Treatment of Pediatric Localized Scleroderma with Methotrexate

PAMELA G. FITCH, PATRICIA RETTIG, JON M. BURNHAM, TERRI H. FINKEL, ALBERT C. YAN, EVREN AKIN, and RANDY Q. CRON

ABSTRACT. ***Objective.*** To analyze the effectiveness of methotrexate (MTX) for the therapy of pediatric localized scleroderma (LS).

Methods. A retrospective chart review was performed for 17 pediatric patients with LS who failed topical therapy and were subsequently treated with MTX (12.5–25 mg weekly) with or without oral corticosteroids. A structured followup telephone call to the families was used to assess patient satisfaction.

Results. Skin findings improved in 16 of 17 patients with a median time to improvement of 2.25 and 2.0 months for MTX alone or in combination with corticosteroids. Only one patient had active lesions at the most recent followup visit. Fifteen of 17 families reported improvement in their child's lesions after beginning MTX. Twelve of 17 patients were treated with MTX and oral corticosteroids. There were no major adverse events.

Conclusion. MTX appears to be a safe and effective therapy for pediatric LS. (J Rheumatol 2006; 33:609–14)

Key Indexing Terms:
LOCALIZED SCLERODERMA METHOTREXATE CORTICOSTEROIDS CHILD THERAPY

Localized scleroderma (LS) is an uncommon disorder in children, with an incidence of about 1/100,000[1]. LS is 10 times more common in the pediatric population than systemic scleroderma, and progression to the systemic disease is rare. The major categories of LS include en coup de sabre as well as linear, plaque, and pansclerotic morphea. Each subset of LS involves similar pathophysiology. Lesions typically begin as areas of inflammation with edema and increased vascularity, followed by sclerosis, collagen formation, and eventual atrophy. Depending upon the location and size of the lesions, outcomes can vary from mild superficial defects to severe functional impairment with contractures, muscle and bone atrophy, and/or limb growth arrest. The active inflammatory phase of LS is usually self-limited, lasting on average 2–6 years. However, effects such as subcutaneous tissue atrophy and localized growth failure may cause significant deformity in actively growing children.

Treatment of LS remains a challenge and the etiology remains unclear. However, there is evidence for immune system abnormalities in LS[2]. Many drug regimens have been tried with variable success, including D-penicillamine[3], cyclosporine[4], oral corticosteroids[5], low dose methotrexate (MTX)[6], ultraviolet light therapy[7-10], psoralen[11,12], and vitamin D analogs[13-17]. The use of a combination of low dose MTX and corticosteroids was explored in a case series by Uziel, *et al*[18] and a published abstract by Walsh, *et al*[19]. Of the 10 patients involved in the Uziel study, 8 responded well to the combination therapy[18]. MTX and corticosteroids have been widely used in the treatment of inflammatory diseases, including dermatomyositis, psoriatic arthritis, juvenile rheumatoid arthritis, sarcoidosis, and localized and systemic scleroderma[20]. MTX is generally well tolerated and has few side effects, although maximal therapeutic response to MTX is generally delayed until several months following initiation of therapy. MTX works, in part, by competitively inhibiting dihydrofolate reductase and the formation of tetrahydrofolic acid, and therefore affects both DNA and RNA synthesis. It has also been shown to reduce the number of soluble interleukin 2 (IL-2) receptors and circulating IL-2, IL-6, and IL-8[18]. In adults with LS, MTX alone was effective therapy in 6 of 9 patients[6]. Hypothetically, coupling MTX with corticosteroids might provide a more rapid antiinflammatory response, and may represent a more effective therapeutic approach to this disease. We investigated the use of MTX therapy with or without (±) corticosteroids for pediatric LS.

From the Department of Pediatrics and Dermatology, Children's Hospital of Philadelphia and University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania, and the Department of Pediatrics, Gillette Children's Specialty Healthcare, St. Paul, Minnesota, USA.

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P.G. Fitch, MD, Resident Physician, Department of Pediatrics; P. Rettig, RN, MSN, CRNP, Nurse Practitioner; J.M. Burnham, MD, Assistant Professor; T.H. Finkel, MD, PhD, Associate Professor, Chief, Division of Rheumatology; A.C. Yan, MD, Assistant Professor, Section of Pediatric Dermatology; R.Q. Cron, MD, PhD, Assistant Professor, Division of Rheumatology, Department of Pediatrics, Children's Hospital of Philadelphia; E. Akin, MD, Assistant Professor, Division of Rheumatology, Gillette Children's Specialty Healthcare.

