

Treatment of Scleroderma

Allen N. Sapadin, MD; Raul Fleischmajer, MD

The treatment of systemic sclerosis (scleroderma) is difficult and remains a great challenge to the clinician. Because the cause is unknown, therapies are directed to improve peripheral blood circulation with vasodilators and antiplatelet aggregation drugs, to prevent the synthesis and release of harmful cytokines with immunosuppressant drugs, and to inhibit or reduce fibrosis with agents that reduce collagen synthesis or enhance collagenase production. The purpose of this review is to critically analyze conventional and new treatments of systemic sclerosis and localized scleroderma. The therapeutic options discussed for the treatment of systemic sclerosis include the use of (1) vasodilators (calcium channel blockers [nifedipine], angiotensin-converting enzyme inhibitors [captopril, losartan potassium], and prostaglandins [iloprost, epoprostenol]), (2) immunosuppressant drugs (methotrexate, cyclosporine, cyclophosphamide, and extracorporeal photopheresis), and (3) antifibrotic agents (D-penicillamine, colchicine, interferon gamma, and relaxin). The treatment options reviewed for localized scleroderma include the use of corticosteroids, vitamin D analogues (calcitriol, calcipotriene), UV-A, and methotrexate. Preliminary reports on new therapies for systemic sclerosis are also considered. These include the use of minocycline, psoralen-UV-A, lung transplantation, autologous stem cell transplantation, etanercept, and thalidomide.

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Scleroderma or systemic sclerosis (SSc) is a connective tissue disease that affects various organ systems, including skin, gastrointestinal tract, lungs, kidney, and heart. The severity of skin and internal organ involvement may correlate with the clinical course of the disease. Based on the degree of skin involvement, SSc can be divided into limited cutaneous SSc or diffuse cutaneous SSc. Limited cutaneous SSc is characterized by sclerodactyly or acrosclerosis, with distal involvement of the extremities (distal to the elbows and knees) with or without face involvement. This clinical picture comprises Raynaud phenomenon, dysphagia, calcinosis cutis, and telangiectasis; it is slowly progressive and is frequently associated with anticentromere antibodies. The most severe complications are pulmonary hypertension and biliary cirrhosis. Diffuse cutaneous SSc is more severe and shows proximal involvement of the extremities

(proximal to the elbows and knees), trunk, or both.¹ Diffuse cutaneous SSc is often associated with pulmonary interstitial fibrosis, renal crises, and gastrointestinal involvement (dysphagia, hypomotility, and other disorders). Diffuse cutaneous SSc is frequently associated with Scl-70 (antitopoisomerase) and nucleolar autoantibodies (polymerase I and III, fibrillarin).

The cause of SSc is unknown and is regarded as an autoimmune disease involving cellular and humoral immunity. Cellular infiltrates, perivascular or diffuse, have been demonstrated in skin, lungs (alveolitis), smooth muscle cells, esophagus, ileum and jejunum, synovium, and liver.² These cells consist of T lymphocytes (CD4⁺, CD8⁺), B lymphocytes, and other nonspecific inflammatory cells, such as macrophages, mast cells, and eosinophils. Adhesion molecules are involved in homing and retention of lymphocytes and other inflammatory cells in the tissues and may play a role in the for-

From the Department of Dermatology, Mount Sinai School of Medicine, New York, NY.

Table 1. Treatment of Systemic Sclerosis

Vasodilators
Raynaud phenomenon
Nifedipine, verapamil hydrochloride
Losartan potassium
Iloprost
Pulmonary hypertension
Epoprostenol
Iloprost (carboprostacyclin)
Captopril
Renal crises
Captopril
Enalapril maleate (Vasotec)
Kidney dialysis
Kidney transplantation
Immunosuppressants
Skin induration
Methotrexate
Cyclosporine
Interstitial lung disease
Cyclophosphamide
Antifibrotics
Skin induration
D-Penicillamine
Colchicine
Interferon gamma
Relaxin

mation of cellular infiltrates in SSc.¹⁻⁶ Vascular involvement in SSc affects mainly capillaries, arterioles, and small arteries. The vascular pathology consists of absence or reduction in capillaries and ectasia of capillaries (telangiectases), often accompanied by an increase in endothelial cell proliferation.⁷ Soluble mediators, adhesion molecules, and cytotoxic factors have been incriminated in the mechanism of endothelial cell damage, including plasma factor VIII (von Willebrand factor), transforming growth factor β , platelet-derived growth factor, granzyme A, vascular cell adhesion molecule-1, intercellular adhesion molecule-1, and endothelin-1.⁸

