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Treatment of Scleroderma with Oral 1,25-dihydroxyvitamin D_3: Evaluation of Skin Involvement Using Non-invasive Techniques

Results of an Open Prospective Trial

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1,25-dihydroxycholecalciferol (1,25 $(OH)_2$ D_3) causes dose-dependent inhibition of fibroblast growth and collagen synthesis and has numerous immunoregulatory activities. We assessed the effects of oral 1,25 $(OH)_2$ D_3 in the treatment of patients with systemic sclerosis (SS). Eleven patients with SS entered an open prospective study. Oral 1,25 $(OH)_2$ D_3 was given at a mean dose of 1.75 µg/day. The effects of the treatment were evaluated using clinical examination and physical measurements. After the treatment period (6 months to 3 years), a significant improvement, as compared with baseline values, was observed. No serious side-effects were observed. These results suggest that high-dose 1,25 $(OH)_2$ D_3 may be a useful therapeutic agent for scleroderma.

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Scleroderma is a chronic connective tissue disease characterized by fibrotic lesions in the skin and various internal organs. Immune system abnormalities have been suggested to play a central role in the pathogenesis of the disease. Excessive fibroblastic activity with collagen deposition in organs and microvascular abnormalities are other pathophysiologic features (1).

The target organs for vitamin D have long been believed to be limited to those associated with calcium metabolism such as the bone, small intestine and kidney. Indeed, receptors for 1,25 $(OH)_2$ D_3 on human dermal fibroblasts (2), as well as on different cells involved in the pathogenesis of scleroderma, have been detected. 1,25 $(OH)_2$ D_3 is extremely potent in inhibiting fibroblast proliferation and collagen deposition (3).

At our centre, one patient with localized scleroderma experienced marked clinical improvement while receiving oral 1,25-dihydroxyvitamin D_3 (4). These observations prompted an exploration of the possible use of the hormone in the treatment of scleroderma.

METHODS

The study was open, prospective and uncontrolled. Eleven patients (1 male, 10 females; mean age 46 years, age range 16 to 77 years) were included in the study. They suffered from systemic sclerosis (SS) (8 with diffuse scleroderma, 3 with the CREST syndrome variant) (Table I). They fulfilled the diagnostic criteria of the American Rheumatism Association (ARA). The duration of disease varied from 1 to 20 years. These patients had either stable disease or experienced worsening of scleroderma during the 6 months before the trial. The patients had already received treatment for their condition in the form of D penicillamine, or systemic corticosteroids, but this had not prevented progression of the disease. No patient was taking any medica-

Table I. *Details of patients with SS*
ANA = antinuclear antibodies

Patient no.	Age	Sex	Internal organs affected	Biological data	Duration of disease (years)	Duration of treatment (months)
1	77	F	Lungs, joints, esophagus	ANA: 1/12800	5	8
2	31	F	Lungs	ANA: 1/2048 Anticentromere	1	28
3	53	F	Lungs, joints, esophagus	ANA: 1/800, Anticentromere	8	9
4	16	M	Lungs, joints, esophagus	ANA: 1/50	5	9
5	31	F	Lungs, joints, esophagus	ANA: 1/3200	6	17
6	66	F	Lungs, esophagus	ANA: 1/3200 Scl-70	1	19
7	64	F	Lungs, joints, esophagus	ANA: 1/1600	17	24
8	17	F	Lungs	ANA: 1/1600	1	20
9	57	F	Lungs, joints	ANA: 1/3200	20	36
10	53	F	Lungs, joints, esophagus	ANA: 1/100 Anticentromere	5	8
11	49	F	Lungs	ANA: 1/3200 Scl-70	18	16

