-ab	None
28	Linear: trunk, limbs	Left trunk, buttock, leg	5·4	NM	Muscle bulk reduction
29	Linear: trunk, limbs	Right leg, groin	2·3	Negative	Limb length discrepancy, muscle bulk reduction
30	ECDS	Right forehead, nose, chin, scalp	7·4	Sm-ab	Jaw deformity, dental problems
31	Linear: trunk, limbs	Right trunk, arm	4·6	NM	Lack of breast growth, deformity
32	ECDS	Right eye, cheek	3·7	Negative	None
33	Linear: trunk, limbs	Left trunk, leg	5·5	ANA 1 : 640 (s)	Vitiligo, muscle bulk reduction
34	Linear: trunk, limbs	Left trunk, arm, leg	9·8	ANA 1 : 80 (s)	Joint restriction, limb length discrepancy, muscle bulk reduction

ECDS, scleroderma *en coup de sabre*; sm, smooth muscle; ab, antibodies; ANA, antinuclear antibodies; h, homogeneous; s, speckled; NM, not measured.

in the duration of inactive disease. The patients who relapsed had a significantly longer follow-up time than those who did not relapse (5·5 ± 1·4 and 2·2 ± 1·5 years, respectively, P-value < 0·001).

The management of relapse included the following measures: repeat administration of IVMP, restart of oral prednisolone and methotrexate and restart of methotrexate only in three, two and two cases, respectively. They all responded

Table 2 Baseline characteristics of children with morphoea

Characteristics	n = 34
Female-to-male ratio	2·1 : 1
Age at disease onset (years), mean (SD)	4·8 (3·4)
Disease duration at diagnosis (years), mean (SD)	2·3 (1·8)
Disease duration at start of treatment (years), mean (SD)	3·4 (2·4)
Age at start of treatment (years), mean (SD)	8·2 (3·5)
Morphoea subtype, n (%)	
Linear: trunk, limbs	18 (53)
ECDS	11 (32)
Generalized	2 (6)
Deep	1 (3)
Combined	2 (6)
Extracutaneous involvement	24 (71)
C-reactive protein > 7 mg dL^{-1}	1/33 (3)
Erythrocyte sedimentation rate ≥ 20 mm h^{-1}	5/31 (16)
Autoantibodies	
Antinuclear antibodies	10/29 (34)
Smooth-muscle antibodies	10/29 (34)

ECDS, scleroderma *en coup de sabre*.

Table 3 Clinical outcome of paediatric patients with morphoea

Outcome measures	n (%)[a]
Arrest of disease progression from the onset of treatment	32/34 (94)
Two-year follow-up	
No detectable clinical activity	14/19 (74)
Number of patients off treatment	1/19 (5)
Last follow-up (range 0·2–7·0 years)	
No detectable clinical activity	24/34 (71)
Number of patients off treatment	10/34 (29)
Flare of disease[b] during MT	4/34 (12)
Stop of MT at inactive disease	16/34 (47)
Duration of MT (months), mean (SD)	32 (12)
Relapse after stop of MT	7/16 (44)

MT, maintenance treatment with methotrexate. [a]Except where noted. [b]With the need for repeat intravenous methylprednisolone.

well to re-treament apart from one patient, who is awaiting follow-up.

We reviewed the patients who had a flare of disease during maintenance treatment and/or a relapse after stopping treatment (n = 9), comparing them with those who did not have a flare or relapse (n = 25). Those with a flare and/or relapse were younger at disease onset (3·3 ± 1·5 vs. 5·3 ± 3·7 years, P-value 0·029) and had a longer follow-up (5·0 ± 1·8 vs. 2·1 ± 1·5 years, P-value 0·001). No other differences were found in this comparison.

We also compared the group of patients who were treated with oral corticosteroids and methotrexate only (n = 6) with those who additionally received IVMP at the initiation of treatment (n = 28). There was no difference found in time of clinical improvement (5·0 ± 3·9 and 5·7 ± 3·9 months, respectively, P-value 0·710) or prevalence of relapse (zero and seven patients, respectively, P-value 0·306).