The mechanism of fibrosis in SSc is not fully understood, although it is known that soluble mediators (transforming growth factor β , platelet-derived growth factor, interleukin [IL] 4, IL-6, tumor necrosis factor [TNF] α) can affect the behavior of fibroblast growth, proliferation, collagen synthesis, and chemotaxis.⁹⁻¹¹ The role of humoral immunity in SSc is unknown, although about 90% of patients with SSc show circulating anti-nuclear antibodies.¹²

The treatment of SSc is difficult and remains a challenge to the clinician. The purpose of this review is to critically analyze conventional and new treatments of SSc and localized scleroderma and briefly review new therapeutic approaches under current investigation.

TREATMENT OF SYSTEMIC SCLEROSIS

Skin Involvement

Vasodilators. Vasodilators are used in SSc to reduce vasospasm (Raynaud phenomenon) and to improve peripheral circulation (ischemia, gangrene) secondary to arterial blood vessel damage (**Table 1**).

Calcium channel blockers inhibit smooth muscle cell contraction by reducing the uptake of calcium, which is needed for muscle contraction. There are 2 groups of calcium channel blockers: (1) the pyridine dicarboxylic acids (nifedipine, nicardipine hydrochloride) and (2) the dimethoxyphenyls (verapamil hydrochloride, diltiazem). Nifedipine, in dosages ranging from 30 to 60 mg daily, reduces the severity of Raynaud phenomenon.¹³ More recently, it was shown that nifedipine was superior to bio-feedback techniques in reducing the frequency of Raynaud phenomenon episodes.¹⁴ Nifedipine is well tolerated, and the most common adverse effects are headaches, flushing, and edema of the feet and ankles. Nifedipine therapy can also be combined with antiplatelet aggregation drugs (low-dose aspirin) and dipyridamole (up to 400 mg daily, in slow increments).⁸ Pentoxifylline (400 mg, 3 times daily), alone or in combination with nifedipine, reduces blood viscosity by increasing red blood cell deformability and can be used to improve capillary function.

More recently, losartan potassium, an antagonist of angiotensin II receptor type I, was found effective in the treatment of Raynaud phenomenon.¹⁵ In this study, a regimen of losartan potassium, 50 mg daily, was compared with nifedipine, 40 mg daily. After 2 weeks, both drugs reduced the severity of Raynaud phenomenon, but only losartan reduced the frequency of episodes. Losartan was well tolerated, and the most common adverse effects were dry cough, muscle cramps, back pain, dizziness, and insomnia.

Prostaglandins are potent vasodilators. Iloprost is a chemically stable prostacyclin antagonist that was found effective in the treatment of Raynaud phenomenon secondary to SSc. Iloprost induces prolonged vasodilation, reduces platelet aggregation, and promotes endothelial cell lining. The drug was administered by continuous intravenous infusion (2 ng/kg per minute) for 8 hours daily for 3 days.¹⁶ More recently, an oral preparation of iloprost was used for the treatment of Raynaud phenomenon.¹⁷ A study comparing iloprost, 50 to 150 μ g daily, vs placebo noted a decrease in duration and severity of Raynaud phenomenon episodes, although the difference was not statistically significant. Another study¹⁸ involving 103 patients showed significant improvement in duration and severity of attacks but not in frequency, compared with the placebo. However, a third multicenter study¹⁹ involving 308 patients showed that oral iloprost, 50 μ g twice daily, was no better than the placebo.

Immunosuppressant Drugs. Because there is evidence for activation of cellular and humoral immunity in SSc, several immunosuppressant drugs have been previously used, with questionable benefits, including purine antimetabolites (6-thioguanine, azathioprine) and alkylating agents (chlorambucil, cyclophosphamide).²⁰ More recently, investigations have been carried out with methotrexate, cyclosporine, cyclophosphamide, and extracorporeal photopheresis.

