

# Scleroderma: A treatable disease

## JOSEPH H. KORN, MD

Director, Arthritis Center, Boston University School of Medicine,  
Chief, Rheumatology Section, Boston Medical Center

### ■ ABSTRACT

Many effective treatments for scleroderma have emerged in recent years, including bosentan, an endothelin receptor antagonist, and epoprostenol, a prostacyclin, both of which target vasoconstriction. Cyclophosphamide may soon be proven effective against interstitial lung disease.

**S**CLERODERMA has always been difficult to treat, and survival rates have traditionally been low. But it can be effectively treated in many cases now, thanks to a better understanding of its pathogenesis and the development of new therapies.

This article reviews our current understanding of scleroderma, strategies for preventing and treating major complications, and avenues for future research.

### ■ MORE THAN SKIN DEEP

Scleroderma means “hard skin,” named for the disease’s prominent feature: thickened, shiny skin. However, it is more properly termed “systemic sclerosis,” because involvement extends throughout the body. It is a complex disturbance of connective tissue, the vasculature, and the immune system.<sup>1</sup>

Multiple genes probably play a role in scleroderma’s development. Some genes may pre-

dispose patients to the vascular problems, some to the immune dysfunction, and some to the fibrotic aspects of the disease. The mixture of genes determines a patient’s overall susceptibility to scleroderma as well as the course of the disease.

### ■ SURVIVAL RATES IMPROVED

Not long ago, patients with scleroderma had a very poor prognosis: 30 years ago the 5-year survival rate was about 50% for the healthiest category of patients (those without lung, heart, or kidney manifestations). For patients who had either pulmonary or cardiac involvement, only about one third survived 5 years, and almost everyone who developed acute renal disease died within 6 months.

This bleak outlook has changed markedly. We can now expect patients to have a better quality of life than in the past, and for 80% to 90% to survive 5 years and 70% to 80% to survive 10 years. Renal, cardiac, and pulmonary involvement, however, remain the major complications that limit survival.

In the past, kidney disease was the leading cause of death, but early detection and treatment have brought this largely under control. Pulmonary disease is today’s major challenge: only 30% of patients with a diffusing capacity of lung for carbon monoxide (DLCO) of less than 60% survive 5 years.

### ■ TWO DISTINCT SUBTYPES

There are two distinct subtypes of scleroderma based on the amount and distribution of skin involvement:

- **Diffuse** cutaneous systemic sclerosis, in which skin disease covers the trunk and proximal extremities, and
- **Limited** cutaneous systemic sclerosis, in which skin involvement is primarily in the fin-

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**TABLE 1**

**Subtypes of systemic sclerosis**

**Diffuse cutaneous systemic sclerosis**

- Skin involvement in trunk, upper arms, and legs
- Raynaud phenomenon
- Gastrointestinal involvement
- Renal involvement (about 30%)
- Interstitial lung disease (30%–40%)
- Pulmonary hypertension—may be primary arterial hypertension (small percentage) or secondary to interstitial lung disease
- Myositis
- Cardiac involvement
- Scl 70 antibodies (30%–40%)—increased risk of interstitial lung disease
- RNA polymerases I, III—increased risk of renal disease, probably cardiac disease

**Limited cutaneous systemic sclerosis**

- (Formerly termed CREST syndrome: calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly [eg, the scleroderma is limited to the fingers and face], telangiectasia)
- Skin involvement of fingers, later hands, face, and feet
  - Raynaud phenomenon
  - Gastrointestinal involvement
  - Primary pulmonary hypertension (25%–50%)
  - Interstitial lung disease (10%)
  - Anticentromere antibodies (50%–60%)—indicates increased risk for pulmonary hypertension

**If a digital ulcer hasn't healed in 3–4 days, start an antibiotic**

gers in the early stages, then arises in the face and feet.

The general skin pattern largely predicts visceral complications (TABLE 1)

**■ RAYNAUD PHENOMENON IS MOST COMMON COMPLAINT**

The Raynaud phenomenon is the most common presenting problem of scleroderma, occurring in about 90% of patients. However, it is not pathognomonic of scleroderma, as it also occurs in 5% to 10% of the general population. Because scleroderma is so uncommon (occurring in only 200 to 300 people per million), most patients with the Raynaud phenomenon do not have scleroderma.