Address reprint requests to Dr. R.Q. Cron, Children's Hospital of Philadelphia, 3615 Civic Center Blvd., Abramson Research Center, Room 1102B, Philadelphia, PA 19104-4318, USA.
E-mail: rqcron@mail.med.upenn.edu

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MATERIALS AND METHODS

Patients. After institutional review board approval of the case study protocol at The Gillette Children's Hospital and The Children's Hospital of Philadelphia (Children's Hospital), 17 patients (12 from the Philadelphia region) were enrolled in the study (Table 1). Charts were reviewed for 17 children (under age 16) with LS who were treated with MTX (±) oral corticosteroid between 1999 and 2004. Each patient was followed in the Rheumatology Clinic at Gillette Children's Specialty Healthcare or Children's Hospital during the specified interval. Patients were identified via diagnostic codes and no patients were excluded. For those who did not have a biopsy diagnosis, LS was diagnosed clinically by experienced pediatric rheumatologists (EA, RQC, or THF) and, with the exception of one patient, by an experienced dermatologist (ACY). Signs of progressive systemic scleroderma were absent. Treatment consisted of low dose MTX (±) oral corticosteroid for the initial 4–7 months. The followup period lasted at least 6 months after the initiation of MTX therapy.

Dermatological review. Fifteen patients were evaluated in the Dermatology Clinic prior to their referral to the Rheumatology Clinic, where low dose MTX (±) corticosteroid was initiated. Another patient was evaluated by Dermatology after the initial visit to Rheumatology, but before the initiation of MTX. One patient was not evaluated by Dermatology. Eight of 17 patients were biopsied to confirm the diagnosis of LS prior to treatment. Prior dermatologic therapies are listed in Table 2 and included topical vitamin D (10 patients) and topical steroid creams (8 patients).

Followup telephone questionnaire. All of the patients' families were contacted, verbally consented, and then asked to answer the following questions: (1) "Overall, how is your child's lesion in comparison to the initial visit to Rheumatology Clinic (improved, no change, or worse)?" and (2) "How difficult was it to take the prescribed medications?". For the second question, parents were given a verbal scale on which to grade their responses (no problem, some difficulty, moderate difficulty, unable to take medicine).

Treatment protocol. All patients were prescribed MTX: 12 received subcutaneous (SC) injections and 5 received oral (PO) MTX at the request of the family. Some may consider treatment with MTX aggressive in patients with isolated plaque morphea, particularly if it is on the trunk or back (Patient 5); however, in the case of Patient 5, the lesion was extensive, measuring roughly 7 × 7 cm, adherent, and enlarging. Over the course of 2 months the borders of the lesion and areas of adherence spread 1.5 cm in height and width.

Initial doses of MTX ranged from 0.4 to 1.0 mg/kg/wk with a maximum of 25 mg per dose. Folic acid (1 mg/day) and/or a daily multivitamin containing 400 µg of folate were prescribed concomitant with the MTX.

At the time of diagnosis at Children's Hospital the following laboratory measures were routinely checked: complete blood count (CBC), liver function panel, antinuclear antibody (ANA), urinalysis, and erythrocyte sedimentation rate (ESR). Other laboratory studies that were done on selected patients included: Scl-70 (4 patients), rheumatoid factor (RF, 2), thyroid studies (2), immunoglobulin levels (1), HLA-B27 (1), Lyme titers (2), and creatine kinase (CK, 1). Patients evaluated at Gillette Children's Hospital had the following measures checked at initial evaluation: CBC, ESR, C3, C4, lactate dehydrogenase, and an ANA panel including Scl-70. In selected patients the following laboratory studies were also done: Lyme titers (2) and immunoglobulins (1).

Patients receiving MTX were screened monthly for 2 months and then every 2 months for toxicity by obtaining liver enzymes and CBC. Six patients were initially treated with oral corticosteroids in addition to MTX at the discretion of the pediatric rheumatologist. The choice to add corticosteroids to MTX for treatment of progressing lesions was solely based on different

Table 1. Patient characteristics at initiation of MTX ± corticosteroid therapy.