A controlled, parallel randomized, double-blind trial with chlorambucil vs placebo was carried out involving 64 patients with SSc. After a 3-year follow-up, chlorambucil had obtained no better results than the placebo.²¹

Methotrexate was used in a randomized, double-blind trial involving 29 patients with SSc. Patients received weekly injections of 15 mg of methotrexate or placebo, and the dosage was increased to 25 mg per week for poor responders. After a 24-week follow-up, significant improvement was noted in skin induration and handgrip strength.²² Additional trials involving larger numbers of patients are necessary to confirm these results. Before initiating methotrexate therapy, a thorough evaluation of the patient should be completed. Baseline laboratory tests should include complete blood cell count, platelet count, liver function tests, serum urea nitrogen, creatinine, and creatinine clearance.

Cyclosporine is an immunosuppressive drug that selectively inhibits the release of IL-2 from activated T lymphocytes. There is evidence that serum levels of IL-2, its soluble receptors, or both are frequently elevated in early SSc.^{23,24} An open clinical trial with cyclosporine was conducted in 10 patients with SSc.²⁵ The starting dosage was 1 mg/kg per day, which was increased progressively until toxicity appeared or when 5 mg/kg per day was reached. After 48 weeks' follow-up, there was a decrease in skin induration but no improvement in pulmonary or cardiac involvement. Nephrotoxicity was frequent but usually transient and appeared mainly in patients receiving more than 3 to 4 mg/kg per day.²⁵

Because renal involvement in SSc is not uncommon, cyclosporine in the treatment of SSc should be used with great caution. Patients must be carefully monitored for the development of nephrotoxicity, hypertension, and malignant neoplasm, particularly lymphoma. Many drug interactions occur, and the patient should be questioned about concomitant medications.

Extracorporeal photopheresis has been used to treat SSc. The principle of this technique is to administer oral 6-methoxypsoralen, followed by extracorporeal activation of lymphocytes by UV-A. The blood carrying covalently cross-linked DNA-psoralen lymphocytes is then transferred into the patient to elicit a specific immune response that may block proliferation of certain T-lymphocyte clones. An initial multicenter trial was encouraging and showed significant improvement in skin induration but no effect on pulmonary function.²⁶ However, additional trials questioned the efficacy of extracorporeal photopheresis.²⁷ Furthermore, extracorporeal photopheresis for SSc is not approved by the Food and Drug Administration.

Another approach for immunosuppression in SSc was the use of antithymocyte globulin (3-5 mg/kg for 5 days). After 6 months' follow-up, no improvement in skin score or pulmonary function was noted compared with a placebo group.²⁸

Corticosteroids are not useful in improving or preventing the progression of skin involvement in SSc. However, they may be helpful in controlling pain caused by arthralgia or myalgia. Similar benefits can be achieved with nonsteroidal antiinflammatory agents.

Antifibrotic Agents. Fibrosis consists of massive deposition of newly synthesized connective tissue, mostly collagens, which is frequently responsible for the development of organ insufficiency. Fibrosis is a prominent feature

in SSc and can develop in other disorders, such as atherosclerosis, cirrhosis of the liver, and idiopathic or secondary pulmonary fibrosis. Pharmacodynamics of antifibrotic agents are geared (1) to reduce synthesis, excretion, or polymerization of collagen fibrils, (2) to enhance collagenase activity, and (3) to neutralize cytokines capable of stimulating collagen synthesis, such as transforming growth factor β , IL-4, and IL-6.

