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Treatment of Linear Scleroderma with Oral 1,25-Dihydroxyvitamin D_3 (Calcitriol) in Seven Children

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Abstract: **Linear scleroderma is a connective tissue disorder that characteristically involves the skin. Skin induration and pigmentary changes present in a linear distribution. Severe functional and cosmetic disability may occur, especially in growing children. No effective therapy for the fibrotic stage of scleroderma is available at present. Recently a beneficial effect of oral 1,25-dihydroxyvitamin D_3 (calcitriol) treatment was reported in adults. Calcitriol has a dose-dependent inhibition on fibroblast proliferation and collagen synthesis and has immunoregulatory activities. We assessed the efficacy of oral calcitriol treatment in seven pediatric patients with linear scleroderma. During the treatment dietary calcium intake was restricted. Calcium, inorganic phosphate, creatinine, and urea in the serum and urine was monitored. The urinary calcium:creatinine ratio was measured. The effects of the treatment were evaluated using a clinical scoring system. No side effects were observed. Five of the seven patients showed a good to excellent improvement of their lesions. One of them partly relapsed after 19 months, but showed an excellent response to a second therapy session with calcitriol. One patient with rapidly progressive disease failed to respond to therapy. Our results indicate that calcitriol can be an effective agent for treating localized scleroderma in children.**

Scleroderma is a connective tissue disorder of unknown etiology that characteristically involves the skin. In systemic scleroderma, the cutaneous induration is accompanied by internal organ involvement and potentially fatal complications.

Localized scleroderma has two variants: morphea and linear scleroderma (LS). Patients with morphea have sclerotic patches with variable changes in pigmentation. Occasionally, morphea has characteristic ''lilac rings'' which represent a continuing edge of inflammatory activity. Patients with LS have linearly distributed sclerotic areas in the skin. The inflammatory and fibrotic process in LS may involve the underlying subcutaneous tissue, muscle, periosteum, and bone. This may lead to serious cosmetic problems. It may also lead to mild, but occasionally severe functional disabilities because of disabling joint contractures and impairment of growth, especially of the limbs. Even vascular abnormalities of the

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brain underlying the linear scalp or facial (''en coup de sabre'') lesions or of the mesentery and kidney beneath abdominal lesions have been observed.

Localized scleroderma may begin as an erythematous or violaceous skin discoloration which progresses in size and may become elevated or depressed. Eventually areas of hyperpigmentation appear, the lesions become smooth and hairless, and subcutaneous atrophy is apparent. Many linear scleroderma lesions eventually fan out at their proximal end and often extend to the midline or very slightly beyond (1–6).

Childhood-onset disease represents 3% of all cases of scleroderma, with 1.5% of cases developing before the age of 10 years. Fewer than 150 pediatric patients have been reported in the literature to date (7). The majority of these children have a localized form of scleroderma, with a predominance of LS.

Localized scleroderma is a self-limiting disease, its activity lasting several years. However, the severe cosmetic and functional disabilities are irreversible. At present there is no accepted or proved treatment for localized scleroderma. Recently the beneficial effects of 1,25-dihydroxyvitamin D_3 (calcitriol) were reported in adults (8–10). The presence of cutaneous receptors for calcitriol suggested that the skin was not only a site for vitamin D synthesis, but also a target organ for this hormone. The relevant actions of calcitriol in scleroderma may be regarded as varied: immunomodulatory effects on functions of lymphocytes and monocytes/macrophages, dose-dependent inhibition of fibroblast proliferation, or direct effects on the regulation of collagen gene expression (11).

To date, there are no reports on the treatment of localized scleroderma in childhood with calcitriol. We assessed the efficacy of oral calcitriol treatment in seven children with LS. Here we report the clinical presentation, laboratory results, efficacy, and side effects of calcitriol treatment.