Patient	Sex	Age at Onset, yrs	Clinical Subtype	Area	Duration of Disease at Therapy Onset, yrs	Comorbidities at Therapy Onset
1	F	14	Linear	Lip, mandible, neck	3	Tongue atrophy; tongue and jaw deviation to affected side
2	F	10	Plaque	Right chest, arm, leg, abdomen, back	5	Limited ROM
3	M	10	Plaque	Chest, back, pelvis	2.5	None
4	M	10	Linear	Left leg	0.5	None
5	M	1	Plaque	Back	1.2	None
6	M	2	Plaque	Right chin	5	Arthralgias (not at site of lesion); asymmetric growth
7	F	9	Plaque/ linear	Right leg, upper and lower	1.3	Muscle atrophy; limited ROM; leg length discrepancy
8	F	11.5	Linear	Forehead, chest, back	1.25	None
9	M	1	Linear	Forehead, scalp	5	Alopecia
10	F	9	Plaque	Right thigh, foot, left axilla	1	Arthralgias
11	M	12	Linear	Left forearm, hand	2	Limited ROM; muscle atrophy; arthralgias
12	F	2	Plaque	Right and L legs, back, L thorax	0.75	Limited ROM (ankle); flexion contractures (knees)
13	F	6	Linear	Right and L legs	0.4	Limited ROM; muscle atrophy
14	F	5.5	Plaque	Right jaw	0.3	None
15	F	8	Plaque, en coup de sabre	Trunk, face	0.8	None
16	F	5	En coup de sabre	Face	0.8	Alopecia
17	F	8.5	Parry-Romberg	Face	2	Subcutaneous fixation; hemiatrophy of face

ROM: range of motion.

Table 2. Treatment response to dermatologic therapy prior to onset of therapy with MTX ± corticosteroid.

Patient	Treatment prior to MTX ± corticosteroid (Y/N)	Biopsy Confirmation (Y/N)	Treatment	Response*	Response Time
1	Y	N	None	NA	NA
2	Y	Y	Betamethasone diprolate 0.05% Topical vitamin D		
3	Y	Y	Topical vitamin D	↑ Size	NA
4	Y	Y	Fluocinalone 0.25% Topical vitamin D	No change	NA
5	Y	Y	Triamcinolone 0.1% Topical vitamin D	Lighter in color	3 mos
6	Y	N	Clobetasol propionate 0.025% Topical vitamin D Betamethasone diprolate 0.05%	↓ Induration and pigmentation 8 mo later ↑ size and ↑ atrophy	1 mo
7	Y	Y	Betamethasone 0.05% Calcipotriene (synthetic vitamin D)	No change	NA
8	Y	N	Clobetasol proprionate 0.05% Topical vitamin D	NA	NA
9	Y	N	Tacrolimus 0.1% Triamcinolone 0.1% Topical vitamin D	↓ Erythema ↑ Depth	6 wks
10	Y	Y	Calcipotriene Pimecrolimus 1%	↑ Size	NA
11	N	N	NA	NA	NA
12	Y	Y	Topical steroid	↑ Size and ↑ atrophy	NA
13	Y	N	Calcipotriene	No change	3 mos
14	Y	Y	Topical steroid	No change	NA
15	Y	N	Calcipotriene, topical steroid	No change	NA
16	Y	N	Topical steroid	No change	NA
17	N	N	None	NA	NA

NA: not applicable. * Prior to addition of MTX ± corticosteroid.

approaches by physicians. EA and RQC preferred to use combination therapy, whereas THF preferred to use monotherapy with MTX. Corticosteroid dosing was initiated at 1 mg/kg/day or every other day, and was gradually tapered and discontinued over 3–6 months according to clinical response.

Times of response were measured according to the clinic date at which an improvement in the lesion(s) was first noticeable. As this is a retrospective case review, there was not a standard protocol for amount of time until the first followup and for subsequent followups. Therefore, appointments were made according to physician recommendations and patient/parent availability. However, the average time to the first followup visit after starting therapy was 5–8 weeks and then subsequent visits spaced every 2–3 months afterwards. A favorable response to MTX (±) corticosteroid therapy was defined as absence of new lesions and one or more of the following: skin softening, skin lightening, or diminished lesion size or depth. Active lesions were defined as erythematous, warm, and/or enlarging.

RESULTS

Patient population. Demographic and clinical data are summarized in Table 1. Seventeen patients were enrolled in the study, 6 male and 11 female, with a mean age at disease onset of 7.3 years. Nine patients had plaque morphea, 3 had linear lesions involving a limb, and 5 had linear or en coup de sabre lesions involving the face. The mean and median durations of disease at the initiation of treatment with MTX (±) corticosteroid were 1.9 and 1.3 years, respectively, with a range of 4 months to 5 years. At onset of therapy, 5 patients had lesions causing limited range of motion, 5 had muscle atrophy and/or asymmetric growth, 2 had alopecia, 2 had arthralgias, and 6 had no comorbid findings.