D-Penicillamine is a copper chelating agent that also blocks aldehyde groups involved in intermolecular and intramolecular cross-linkages of collagen. Early clinical trials showed that D-penicillamine was beneficial in the treatment of SSc, resulting in skin softening, slower progression of internal involvement, fewer renal crises, and increased survival time.²⁹ The usual dosage was 250 mg, 3 times daily. Several adverse effects may occur, including bone marrow depression, nephrotic syndrome, gastrointestinal distress, and skin reactions, such as pemphigus vulgaris. A recent multicenter, double-blind, randomized clinical trial was conducted in 134 patients with diffuse SSc of early (<18 months) duration. One group of patients received 750 to 1000 mg of D-penicillamine daily, while the other group was treated with 125 mg every other day. After 24 months' follow-up, there were no statistical differences between the groups in skin score (induration), incidence of renal crises, or survival time.³⁰ Furthermore, 80% of adverse effects occurred in the high-dosage group. This study raises serious questions about the therapeutic efficacy of D-penicillamine in SSc. However, if patients are treated with D-penicillamine, there is no advantage in using more than 125 mg every other day.

Colchicine has been suggested for the treatment of SSc, based on the rationale that it interferes with collagen synthesis by depolymerizing microtubules, reduces fibroblast proliferation, enhances collagenase activity, and has some antiinflammatory properties.³¹ An early uncontrolled study³² involved 19 patients with a follow-up of 19 to 57 months. This study noted improvement in skin elasticity, mouth opening, and finger motility, and a reduction in dysphagia. The mean dosage is 0.6 mg twice daily. The drug is well tolerated, and the main adverse effect is diarrhea. Blood cell counts and liver function tests should be performed periodically for patients receiving long-term therapy. It is unfortunate that double-blind placebo-controlled clinical trials are not available.

Interferon gamma has been shown *in vitro* to reduce collagen production and interfere with fibroblast proliferation. Interferon alfa also inhibits collagen production but to a lesser degree than interferon gamma.¹¹ Early investigations in the treatment of SSc with interferon gamma or interferon alfa showed a modest improvement in skin score.¹¹ Recent multicenter clinical trials were carried out with recombinant interferon gamma (50 μ g subcutaneously, 3 times weekly for 1 year)³³ or with recombinant interferon gamma (0.01 mg/m² per day for 18 weeks).³⁴ Both studies showed a modest improvement in skin score. Adverse effects were common, mostly consisting of a flulike syndrome. Another multicenter, randomized controlled clinical trial with interferon gamma concluded that this drug has mild beneficial effects in skin sclerosis and disease-associated symptoms.³⁵ A 1-year

double-blind placebo-controlled trial with interferon alfa showed no benefit in the treatment of scleroderma, and in some patients it was deleterious.³⁶

Relaxin is a pregnancy polypeptide, cytokine growth factor that *in vitro* decreases the synthesis and secretion of interstitial collagens, blocks transforming growth factor β overexpression of type I and II procollagens, increases overexpression of matrix metalloproteinases, and reduces the production of tissue inhibitor of metalloproteinases.³⁷ Early investigations using porcine-derived relaxin in the treatment of SSc were inconclusive. However, recently, a multicenter, randomized, double-blind clinical trial was carried out with human recombinant relaxin. Sixty-eight patients with moderate to severe diffuse SSc of less than 5 years' duration received 25 or 100 $\mu\text{g}/\text{kg}$ per day or a placebo, both administered by continuous subcutaneous infusion for 24 weeks. Patients receiving relaxin showed improvement in skin induration, oral aperture, hand extension motion, and pulmonary forced vital capacity. Adverse effects consisted of menometrorrhagia, reversible anemia, and irritation and focal infections at the site of the subcutaneous drug delivery.³⁸ However, additional follow-up observation did not corroborate the efficacy of relaxin, and the study was discontinued.

Kidney Involvement

Angiotensin-converting enzyme (ACE) inhibitors, including captopril and enalapril maleate, have been shown to be effective in controlling high blood pressure in SSc secondary to renal crisis. Furthermore, early treatment may prevent the onset of renal failure.³⁹ In addition, oral captopril in dosages of 12.5 to 50 mg daily may reduce pulmonary vascular resistance during pulmonary hypertension.⁴⁰

A retrospective study⁴¹ on renal transplantation in SSc gave encouraging results. The data were obtained from the United Network for Organ Sharing Scientific Renal Transplant Registry. Eighty-six patients with SSc from 1987 to 1997 received renal transplants. After a 5-year follow-up, 47% of the patients were alive, and the 5-year graft survival was similar to that seen with renal transplantation in patients with systemic lupus erythematosus. This study suggests that patients with severe renal insufficiency who do not improve after receiving angiotensin-converting enzyme inhibitors or kidney dialysis should be considered as candidates for renal transplantation.