PATIENTS AND METHODS

Seven children, ages 3 to 13 years, were evaluated. The diagnosis of LS was based on physical examination. No efficient skin score system is available for children, therefore a simple clinical scoring system was used in our department. The most affected skin lesion was scored. Pigmentary changes were indicated as absent (0) or present (+). The degree of induration was classified as follows: none (0), mild (1), moderate (2) or severe (3). The progression of the lesions was measured objectively and compared with clinical photographs. Joint mobility was evaluated subjectively by the patients and their parents and objectively by the patients' physiotherapists. Finally, the follicle pattern and recurrent hair growth on the skin were assessed. A skin biopsy was obtained in five of the seven children; the biopsy was refused by the parents of two patients. Special instruments such as the 15, 20, or 25 mHz B-mode ultrasound were not used. No other diagnostic tools are available to obtain an objective evaluation of the cutaneous lesions in children. Blood samples were obtained at the time of referral to assess the immunologic profile, including the presence of antinuclear antibodies (ANA), antibodies to extractable nuclear antigens and rheumatoid factor, and levels of serum complement (C3, C4) and immunoglobulins (IgG, IgM, IgA). Antibodies against *Borrelia burgdorferi* were measured.

Internal organ involvement was excluded by anamnesis and clinical examination followed by baseline renal function tests including urinalysis, urea, creatinine and albumin levels, and serum electrolytes. Hypercalciuria was evaluated by the calcium:creatinine ratio. This ratio, measured in the second morning urine sample after an overnight fast, reflects the daily calcium excretion (12). Liver function tests included serum transaminases.

Oral and written informed consent was obtained from the parents of all seven children prior to treatment with calcitriol. Oral calcitriol (Rocaltrol®, Roche) was given at a dose of 0.25 μg/day in the first week, according to the protocol described by Hulshof et al. (10). This dose was increased every week to reach 0.75 μg/day during the third week. Patient 4 remained at a dose of 0.5 μg/day because of a limited body surface area. In patient 7, the dose was increased to 1.25 μg/day (maximum dose) because of a sudden relapse during treatment.

The treatment protocol is shown in Table 1. The patients were examined every 2 weeks for the first 3 months and monthly thereafter to determine the efficacy of the treatment. This was evaluated by the clinical scoring system, and comparative photographs were also taken. Calcium, inorganic phosphate, alkaline phosphatase, and creatinine levels in the blood and urine were monitored. Renal ultrasound examination was performed to exclude lithiasis. The dietary calcium intake was restricted to 600 mg/day, because of the increased intestinal absorption of calcium caused by calcitriol.

CASE REPORTS

The following two patients highlight the clinical presentation and different responses to therapy.

Patient 2

A 7-year-old girl presented with white, linear lesions on her right leg and abdomen. The lesions became indurated and spread in the direction of the lower leg and foot over

TABLE 1. *Protocol for Treatment with Calcitriol*

Start	—Clinical scoring:	Pigmentation Induration Progression Joint immobility Follicle pattern and hair growth
	—Clinical photographs	
	—Immunologic evaluation	
	—Product information and informed consent	
	—Blood and urinalysis for calcium, phosphate, creatinine, and urea	
	—Renal ultrasound examination	
	—Diet: calcium intake restricted to 600 mg/day	
Follow-up		
First 3 months	—Clinical scoring at 2 week intervals	
	—Clinical photographs (at 3 months)	
	—Blood analysis at 2 week intervals	
	—Urinalysis monthly	
	—Renal ultrasound (at 3 months)	
After 3 months	—Clinical scoring monthly	
	—Clinical photographs (end of treatment)	
	—Blood and urinalysis monthly	
	—Renal ultrasound (end of treatment)	

the following months (Figs. 1 and 2). Because of decreased mobility of the knee and ankle, physiotherapy was started.

At referral to our clinic, the induration of the skin lesions was classified as degree 3. The disease was still in a progressive phase as reflected by a remarkable impairment in the function of the leg. Oral calcitriol was started. Three months later there was a decrease in induration of the lesions (degree 2). There was no further progression of the lesions and physiotherapy was discontinued; the stiffness and decreased joint mobility had resolved. Therapy was discontinued after 10.5 months. At that time there were only small residual sclerotic lesions (Fig. 3 and 4).

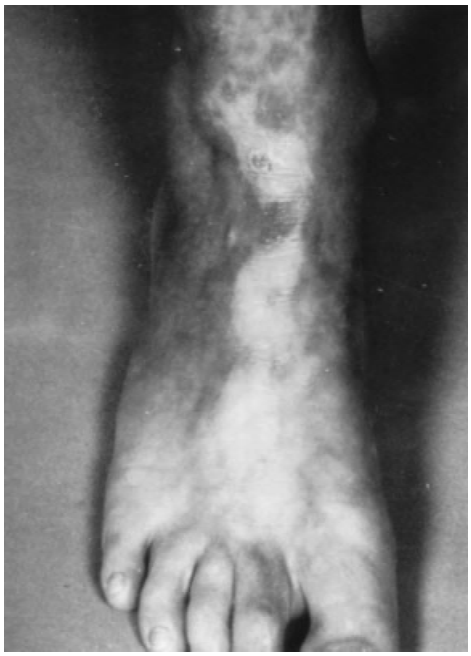

Figure 1. Linear scleroderma on the right foot before treatment (patient 2).