Fourteen patients had dermatologic evaluations prior to initiation of therapy and one immediately after the initial visit to Rheumatology. Eight patients had skin biopsies to confirm the diagnosis of LS. There was no difference in the presentations of those who received skin biopsies and those who did not. Three patients initially responded well to topical therapy alone; 2 of those patients later had disease progression and were referred for systemic therapy. Eleven patients either did not respond or became worse with topical therapy.

Concomitant to initiating therapy for LS, 3 patients (Patients 9, 11, and 12) had further imaging to exclude involvement of underlying structures. Patient 9 had magnetic resonance imaging (MRI) of the brain and an ophthalmology evaluation to exclude involvement of the brain and eye. Patient 11 had radiographs of the hands to exclude underlying bone and joint involvement. Patient 12 had radiographs and an ultrasound of the knees and ankles to exclude tendon involvement and joint effusions.

No major adverse events occurred secondary to treatment with MTX (±) corticosteroids. One patient experienced a transient elevation in transaminases following MTX therapy. Another patient experienced a 20-pound weight loss during treatment; subsequently the MTX dose was decreased and the weight stabilized. One patient stopped taking corticosteroids secondary to weight gain. Several patients developed mild cushingoid features and weight gain while taking corticosteroids. Three patients reported mild mood swings. One patient had transient glucose elevation necessitating a more rapid corticosteroid taper.

Clinical evaluation. After starting MTX (±) corticosteroid therapy, one patient (Patient 7) was lost to followup for 16 months, at which time therapy was restarted; the remaining 16 patients responded to therapy (Tables 3 and 4). Five patients were treated with MTX alone, and 12 were treated with MTX and corticosteroids. The median response times were 2.25 and 2.0 months, respectively. One patient (Patient 5) who had a favorable initial response experienced a flare of LS after 4 months of therapy, despite therapy escalation with both MTX and corticosteroid. The flare consisted of increased depth of existing morphea lesions, as well as the appearance of new lesions. The mean followup time for patients taking MTX and MTX plus corticosteroids was 33 months and 25 months, respectively. At their most recent followup visits, 16 of 17 patients had inactive lesions. Further, most of the comorbidities were improved or completely resolved at the most recent visit.

Response to therapy with MTX (±) corticosteroid was evaluated retrospectively by the parents via a telephone questionnaire. Parents of 15 children stated that their child's lesion(s) had improved on therapy; 2 stated their child's lesion(s) were worse, including the patient who experienced a clinically apparent disease flare. The parents of 7 children reported no problems with administration, while 4 children had some difficulty, and 6 had moderate difficulty.

DISCUSSION

LS in childhood, although a non-life-threatening disease, can cause severe local cutaneous changes and growth abnormalities. Lesions occurring across joints can lead to significant joint contractures and disability. At present, there is no consensus among pediatric rheumatologists regarding the care of children with LS. Previously, Seyger and collaborators reported that MTX was effective in the absence of corticosteroids for widespread morphea in adults[6]. Recently, Kreuter and colleagues reported that the combination of pulsed methylprednisolone and oral MTX was beneficial in 14 of 15 adult patients with LS[21]. Uziel and colleagues reported that MTX, in conjunction with frequent high dose pulse intravenous corticosteroids, was effective in treating 8 of 10 children with LS[18]. They speculated that the early use of corticosteroids led to a rapid improvement in the LS and that the MTX was effective as maintenance therapy. Our study differed somewhat from that of Uziel, *et al*[18] in that their patients received 9 days of high dose intravenous pulse methylprednisolone over a 3-month period. In contrast, a subset of our patients received daily, or every other day, oral prednisone over the first few months of therapy. Oral corticosteroid treatment spares the child the necessity of intravenous catheters and multiple hospital visits. In addition, oral therapy allows for tapering based on response. Indeed, Uziel, *et al* resorted to oral corticosteroids, in addition to the pulse intravenous dosing, for one of their patients[18].

We report that weekly MTX was effective in improving LS lesions and their associated comorbidities that had failed to

Table 3. Therapy and response to MTX.