Table II. *Evaluation of monitored parameters in patients with SS*

Patient no.	Ue × ST		Maximal oral opening (mm)		Palmar flexion index (mm)	
	Before	After	Before	After	Before	After
1	1.04	1.68	32	36	32	18
2	2.00	4.00	25	27	0	0
3	1.98	2.32	19	25	24	14
4	1.25	1.09	29	30	35	26
5	0.82	1.50	20	26	35	18
6	1.55	1.60	33	40	20	0
7	0.96	2.88	23	25	41	38
8	1.98	3.60	37	43	32	0
9	1.92	2.44	28	44	33	0
10	1.20	1.36	35	41	25	0
11	1.67	3.03	27	30	10	6

tion that could have influenced the course of the disease during the trial. Patients received oral 1,25 $(OH)_2$ D_3 (Rocaltrol®, Roche Lab., Neuilly-sur-Seine). The daily doses of 1,25 $(OH)_2$ D_3 were 0.25 μg/day the first week. When there was no increase above normal in urine and serum calcium values, the daily dose of 1,25 $(OH)_2$ D_3 was increased by 0.25 μg every week, up to a therapeutic dose of between 1.00 and 2.50 μg (mean dose: 1.75 μg/day). Concurrent treatment that was permitted included non-steroidal antiinflammatory drugs, analgesics, nifedipine and antihypertensive drugs. This treatment had not been modified for at least 6 months before the study.

Parameters monitored

During the trial period, patients' cases were evaluated every month. Initial assessment and evaluation after the treatment period included: clinical examination, oral aperture measurements by measuring the interincisor distance after maximum voluntary opening of the mouth, and palmar flexion index (distance between the third finger and the median palmar fold), skin torsion measurements using a torsional device (Twistometer®, l'Oreal Paris) and skin thickness using a 15 MHz echometer, measured on the volar aspect of the forearm.

Blood and urine analyses of calcium, inorganic phosphate and creatinine levels were monitored every 2 weeks. Urine was collected over 24 h. Normal ranges for serum calcium, serum inorganic phosphate and urinary calcium/creatinine levels were: 2.20–2.60 mmol/l, 0.70–1.45 mmol/l and < 0.20, respectively.

Statistical methods

The differences between the initial and last recorded values were examined using Student's paired *t*-test for continuous variables and Wilcoxon's rank-sum test for discrete variables. Differences were considered significant if $p < 0.05$.

RESULTS

Of the 11 patients entering the trial, none failed to complete the treatment. Oral aperture and flexion index distance improved significantly from 28 to 33 mm ($p < 0.05$) and 28.7 mm to 12 mm ($p < 0.05$) respectively. Since skin torsion measurements provide a quantitative assessment of the mechanical properties of the human skin, in vivo, changes in physical state were measured with a torsional device. Ue is the immediate angular deformation which represents, in part, skin extensibility. The skin thickness (ST) was measured in the same area using a 15 MHz echometer. In line with the clinical results, a significant increase in the immediate angular deformity Ue appeared after the period of therapy. By normalizing the results of the assessment of extensibility by the skin thickness, the intrinsic extensibility Ue × ST was obtained, which corresponds to the extensibility of a given volume of skin (5). A significant improvement in the intrinsic skin extensibility was noted at the end of the trial ($p < 0.01$) (Fig. 1).

No serious side-effects were observed except for transient hypercalciuria (always below 350 mg/24 h), which responded immediately to a temporary reduction in the dosage of 1,25 $(OH)_2$ D_3 (from 2.00 μg to 0.75 μg/day) in 4 patients. Serum calcium levels did not exceed 105 mg/l in each patient during the study.

DISCUSSION

The results of this pilot study suggest that 1,25 $(OH)_2$ D_3 at high dosages may be beneficial in the treatment of patients with SS. After a 1 to 3-year treatment period, a significant improvement was observed in skin parameters. Skin thickness and extensibility (assessed by a torque method using a twistometer) are the most useful parameters in the study of the progression of localized scleroderma and SS, as demonstrated by Kalis et al. (6).