The phenomenon involves a triphasic response to cold or emotion. The fingers successively turn white (pallor, as described by Maurice Raynaud), blue (cyanosis), then red (hyperemia).

**Hallmark blood vessel changes**

The Raynaud phenomenon starts as a functional abnormality, but eventually structural

changes in the blood vessels occur. These changes are visible by angiography: the transition from normal vessel to disrupted areas to vessel blockage can be seen in a single artery. Such abnormalities occur in vessels ranging in size from digital arteries to precapillary arterioles.

Blood vessel changes are caused by the proliferation of intimal cells, endothelial cells, and smooth muscle cells, which lay down a matrix of connective tissue. There is also a characteristic perivascular band of fibrosis. This results in obliteration of the vascular lumen and decreased blood flow.

**Vascular injury to blame**

Exactly why these structural changes occur is unclear, but vascular injury is known to be involved. Scleroderma patients have signs of endothelial cell injury in their circulation, including elevated von Willebrand factor. Cold appears to be a trigger both clinically and in vitro: refrigerating endothelial cells causes release of factor VIII antigen and other molecules characteristic of cell injury.

When endothelial cells are injured, they

release vasoconstrictors such as thromboxane and endothelin, which counteract normal vasodilation. Endothelin is also a profibrotic stimulus, as is transforming growth factor beta (TGF beta). Not only do they cause vasoconstriction, but they also damage blood vessels. Then a mixture of thrombotic and inflammatory events, including action of TGF beta, oxidation products, and platelet aggregation, leads to vascular occlusion.

The loss of normal endothelial cells also results in reduced levels of the beneficial trophic factors that they produce, including prostacyclin and nitric oxide, which contribute to vasodilation and intimal integrity.

### Treat with warmth and medications

The best treatment for Raynaud phenomenon when it is still a functional problem is by having the patient stay warm to avoid vasoconstriction. Not only the hands, but the entire body should stay warm, because core temperature determines peripheral vasoconstriction.

A variety of medications are also effective, including calcium channel blockers, alpha-adrenergic inhibitors, nitroglycerin, and angiotensin-converting enzyme (ACE) inhibitors. If one medication doesn't work, physicians should try another: for unknown reasons, some patients respond only to a single category of drugs or even only to an individual medication within a category. The severity of the Raynaud phenomenon, its impact on patient function, and the presence of tissue injury such as infarct or ulcer determine when pharmacologic approaches are used.

### Digital ulcers are not trivial

It is important to treat Raynaud phenomenon, both for patient comfort and to prevent the resultant dryness and cracking of the skin. Dry, cracked skin, combined with the inadequate vascular supply characteristic of scleroderma, provides an environment highly conducive to developing digital ulcers.

Digital ulcers form around the nail and at the fingertips. Although they may seem to be a relatively minor problem, digital ulcers are a major source of disability: they cause severe pain, preventing many activities of daily living. If a digital ulcer hasn't healed in 3 or 4 days, the patient should be treated with

antibiotics such as cephalexin, dicloxacillin, or ciprofloxacin. Established ulcers may take months to heal, and patients may require several-week courses of rotating antibiotics.

### Treat severe ulcers aggressively

Superinfections can develop and spread to the bone, sometimes requiring amputation of the digit. For advanced infections, intra-arterial vasodilators are indicated. Prostenoids are most effective, such as the intravenous prostacyclin, epoprostenol (Flolan). Some patients do well on sildenafil (Viagra), 75 mg every 6 hours, over 3 to 14 days, depending on response.

The new medication bosentan (Tracleer) is an endothelin receptor antagonist that targets the potent vasoconstricting effects of endothelin. Although it is not the best treatment for existing ulcers, in one preliminary study it appeared to prevent multiple ones from occurring.

For patients who get recurrent ulcers or infections despite treatment, a sympathetic nerve block or digital or cervical sympathectomy may be indicated.

## ■ VASCULAR CHANGES OCCUR SYSTEMICALLY

Raynaud phenomenon is the most obvious vascular manifestation of scleroderma, but blood vessel disruption is also the underlying basis for the myriad other problems of the disorder. The vascular pathology seen by angiography in the digits is, in fact, widespread throughout the body. Even organs that are not clinically involved, like the pancreas, have evident vascular disease.