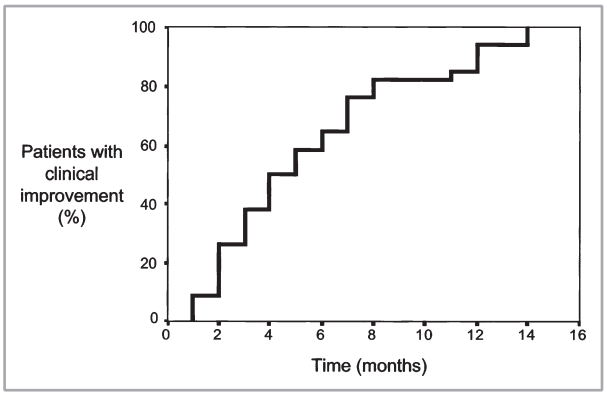

Fig 2 This curve demonstrates the clinical improvement (defined as softening of the skin, fading signs of inflammation and improvement of previous joint impairment and/or pain) of the 34 patients over time after starting treatment with systemic corticosteroids and methotrexate.

Thermography

All but one patient had thermography performed prior to the start of treatment (Table 4, Fig. 3). In nine (35%) patients thermography became inactive during follow-up (Fig. 4). Of the 13 patients in whom follow-up thermography remained 'active', 10 (77%) had clinically inactive lesions at the same time of follow-up. For this reason, thermography was considered to be 'false positive' in these cases. All these 10 patients had linear scleroderma (morphoea) and five of them had *en coup de sabre*. Seven of the 10 patients had stopped treatment but three of these seven (43%) subsequently developed a relapse of their condition. The risk of relapse was therefore no greater in the 'false positive' group compared with all the other treated patients.

Table 4 Thermography

Details	n = 34 (%)
Thermography prior to treatment[a]	
Active	26/33 (79)
Inactive	6/33 (18)
No agreement between observers	1/33 (3)
Follow-up of active lesions on initial thermogram[a]	
Became inactive	9/26 (35)
No change	13/26 (50)
No agreement between observers	4/26 (15)

[a]All thermal images of at least 2 years of follow-up were reviewed independently by two observers experienced in thermography and blinded to both the clinical description of activity and to the thermography report.

Fig 3 An example of clinical and thermographic presentation of a patient (no. 14) with linear morphoea. The lesion on the right arm is causing limb length discrepancy and joint restriction with flexure contractures of the fingers. The correlating thermal image prior to treatment shows increased temperature on the affected area representing an active lesion.

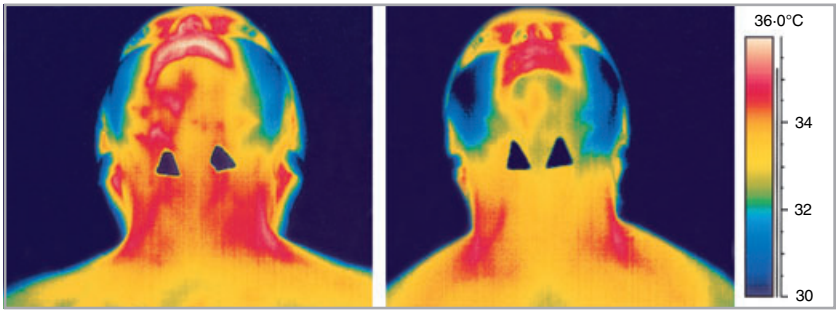

Fig 4 An example of thermographic response to treatment of a patient (no. 21) with scleroderma *en coup de sabre* affecting the right side of the face and neck. Thermography 6 months after the onset of treatment (right picture) shows cooling of the initial 'hot', active lesion on the right neck and chin.