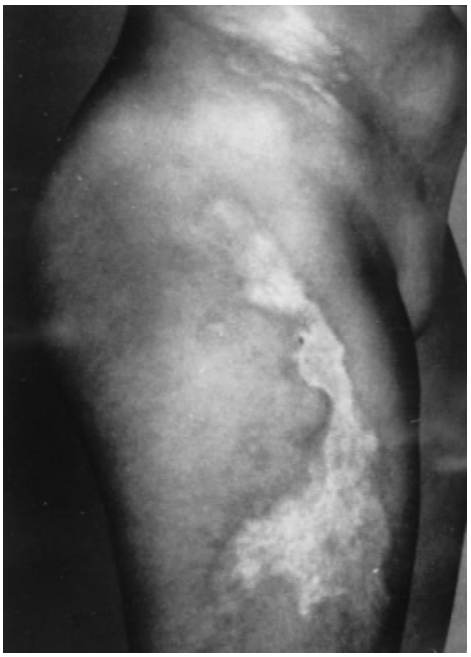

Figure 2. Linear scleroderma on the right leg and abdomen before treatment (patient 2).

Patient 4

This almost 4-year-old boy had white, indurated lesions (degree 3) on his left shoulder, the upper and lower part of his left arm, and his left hand. His thumb showed altered pigmentation with progressive stiffness and joint immobility. He had already started physiotherapy.

Oral calcitriol was started because of the continuing progression of the lesions and the restricted joint movement. After 3 months of treatment, the lesions still progressed and involved the entire left extremity and shoulder. The degree of induration remained unchanged. Therefore we decided the calcitriol therapy was not successful and discontinued it. We then started treatment with oral corticosteroids (prednisolone 1 mg/kg daily) in combination with methotrexate (10 mg/m^2 once a week).

After 6 months of this combination therapy, the lesions remained in a stable fibrotic state. The function of the thumb did not improve (Fig. 5). Calcitriol was added

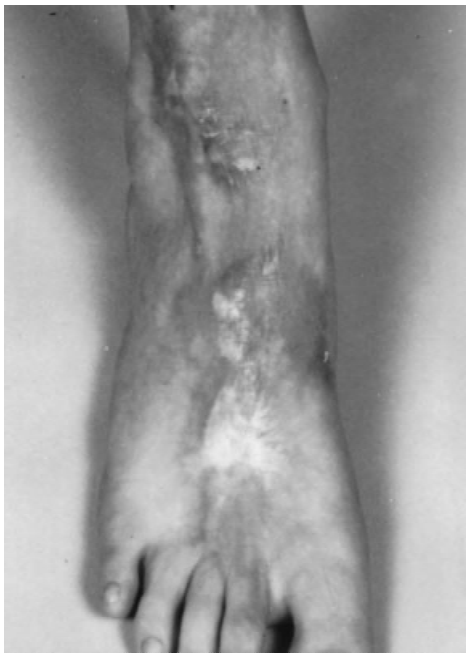

Figure 3. Improvement of lesions on the right foot after treatment (patient 2).

to the therapy. After another 3 months of treatment, the first signs of a mild improvement were noted.

RESULTS

Seven patients with linear scleroderma were treated with calcitriol. The clinical and laboratory findings of each patient are summarized in Table 2. The average age of onset of LS was 8 years 7 months (range 3–13 years). The female:male ratio was 6:1. Sclerotic lesions on an extremity were seen in six patients, whereas one patient had facial scleroderma (''en coup de sabre''). The mean duration of active disease was 11 months. The onset of LS was slow and insidious in the six girls, but patients 1 and 2 already had received physiotherapy because of limited joint mobility. Patient 5 needed orthodontic correction because of the involvement of the oral mucosa and gingiva, and asymmetric growth of the maxilla. The only male patient showed rapid progression of his lesions with a serious joint contracture of his thumb. He was also the only patient with positive antinuclear antibodies. In all seven patients, further laboratory results including immunologic profile, antibodies against *Borrelia burgdorferi*, renal and liver function tests, serum electrolytes, total blood count, and urinalysis were normal.