Lung Involvement

Epoprostenol is an arachidonic acid, naturally occurring prostaglandin with vasodilator activity and inhibitory effect on platelet aggregation. Epoprostenol was used by continuous intravenous infusion in 111 patients with moderate to severe pulmonary hypertension secondary to SSc. After 2 weeks of treatment, there was improved exercise capacity and cardiopulmonary hemodynamics. There was also improvement in the severity of Raynaud phenomenon and healing of digital ulcers. Adverse effects included jaw pain, nausea, and anorexia. Local complications consisted of sepsis, cellulitis, hemorrhages, and

pneumothorax (4% incidence for each condition).⁴² Intravenous iloprost was also effective in the treatment of pulmonary hypertension.⁴³

Cyclophosphamide alone or in combination with low-dose prednisone was found effective in the treatment of severe interstitial lung disease in SSc.^{44,45} More recently, cyclophosphamide was used in a retrospective cohort study⁴⁶ involving 103 patients with SSc associated with lung inflammation (alveolitis) proved by bronchoalveolar lavage or by lung biopsy. The dosage consisted of 1 to 1.5 mg/kg per day orally to up to 2 mg/kg per day. In addition, they received intravenous cyclophosphamide, 800 to 1400 mg monthly, for 6 to 9 months. The patients treated with cyclophosphamide showed stabilization of forced vital capacity and carbon monoxide diffusing capacity. Improvement in survival was also demonstrated. Myelosuppression, bladder toxicity (hemorrhagic cystitis, bladder carcinoma), and carcinogenicity are complications of cyclophosphamide therapy. Baseline monitoring includes complete blood cell count with differential and platelets, serum chemistry profile, and urinalysis.

NEW THERAPIES—PRELIMINARY REPORTS

Minocycline

Eleven patients with early SSc were treated with minocycline (100 mg daily for 4 weeks; 200 mg daily for 11 months). Complete resolution of skin involvement was noted in 4 patients following 9 and 12 months of therapy. The mechanism of action of minocycline in SSc remains unknown.⁴⁷ This is an unexpected result and should be pursued further with controlled trials.

Psoralen-UV-A

A small uncontrolled study⁴⁸ treated 4 patients with SSc with psoralen-UV-A (total dosage, 3.5-9.6 J/cm²). All patients showed significant improvement in skin induration, hand closure, and flexion range of fingers and knee joints. Because UV-A was also shown to improve localized scleroderma (see the "Psoralen-UV-A and UV-A" subsection of the "Treatment of Localized Scleroderma" section), further controlled clinical trials are warranted.

Lung Transplantation

In a recent study,⁴⁹ 6 patients with limited cutaneous SSc and 1 with diffuse SSc underwent lung transplantation. Five patients were alive after a follow-up of 2 to 15 months. These results compare favorably with the overall survival reported for lung transplantation. Furthermore, 3 patients maintained satisfactory forced vital capacity (53%-71%). This study suggests that lung transplantation is a feasible procedure and may prolong survival of patients with both SSc and severe lung involvement.

Oral Etretinate

Thirty-two patients with chronic graft-vs-host disease who did not respond to previous therapies were treated with oral

etretinate in an open clinical trial. Among 27 patients who completed 3 months of therapy, 24 showed improvement in skin induration, flattening of cutaneous lesions, increased range of motion, and improvement in performance status.⁵⁰ Because sclerodermalike lesions in chronic graft-versus-host disease closely resemble SSc, a controlled clinical trial investigating the use of etretinate in the treatment of SSc may be desirable.