Adverse events

Adverse events over the treatment period are shown in Table 5. They were all mild and transient and no patients dropped out of treatment due to adverse events. Because of gastric intolerance nine (26%) patients switched from oral to subcutaneous administration of methotrexate with good improvement. In one case (no. 16) the infusion of IVMP was stopped because of raised blood pressure. Methotrexate was stopped for 3 weeks and transiently reduced in one and two patients, respectively, because of a raised ALT. Methotrexate was stopped for a week in one case, because of lymphopenia.

Table 5 Adverse events over treatment period

Adverse events over treatment period	n = 34 (%)
Total	26 (76)
Nausea during MT	14 (41)
Elevated liver enzymes[a] during MT	6 (18)
Glucosuria during IVMP and/or oral prednisolone	5 (15)
Cushingoid habitus after IVMP and during oral prednisolone	5 (15)
Lymphopenia < 1500/μL during MT	4 (12)
Abdominal discomfort during oral prednisolone and MT	4 (12)
Mild systemic hypertension during IVMP	3 (9)
Hyperglycaemia during IVMP	3 (9)
Headache during MT	3 (9)
Mouth ulcers during MT	3 (9)
Neutropenia < 1500/μL during MT	2 (6)

MT, maintenance treatment with methotrexate; IVMP, intravenous methylprednisolone. [a]Serum alanine aminotransferase above age-adjusted cut-off levels.

Discussion

This retrospective study is the largest published series of children with LS treated with corticosteroids and methotrexate. Clinical assessment revealed that all patients improved markedly with this treatment and that no patient had to discontinue therapy due to adverse events.

LS may be limited to the skin and subcutaneous tissue only and show a self-limiting course without significant sequelae. However, the course and prognosis of LS is unpredictable and depends on the variant of the disease.[15] The linear subtype of LS is the most common form in children, and together with the deep variant, it can be responsible for severe morbidity as described in a recent multinational study including 750 children with LS.[3] The clinical activity of LS generally persists for 3–6 years, but re-activation can occur.[1]

For the treatment of localized plaque lesions topical steroids, calcipotriol ointment, imiquimod or UVA irradiation may be appropriate.[7,8,16] All other forms of LS must be considered as potentially severe.

In adult patients beneficial effects of oral corticosteroids were reported in a follow-up study that included 17 patients with severe LS.[17] However, after a mean treatment duration of 18 months, six (35%) experienced a relapse after discontinuing therapy. Within the last decade, methotrexate has gained

attention as a new approach for sclerotic skin diseases. In systemic sclerosis, methotrexate was shown to be effective in a double-blind, placebo-controlled study of 29 adult patients.[18] Beneficial effects of low-dose methotrexate (15 mg weekly) were demonstrated in nine adult patients with widespread morphoea during a 24-week trial.[11] The mechanism through which low-dose methotrexate improves skin fibrosis remains poorly understood. It may act directly on the skin fibroblasts or the skin improvement might be due to its anti-inflammatory effect.[19] Again, in adults, Kreuter *et al.*[12] showed pulsed high-dose IVMP (1000 mg daily on three consecutive days monthly for at least 6 months) combined with low-dose methotrexate (15 mg weekly) to be beneficial and safe in 15 patients with LS.

In children, there are only limited data to validate treatment with systemic corticosteroids and methotrexate for LS. Uziel *et al.*[10] described beneficial effects of combined methotrexate (0·3–0·6 mg kg^{-1} weekly) and pulsed IVMP (30 mg kg^{-1} daily on three consecutive days monthly for 3 months) in 10 children with LS. To our knowledge, no other reports have previously evaluated this treatment regimen in children.