Patient	Medication	Response	Initial Response Time, mo	Status of Comorbidities at Last Visit	Active Lesion(s) at Last Visit (mo of therapy)
1	MTX (oral) 0.3 mg/kg/wk	Softening, ↓ pigmentation	15	↓ Tongue atrophy and jaw deviation	No (60)
6	MTX (SC) 0.5 mg/kg/wk × 4 mo, then 0.9 mg/kg/wk	Softening, ↓ adherence	2.25	Arthralgias continued (not at site of lesion) Asymmetric jaw growth improved with orthodontics	No (37)
9	MTX (SC) 1 mg/kg/wk	↓ Size	1.25	Alopecia present	No (24)
11	MTX (SC) 0.3 mg/kg/wk × 3 mo, then 0.4 mg/kg/wk × 12 mo, then 0.2 mg/kg/wk Naprosyn 375 mg bid × 3 mo, then 500 mg bid	↑ ROM, ↓ pigmentation	11	↑ ROM ↓ Arthralgias ↓ Atrophy	No (32)
12	MTX (PO) 0.8 mg/kg/wk	Softening, ↓ pigmentation, ↑ ROM knee	1	Resolution of knee flexion contractures, continued ↓ ROM ankle	No (12)

MTX: methotrexate, SC: subcutaneous administration, PO: oral administration.

Table 4. Therapy and response to MTX and prednisone.

Patient	Medication	Reponse	Initial Response Time, mo	Status of Comorbidities at Last Visit	Active Lesion(s) at Last Visit (mo of therapy)
2	MTX (SC) 0.4 mg/kg/wk Prednisone 1 mg/kg/QOD	Thinner ↓ Pigmentation	1.25	↑ ROM (knee and ankles)	No (13)
3	MTX (SC) 0.5 mg/kg/wk Prednisone 1 mg/kg/day	Softening ↓ Induration Smaller	1.25	NA	No (54)
4	MTX (SC) 0.7 mg/kg/wk Prednisone 1 mg/kg/day	Softening	1	NA	No (13)
5	MTX (SC) 1 mg/kg/wk × 6 mo, then 1.3 mg/kg/wk Prednisone 1 mg/kg/day	↓ Induration Deeper New lesions	2 4	NA	Yes (6)
7	MTX (SC) 0.4 mg/kg/wk Prednisone 0.5 mg/kg/day × 1 mo, then QOD	Softening ↓ Pigmentation	5	Full ROM; ↓ Asymmetry of muscle bulk affected calf and thigh	No (54)
8	MTX (SC) 0.8 mg/kg/wk Prednisone 1.5 mg/kg/day	No change	NA	NA	No (16)
10	MTX (SC) 0.7 mg/kg/wk Prednisone 2 mg/kg/day	Softening ↓ Pigmentation	2	↓ Arthralgias	No (28)
13	MTX (SC) 0.8 mg/kg/wk Prednisone 2 mg/kg/day	Softening	3	↑ ROM	No (26)
14	MTX (SC) 0.7 mg/kg/wk Prednisone 1 mg/kg/day	Softening	1.5	NA	No (22)
15	MTX (PO) 0.4 mg/kg/wk Prednisone 1 mg/kg/day	Smaller	3	NA	No (26)
16	MTX (PO) 0.7 mg/kg/wk × 6mo, then MTX (SC) 1 mg/kg/wk Prednisone 1 mg/kg/day	↓ Induration, hair regrowth	2	↑ Hair regrowth	No (28)
17	MTX (PO) 0.6 mg/kg/wk × 3 mo, then MTX (SC) 0.8 mg/kg/wk Prednisone 1 mg/kg/day	↓ Induration	2	↓ Subcutaneous fixation Facial hemiatrophy still present	No (18)

QOD: every other day, NA: not applicable.

respond to a variety of topical therapies (corticosteroids, vitamin D, tacrolimus). The response time on combination therapy is not directly comparable to that of MTX alone, given the variability of MTX dosing among the 2 groups. In general, the MTX doses (SC) were lower in the group on MTX monotherapy. Further, 2 out of 5 patients taking MTX alone were treated orally rather than subcutaneously, again making the data more difficult to interpret. Consequently, to make any conclusions regarding the use of corticosteroids in addition to MTX, a larger group of patients taking similar doses of background MTX will have to be evaluated.

Small nonrandomized studies such as this are subject to multiple limitations, including the lack of blinded observers; bias on the parts of physicians, patients, and families; lack of a protocol for standardized followup screening; and reliance on subjective interpretations of lesion improvement. Despite these limitations, however, our study is consistent with Uziel, *et al*[18], and is in agreement with the responses to the parental satisfaction questionnaire. Additional objective measures such as thermography, ultrasound, imaging with MRI, or innovative ways to measure and record lesion sizes from visit to visit may prove useful[21,22]. Our data indicate that a larger clinical trial evaluating the use of MTX and corticosteroids for pediatric LS is warranted.

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