Autologous Stem Cell Transplantation

Autologous stem cell transplantation has been suggested for the treatment of autoimmune disease. Such a procedure was carried out in a 10-year-old patient with SSc of 6 years' duration who did not respond to various forms of therapy. This patient was conditioned with CD34⁺ selection, cyclophosphamide, and infusion of a CAMPATH-1G monoclonal antibody. After 2 years' follow-up, there was a 50% improvement in skin score, disappearance of exertional dyspnea and alveolitis, and improvement in growth rate.⁵¹ Another study⁵² included 8 patients with severe SSc treated with high-dose immunosuppressive therapy and radiation, followed by autologous stem cell transplantation. After a 1-year follow-up, 5 patients were alive and showed improvement in skin score and in results on a modified Health Assessment Questionnaire, while pulmonary function remained stable. Two patients died from interstitial pneumonitis, probably related to radiation toxicity.

Etanercept

Tumor necrosis factor α is a proinflammatory cytokine produced by activated T cells and macrophages. Tumor necrosis factor α stimulates the synthesis of other proinflammatory cytokines (IL-1, IL-8, IL-6, and granulocyte-macrophage colony-stimulating factor), promotes fibroblast proliferation, and enhances matrix metalloproteinase activity. Specific blocking agents against TNF- α have been developed, including monoclonal antibodies (infliximab)⁵³ and a fusion protein of soluble TNF receptor linked to human immunoglobulin (etanercept).⁵⁴ Etanercept has been shown to be effective in various forms of arthritis. In a preliminary pilot study,⁵⁵ 10 patients with diffuse SSc were treated with etanercept, 25 mg subcutaneously, twice weekly. After 6 months of therapy, there was improvement in skin score (4 patients) and healing in digital ulcers, while pulmonary function remained stable. The patients' sense of well-being improved, and tolerance was good.

Thalidomide

Because thalidomide may be effective in treating chronic graft-versus-host disease, it was also used in an open trial involving 10 patients with SSc. There was improvement in skin repigmentation, healing of digital ulcers, regrowth of hair, and a decrease in gastrointestinal reflux.⁵⁶ Histopathological examination of skin suggested a reduction in fibrosis. Immunologic studies revealed up-regulation of CD4⁺ ligand in T cells and increased expression of IL-2 and IL-8.

Table 2. Treatment of Localized Scleroderma

Morphea
Corticosteroids (topical and intralesional)
Topical calcipotriene
Linear scleroderma
Corticosteroids (intralesional for coup de sabre)
Psoralen-UV-A baths
UV-A alone (340-400 nm)
Oral calcitriol
Topical calcipotriene
Widespread morphea
Psoralen-UV-A baths
UV-A alone (340-400 nm)
Oral calcitriol
Methotrexate
Methotrexate plus corticosteroids

TREATMENT OF LOCALIZED SCLERODERMA

Localized scleroderma is a connective tissue disorder that affects the skin and subcutaneous tissue. The disease occurs in children and adults and, clinically, can be divided into morphea, localized or diffuse, deep morphea, and a linear form that usually affects arms and legs. Histopathological examination reveals an early inflammatory stage consisting mostly of mononuclear cell infiltrates and a late stage of severe fibrosis.⁵⁷ Although the cause of localized scleroderma remains unknown, an autoimmune mechanism is suspected because of its frequent association with antinuclear antibodies, rheumatoid factor, anti-single-stranded DNA, and antihistone antibodies.⁵⁸ Although spontaneous resolution is possible, the disease may cause severe functional (muscle atrophy) and cosmetic (severe scarring) disability, particularly in children during the growing stage. The treatment is difficult, although new therapeutic approaches appear encouraging (**Table 2**).

Topical Corticosteroids

Topical corticosteroids (fluorinated, medium potency, and hydrocortisone) may be of some help during the early inflammatory stage, although controlled clinical trials are not available. Intralesional triamcinolone, 5 mg/mL, once a month for 3 months, may improve or stop the progression of morphea and linear scleroderma affecting the scalp and forehead (coup de sabre).