## ■ RENAL INVOLVEMENT COMES ON ABRUPTLY

Renal disease was once the chief killer of scleroderma patients: it can come on suddenly and lead to permanent kidney failure within days after symptom onset. Its vascular origin is apparent by the large infarcts visible by renal angiography. There is loss of cortical vessels, reduced blood flow, and pruning of the normal arterial tree.

Acute severe hypertension is the presenting sign in 9 out of 10 patients during a scleroderma crisis.

**Acute severe hypertension is the presenting sign in 90% of scleroderma renal crises**

roderma renal crisis. The remaining 10% develop an identical renal pathology, with functional loss but without clinical hypertension. All patients develop proteinuria, and most have microangiopathic hemolytic anemia due to trauma in the blood vessels.<sup>1,2</sup>

**Home blood pressure and urine checks save lives**

Early detection and prevention of a renal crisis is key. All patients with diffuse scleroderma should screen themselves two or three times a week with a home blood pressure device. They should also check their urine for protein using a dipstick once a week; this ensures that the 10% of patients with renal failure who never develop hypertension are also caught in time.

**Treat crises aggressively with ACE inhibitors**

Increasing blood pressure or proteinuria, even in the absence of rising creatinine, should be a signal to start ACE inhibitor therapy. Even mild but persistent increases in blood pressure, eg, from 120/60 to 140/85 mm Hg, should be treated. Patients who develop renal crises, severe blood pressure elevations with or without rising creatinine, or proteinuria should be aggressively treated in the hospital with increasing doses of ACE inhibitors to rapidly bring the diastolic blood pressure to under 80 mm Hg. Angiotensin II receptor antagonists are also useful but may be less effective.

Sometimes the creatinine level rises after patients are started on ACE inhibitors, and the temptation is to change medications. However, very rarely is the ACE inhibitor at fault in such cases. The creatinine level may continue to rise for several days but should return to normal.

Despite treatment, some patients progress to needing dialysis, particularly if treatment is delayed. Of those requiring dialysis, 30% to 40% eventually recover renal function if blood pressure is controlled.

ACE inhibitors do more than control blood pressure; they also affect endothelin and many growth factors. Because of this, some researchers have treated patients prophylactically with normal doses of ACE inhibitors to try to avert a renal crisis. This approach has not proven successful, however, and is not recommended.

**LUNG INVOLVEMENT IS THE BIGGEST CHALLENGE**

Pulmonary complications are responsible for the greatest number of deaths from scleroderma today. The two main problems are interstitial fibrosis and pulmonary hypertension. Other problems sometimes develop secondary to these conditions:

- Bronchiectasis—a result of pulling on the bronchi by fibrosis
- Aspiration pneumonia
- Pleural disease with pleural effusion (associated with a poor prognosis).

A small percentage of patients also develop chest wall restriction and decreased function, probably from fibrosis of the chest wall.

**Interstitial fibrosis associated with diffuse-type scleroderma**

Interstitial fibrosis is the leading cause of scleroderma-related deaths. It develops in 30% to 40% of patients with the diffuse type of scleroderma and tends to occur in the first 2 to 4 years after onset of scleroderma symptoms.

The extent of pulmonary fibrosis determines a patient's prognosis, and thus detecting it early is important to prevent the disease from progressing. Timely detection is not easy, however, because early signs are often subtle. A typical patient with interstitial fibrosis might be extremely short of breath, but have only a few crackles at the bases detectable by lung examination and a completely normal chest radiograph.

High-resolution computed tomography (CT) is a better diagnostic tool; it shows "ground-glass" changes, indicative of extensive alveolitis. Scans should be performed with the patient prone; otherwise, it is difficult to distinguish fibrosis from blood pooling. We also use bronchoalveolar lavage to confirm inflammatory disease.

Interstitial fibrosis starts as inflammatory alveolitis, with mononuclear cells infiltrating the alveoli and destroying their structure. Lung biopsy reveals both inflammation and areas of fibrosis.

Pulmonary function tests are useful for screening asymptomatic patients.