The baseline characteristics of the patients included in our study were similar overall to those reported by Uziel *et al.*[10] The high prevalence of extracutaneous manifestations in our group is likely to be related to the selection of patients having acute progressive disease and the high number with the linear subtype of LS.[3]

Unlike in the previous studies, we used a slightly different treatment protocol by giving a course of pulsed IVMP on three consecutive days, repeated after 1 week, as an induction therapy, followed by oral corticosteroids on a reducing regimen.[10,12] However, the treatment response with an immediate lack of disease progression and definite clinical improvement corresponds well with the outcomes previously reported.[10,12] These findings support the role of corticosteroids as effective 'inducing agents' for rapidly reducing the early inflammatory phase of the disease. Like Kreuter *et al.*,[12] we did not find a correlation between duration of disease and time of response to treatment.

The group of patients who were treated only with oral corticosteroids and methotrexate did not show a difference in time of response or prevalence of relapse. This result is limited by selection bias, as these patients were considered to have a milder disease.

In the patients who discontinued therapy, a relatively high relapse rate of 44% was observed. It was felt that in all these patients maintenance treatment was discontinued only after an adequate time of therapy and duration of inactive disease. However, re-activation occurred in almost half within 4–28 months after stopping treatment. The only risk factor we were able to identify for flare of disease during maintenance treatment and/or relapse, was young age at disease onset. From our data we would advocate that maintenance treatment should be continued for at least 2 years and that after stopping treatment these patients are regularly monitored for at least 5 years.

In the present study the overall tolerability of the treatment protocol was high and no patient had to discontinue therapy due to adverse events. The mild and reversible adverse effects observed in our study correspond to the frequently occurring adverse reactions of low-dose methotrexate and/or high-dose corticosteroids that have previously been reported.[10,12] However, prior to start of treatment patients need to be carefully assessed for associated medical problems of a renal, cardiac or endocrine nature. We suggest that monitoring during the treatment period should include blood tests every 4–6 weeks (full blood count, electrolytes, urea, creatinine and liver function tests, in particular ALT), weight and height at clinic visits, and while on corticosteroids, blood pressure and urinalysis.

Evaluation of activity of skin lesions in patients with LS has proved challenging to clinicians and investigators. Thermography has been validated as an assessment tool in patients with LS to detect disease activity with a sensitivity of 92% and specificity of 68%.[13,14] In our study, thermography assessment prior to treatment revealed a sensitivity of 78·8% with full agreement between the two observers. It proved to be a helpful tool in demonstrating and measuring disease activity prior to treatment and in guiding the clinician in the decision about whom, when and how to treat. However, looking at thermography during the follow-up of treatment, thermography was considered to be 'false positive' in 10 patients, i.e. clinically inactive but thermographically positive. As described earlier by Martini *et al.*,[14] this is probably due to skin atrophy, loss of subcutaneous fat and reduction in muscle bulk, characteristic of old LS lesions. The fact that the two observers experienced in thermography did not reach an agreement in 15% of the evaluations of follow-up thermograms underlines the difficulties in interpreting thermography during follow-up. Despite standardized conditions the patients' general temperature levels often varied between follow-up visits causing difficulties in comparing thermograms over time. However, with the lack of other validated methods to detect disease activity in LS, we feel that thermography remains a useful, noninvasive tool that we would recommend for baseline assessment. We have further work in progress to evaluate the application of thermography in monitoring response to treatment and to investigate other techniques to detect disease activity in LS in a prospective setting.

This study is subject to a number of important limitations: study design, which is retrospective and not double-blinded and placebo-controlled; the lack of correlative laboratory disease activity markers; and the predominant use of clinical judgement as the marker of response. Skin scoring systems have been validated for the assessment of widespread skin thickening in patients with systemic sclerosis.[11,20] However, we believe their use for monitoring isolated lesions of LS in children is limited. Measuring the size of skin lesions over time is considered to be inaccurate because it is often difficult to define the exact borders of the lesions and in a growing child an increase in lesion size can mean normal growth.

In conclusion, we believe that children with LS should be identified early, evaluated appropriately, treated promptly and

monitored carefully. Despite the limitations, our data suggest that a combination of systemic corticosteroids and methotrexate is beneficial and well tolerated as treatment for LS in children.

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