Calcitriol and Calcipotriene

Calcitriol (1 α ,25-dihydroxyvitamin D₃) and calcipotriene are analogues of vitamin D and have been used for the treatment of psoriasis. Both compounds have a similar receptor binding and affinity, although calcipotriene is less potent and has minimal effects on calcium metabolism. Besides affecting keratinocyte differentiation and proliferation, calcitriol also inhibits fibroblast proliferation, collagen synthesis, and, possibly, T-lymphocyte activation.⁵⁹ Oral calcitriol, in dosages of 0.50 to 0.75 μ g daily, improved joint mobility and skin extensibility in

adult patients with generalized morphea, following 3 to 7 months of therapy.⁶⁰ In a more recent study,⁵⁹ 7 children with linear scleroderma were treated with this agent, and 5 showed an excellent response. Because oral calcitriol may have a dose-dependent effect on calcium metabolism, monitoring of serum and urine calcium, inorganic phosphate, creatinine, and urea is advised, particularly when treating children.⁵⁹

Topical calcipotriene ointment (0.005%) was used in 12 patients aged 12 to 38 years with biopsy-documented active morphea or linear scleroderma. After 3 months of therapy, all patients showed improvement, including decreases in erythema, telangiectases, and depigmentation.⁶¹ The ointment was well tolerated, and there were no adverse effects. Furthermore, there were no alterations in calcium metabolism as measured by serum levels of ionized calcium, parathyroid hormone, $1\alpha,25$ -dihydroxyvitamin D₃, and urinary calcium excretion. These results are encouraging but will have to be confirmed by a controlled clinical trial.

Psoralen-UV-A and UV-A

Psoralen-UV-A bath phototherapy has been shown to be effective in the treatment of widespread morphea and linear scleroderma.⁶² In this study, 17 patients were evaluated clinically and by ultrasound before and after treatment. The patients were immersed for 20 minutes in a warm water bath containing 1 mg/L of methoxsalen, followed by UV-A exposures, 0.2 to 0.5 J/cm², increased every third day to a maximum tolerable dosage of 1.2 to 3.5 J/cm². After about 15 treatments, clearance or marked improvement was noted in 13 of 17 patients. More recently, it has been reported that marked improvement was achieved in 18 (75%) of 24 patients by using low-dose UV-A alone in the range of 340 to 400 nm, 20 J/cm², to a cumulative dosage of 600 J/cm².⁶³ Two patients in this series with subcutaneous localized scleroderma failed to respond to UV-A therapy. Histopathological findings corroborated the clinical results. Although the mechanism of UV-A in localized scleroderma is unknown, it is noteworthy the UV-A may activate interstitial collagenases.⁶⁴

Methotrexate

It is known that methotrexate is an effective drug for the treatment of rheumatoid arthritis and juvenile rheumatoid arthritis.⁶⁵ Adult widespread morphea has been treated with oral methotrexate, 15 mg/wk, and the dosage was increased to 25 mg/wk in resistant cases. After 24 weeks of therapy, 6 of 9 patients showed significant improvement in skin induration. There were no serious adverse reactions.⁶⁶ Ten patients with active localized scleroderma (mean age, 6.8 years) of 4 years' mean duration were treated with methotrexate (0.3-0.6 mg/kg per week) combined with pulse intravenous methylprednisolone (30 mg/kg for 3 days monthly). Following 3 months of treatment, 9 patients showed significant benefit, and there were no serious adverse effects.⁶⁷ Although these data appear interesting, the use of methotrexate alone or in combination with corticosteroids will have to be restricted to children with severe active, disabling disease.

CONCLUSIONS

Although research continues to contribute to our understanding of the pathogenesis of SSc, its cause is still unknown. Present therapies are directed (1) to improve peripheral blood circulation with vasodilators and antiplatelet aggregation drugs, (2) to prevent the synthesis and release of harmful cytokines with immunosuppressants, and (3) to inhibit or reduce fibrosis with agents that interfere with collagen synthesis or enhance collagenase production. Although some progress has been achieved, the treatment of scleroderma remains a challenge to the clinician. Further elucidation of the events that precipitate the initial activation of the immune system in this disease is crucial for the emergence of new therapeutic approaches.

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Corresponding author: Raul Fleischmajer, MD, Department of Dermatology, Mount Sinai School of Medicine, 1425 Madison Ave, PO Box 1047, New York, NY 10029 (e-mail: rrfleischmajer@worldnet.att.net).

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