**Scleroderma patients should take their blood pressure at home 2 or 3 times a week**



### **Cyclophosphamide may be future treatment**

Studies are now underway with the National Institutes of Health to determine the effectiveness of cyclophosphamide (Cytoxan, Neosar) for interstitial lung disease. Early results are encouraging. Not only does alveolitis largely clear up, but pulmonary function improves, as does mental function. Cyclophosphamide probably does not restore normal alveolar architecture, but by reducing fibrosis, it allows better lung expansion in healthy tissue. Skin manifestations of scleroderma also improve.

An earlier retrospective study<sup>3</sup> found that patients with interstitial fibrosis who had received cyclophosphamide had a small increase in their functional vital capacity and essentially no change in their DLCO. Patients who had not received the drug had an 8% to 10% decrease in both these measures.

We use cyclophosphamide as a monthly intravenous infusion, 600 to 800 mg/m<sup>2</sup>. We also give prednisone 30 mg/day, tapering over a few months.

### **Pulmonary hypertension associated with limited scleroderma**

Pulmonary hypertension is a serious complication that occurs in 25% to 50% of people with the limited type of scleroderma. Only 40% of those patients subsequently survive 2 years if untreated. It usually occurs late in the disease, often 10 to 15 years after symptom onset. A rapidly fatal form occurs in a small percentage of patients and tends to appear earlier.

Early detection and treatment may improve survival rates, so it is worthwhile to regularly screen asymptomatic patients with limited scleroderma by echocardiography.

Pulmonary hypertension typically comes on insidiously. It should be suspected in patients with late scleroderma, such as those who have prominent telangiectasia and the CREST syndrome (calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, telangiectasia). Patients with pulmonary hypertension may be short of breath but have a normal lung examination. Other signs are:

- Increased second pulmonic heart sound (P<sub>2</sub>)
- A right ventricular heave

- Normal pulmonary function tests
- Markedly decreased DLCO, or DLCO that is disproportionately decreased compared with vital capacity.

### **Characteristic vascular origins**

Pulmonary hypertension seems to have the same vascular origins as scleroderma kidney disease and finger ulcers. Angiography reveals the same kind of intimal occlusion and proliferation that are seen in peripheral vessels. The interior elastic lamina stays preserved, so the problem is not vasculitis. Some hypertrophy of smooth muscle occurs, and a perivascular cup of connective tissue develops.

The role of genetic factors is becoming clearer. A form of primary pulmonary hypertension is due to a mutation in the bone morphogenic protein receptor type 2. A recent finding also links other forms of pulmonary hypertension with defects in the signaling pathway involving angiotensin-1, bone morphogenic protein receptor type 2, and other factors.<sup>4</sup>

### **Treating pulmonary hypertension**

Calcium channel blockers are the first line of treatment for patients without scleroderma who develop idiopathic pulmonary hypertension. For patients with scleroderma, calcium channel blockers may be helpful in early pulmonary hypertension but do not seem to prevent disease progression.

Anticoagulation also improves survival for patients without scleroderma. It is also used for patients with scleroderma, although its effectiveness for this group has not been confirmed.

Aerosolized prostacyclin analogs, subcutaneous prostacyclin analogs, and treprostinil (Remodulin) have become available this year to treat pulmonary hypertension. Inhaled nitric oxide, another endothelium-derived vasodilator, is used in some centers, although it has some inconveniences.

### **Epoprostenol improves survival and quality of life**

Epoprostenol offers the most effective therapy for pulmonary hypertension in scleroderma patients. The drawbacks are that it is difficult to obtain, and with a half-life of only minutes,

**Interstitial fibrosis is the leading cause of scleroderma death**



it must be given continuously by central infusion.

My colleagues and I treated 14 patients with epoprostenol, four of whom had New York Heart Association class IV disease (symptomatic at rest). Three of those four improved to a higher class, one to the level of class II (symptomatic with ordinary activity). The mean decrease in pulmonary vascular resistance was about 40%, and about two thirds of patients had a more than 25% improvement. Cardiac output increased by about 40%; in some patients it doubled. One patient would have died within months without epoprostenol, and she is still alive 3 years later, albeit in poor health.

A larger randomized controlled study<sup>5</sup> of 111 patients found that 38% of patients treated with epoprostenol improved functionally as measured by the New York Heart Association classification, while almost all the control patients got worse. As an added benefit, treated patients also had a reduction in Raynaud syndrome, with fewer digital ulcers.