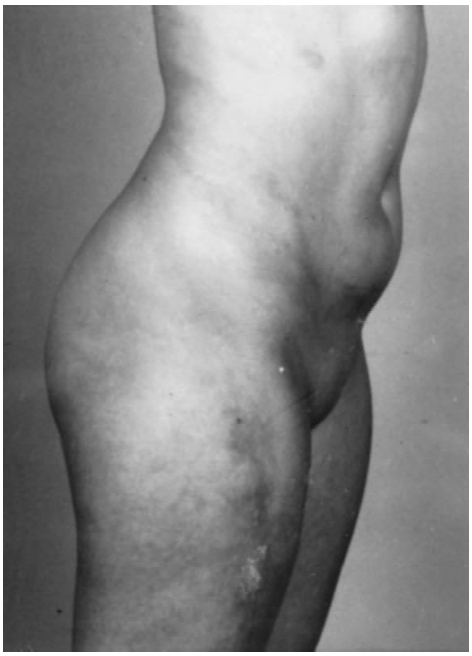

Figure 4. Improvement of lesions on the right leg and abdomen after treatment (patient 2).

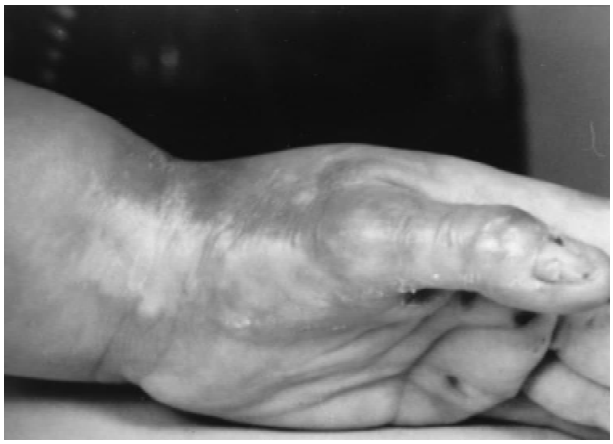

Figure 5. Linear scleroderma on the hand with joint contracture and growth impairment of the thumb (patient 4).

Calcium excretion was documented by the calcium: creatinine ratio. This ratio, measured in the second morning urine sample after an overnight fast, reflects the daily calcium excretion: the 97th percentile level for British children eating an unrestricted diet found in a study by Shaw et al. (12) was 0.69 mmol/mmol. Table 3 shows the results of the calcium:creatinine ratio in the seven patients at baseline and at the end of treatment. The results are within normal limits. Renal ultrasound performed at the start of treatment and repeated after 3 months and at the end of treatment gave no indication of nephrolithiasis. Histopathologic examination of skin biopsy specimens from patients 1, 2, 4, 6, and 7 confirmed the diagnosis of LS.

All seven patients started therapy according to the treatment protocol (Table 1). The beneficial effects of the calcitriol treatment are shown in Table 4. Six patients ended the therapy after 6 to 10.5 months. They showed

TABLE 2. *Clinical Findings in Pediatric Patients with Linear Scleroderma*

	Patient						
	1	2	3	4	5	6	7
Age of onset	12 years 6 months	7 years 4 months	7 years 6 months	3 years 10 months	11 years	4 years 3 months	13 years 6 months
Sex	F	F	F	M	F	F	F
Duration of disease	16 months	12 months	14 months	7 months	10 months	12 months	6 months
Extent of disease	Leg	Legs, foot, anbdomen	Leg, abdomen, back	Thumb, arm, shoulder	Filtrum, oral mucosa	Leg	Arm, hand
Duration of treatment	7 months	10.5 months	6 months	3 months	6 months	9 months	9 months

decreased induration of the sclerotic lesions after 3 and 6 months, with five children having only a mild degree of induration. Joint immobility was still present in one patient. Reappearance of the follicle pattern and hair growth was noted in the six girls who ended treatment. One of the girls (patient 1) relapsed after 19 months and started calcitriol therapy again. The other five girls showed no recurrence of the disease after a follow-up period of 1 to 20 months. Only one patient did not show any response to this therapy, and after 3 months of treatment calcitriol was discontinued. The patient was then started on oral corticosteroids in combination with methothrexate. Calcitriol treatment was added again later because of lack of improvement. After 3 months of this regimen the lesions seemed to stabilize. During treatment with calcitriol, none of the seven patients showed any side effects.