One of the principal drawbacks of this study is its open-label design. The lag period prior to treatment showed worsening or stable disease. Thus, the changes observed after treatment might not be considered to be due to a placebo effect. Another limitation of the study is that the number of patients is small. However, the finding of statistically significant improvement, despite the sample numbers, makes these findings more impressive. Several recent reports indicate that 1,25 $(OH)_2$ D_3 could be involved in immunoregulation. In scleroderma, skin fibrosis is preceded by an initial cellular infiltrate with T-helper lymphocytes predominating. A hyperactivity of T-helper cells in SS patients was demonstrated (7), as well as an elevated ratio of T4/T8 lymphocytes (8) together with augmented T-helper cell function (9). 1,25 $(OH)_2$ D_3 inhibits in a dose-dependent fashion the rate of proliferation of the helper subset

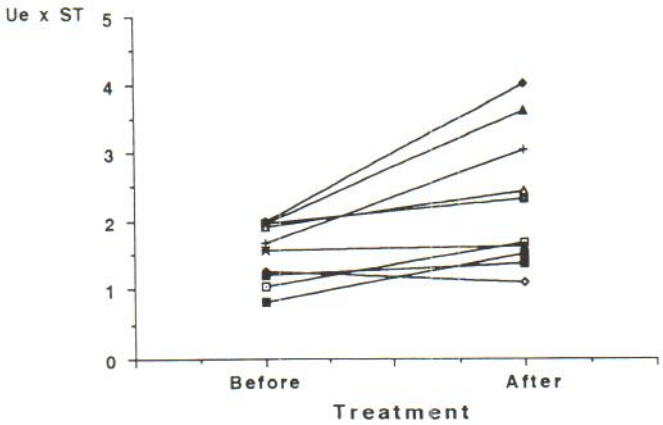

Fig. 1. Significant increase in the intrinsic skin extensibility (Ue × ST) at the end of the trial ($p < 0.01$) in patients with SS.

(10, 11) but had no effect on the proliferation of suppressor cells (12).

Surprisingly, the activity of collagenase is lowered significantly in SS skin (13). 1,25 $(OH)_2$ D_3 induces the differentiation of granulocyte colony-forming units into macrophages and monocytes. These white blood cells may produce collagenase (14).

Interleukin-1 activities in peripheral blood mononuclear cells from patients with SS have been shown to be low (15). 1,25 $(OH)_2$ D_3 produced a significant increase of IL-1 production by the murine macrophage cell line P 388D1 (16). The action of IL-1 on fibroblasts resulted in the inhibition of fibronectin synthesis (17) and enhancement of collagenase production (18).

Enhanced production of interleukin-2 (IL-2) in phytohemagglutinin-stimulated peripheral lymphocytes has been reported in patients with SS. Serum levels of IL-2 in patients with SS are higher than levels of controls, and high serum levels of IL-2 in patients with high skin progression were found (19). 1,25 $(OH)_2$ D_3 suppressed IL-2 production by phytohemagglutinin stimulated peripheral blood mononuclear cells in a concentration-dependent manner. Moreover, the release of IL-2 by mixed T lymphocytes activated by a mitogen is inhibited by 1,25 $(OH)_2$ D_3 (20).

Recombinant interferon (IFN) gamma may be beneficial in the treatment of patients with SS (21). Human macrophages activated by IFN gamma synthesize 1,25 $(OH)_2$ D_3 (22).

In summary, these findings suggest a mechanism by which calcitriol is active in the treatment of immune processes. 1,25 $(OH)_2$ D_3 may be an immunomodulatory drug which could have a role in controlling collagen deposition in some tissues. This open-label trial suggests a possible beneficial effect of oral 1,25 $(OH)_2$ D_3 in patients with scleroderma. If this beneficial effect is confirmed in future controlled trials, then 1,25 $(OH)_2$ D_3 offers an attractive alternative therapy for scleroderma since its only known side-effects are hypercalcemia and hypercalciuria, which can be monitored easily and can respond quickly to a reduction in dosage.

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