DISCUSSION

Our results with a limited number of patients (seven) indicate that systemic 1,25-dihydroxyvitamin D_3 may be an effective therapeutic agent for localized scleroderma in childhood. All seven of them had chronic disease of at least 7 months duration before treatment was started. Clinical improvement in skin stiffness and joint mobility was seen in six children after 3 months of treatment.

TABLE 3. *Calcium: Creatinine Ratio (mmol/mmol) Before and During Treatment with Calcitriol*

Patient	Baseline	3 months	End of treatment
1	0.29	0.65	0.26
2	0.13	0.56	0.55
3	0.43	0.58	0.20
4	0.19	0.60	—
5	0.22	0.27	0.24
6	0.46	0.68	0.62
7	0.24	0.31	0.21

Therefore it is highly likely that the beneficial effect that was observed was due to calcitriol therapy. One patient failed to respond to the therapy. This patient had rapidly progressive, active disease and positive antinuclear antibodies (ANA). The presence of ANA correlates directly with more extensive cutaneous lesions and a prolonged disease duration (4). More aggressive therapy is warranted in such patients.

There are few reports in the literature on the effect of calcitriol in patients with scleroderma. Humbert et al. (8,9) obtained good results in 18 adult patients with scleroderma (11 with systemic scleroderma and 7 with localized scleroderma), without any side effects except for transient hypercalciuria and hypercalcemia, which could be monitored easily and responded quickly to a reduction in dosage. Hulshof et al. (10) observed some beneficial effect of calcitriol treatment in three patients with generalized morphea. To our knowledge there are no reports available of children with scleroderma who were treated with calcitriol.

Increased collagen content of affected tissues is a fundamental pathologic change in scleroderma. Accumulation of collagen is generated by an increase in the number of metabolically active fibroblasts and an increase in collagen synthesis (11). These fibroblasts (in vitro) were shown to synthesize collagen at a faster than normal rate (10). Calcitriol was demonstrated to cause a dose-dependent inhibition of fibroblast proliferation and collagen synthesis.

Calcitriol is also involved in immunoregulation. In scleroderma, skin fibrosis is preceded by an initial cellular infiltrate, predominantly with T-helper lymphocytes (9). 1,25-dihydroxyvitamin D_3 inhibits in a dose-dependent fashion the rate of proliferation of the helper subset. Calcitriol induces the differentiation of granulocyte colony-forming units into macrophages and monocytes. These white blood cells may produce collagenase, an enzyme which is deficient in scleroderma. Thus calcitriol has an antiproliferative and antisynthetic effect on fibroblasts.

TABLE 4. *Benefit of Treatment: Clinical Scoring During Treatment with Calcitriol*

	Pigmentation			Induration			Progression			Joint immobility			Follicle pattern		
Patient	0	3 months	6	0	3 months	6	0	3 months	6	0	3 months	6	0	3 months	6
1	+	+	+	3	1	1	+	−	−	+	−	−	−	+	+
2	+	+	+	3	2	1	+	−	−	+	−	−	−	−	+
3	+	+	+	3	1	1	+	−	−	−	−	−	−	+	+
4	+	+	+	3	3	3	+	+	+	+	+	+	−	−	−
5	+	+	+	3	1	1	+	−	−	+	−	−	−	+	+
6	+	+	+	3	2	2	+	+	−	−	−	−	−	−	+
7	+	+	+	3	1	1	+	+	−	−	−	−	−	−	+

+ = present; − = absent.
Induration: 0 = none; 1 = mild; 2 = moderate; 3 = severe.

Its effect on the modulation of immunologic mediators may be important.

Calcitriol may therefore be of use in the treatment of debilitating linear scleroderma in growing children. Our clinical and laboratory results during treatment of seven children indicate an attractive beneficial effect of this hormone on the fibrotic stage of the disease. No important side effects were observed during the treatment with calcitriol. We suggest starting with calcitriol for at least 3 months in children with linear scleroderma before introducing more aggressive therapy. If an improvement is noted, then this therapy may be continued for 6 to 9 months.

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