### **Other prostacyclins show promise**

A European trial<sup>6</sup> studied inhaled iloprost (Ilomedin), a synthetic prostacyclin. Patients improved functionally, although not as dramatically as with epoprostenol. Pulmonary vascular resistance improved 20% over baseline, which was actually a 30% improvement over placebo because the patients without medication worsened. Cardiac output improved by 15%.

Treprostinil, a subcutaneously active prostacyclin, recently became available. It causes functional and hemodynamic improvements comparable to epoprostenol, but severe injection-associated local reactions limit its use.

### **Endothelin: An important vasoconstrictor**

Endothelin is a 21-amino acid peptide and the most potent vasoconstrictor known. It binds to receptors on endothelial and smooth muscle cells, causing smooth muscle contraction. Scleroderma patients have increased blood levels of endothelin, as well as increased endothelin in pulmonary macrophages.

Endothelin also apparently plays a role in fibrosis, stimulating fibroblast proliferation in collagen synthesis. In addition, animals that are transgenic for endothelin I and produce

excess endothelin develop pulmonary fibrosis.

### **Counteracting vasoconstriction with bosentan**

Endothelin receptor antagonists block lung antigen-induced inflammation and have proven effective against pulmonary hypertension in animal models. An important new medication in this class is bosentan.

An early placebo-controlled study<sup>7</sup> looked at patients with pulmonary hypertension treated with bosentan. Those on placebo had increased pulmonary artery pressure, while patients on bosentan had unchanged pulmonary artery pressure, as well as improved pulmonary vascular resistance and an improved cardiac index. Patients treated with bosentan improved dramatically in their performance on the 6-minute walk test, while the placebo group deteriorated.

A more recent larger study,<sup>8</sup> known as BREATHE-1, examined the effect of bosentan on function and hemodynamics in patients with pulmonary hypertension from a variety of causes. Bosentan was found to be effective for both scleroderma and idiopathic pulmonary hypertension: patients stabilized on medication and got worse with placebo. Patients on bosentan were able to walk about 40 meters farther in 6 minutes than those on placebo.

### **■ GASTROINTESTINAL PROBLEMS CAN BE EXTENSIVE**

Gastrointestinal manifestations of scleroderma cause few deaths but do contribute to significant morbidity. Again, the underlying problem is vascular. The blood supply to the myenteric plexus is compromised first, resulting in the loss of normal, rhythmic peristalsis. This loss of normal motility leads to bacterial overgrowth, deconjugation of bile acids, and malabsorption. Muscular atrophy and fibrosis eventually set in. Patients develop a wide range of symptoms (TABLE 2), and a small number die from anorexia and weight loss.

### **Manage reflux with proton-pump inhibitors**

By high-resolution CT the "scleroderma esophagus" looks large and dilated throughout its entire length. Ulcers and strictures may develop from the continual reflux, but this has

**Epoprostenol is the most effective therapy for pulmonary hypertension in scleroderma**

**TABLE 2**

**Gastrointestinal manifestations of scleroderma**

- Reflux
- Difficulty swallowing
- Early satiety
- Bloating
- Bleeding
- Diarrhea
- Malabsorption
- Weight loss
- Constipation
- Bowel pseudo-obstruction
- Colonic perforation

**Lifestyle modifications are key to managing reflux disease**

become less common thanks to effective medications. Nowadays we see changes characteristic of Barrett’s esophagus but very rarely of esophageal cancer.

Key to managing reflux disease is lifestyle modification: elevating the head of the bed; eliminating triggers like tobacco, alcohol, peppermint, and high-fat foods; and waiting several hours after eating to lie down.

I also prescribe proton-pump inhibitors, which are more effective than H<sub>2</sub> blockers in relieving symptoms and promoting healing. Some patients need very high doses, such as omeprazole 160 mg or equivalent doses of other proton-pump inhibitors. Although the long-term use of proton pump inhibitors is expensive and sometimes difficult to negotiate with health insurers, it is invaluable in helping to prevent strictures.

**Promotility agents are useful early, then erythromycin**

Promotility agents, such as metoclopramide (Reglan), can also be helpful, especially early in the disease while neural innervation is still intact. Cisapride (Propulsid) is also effective but no longer generally available because of the risk of arrhythmias.

For patients who no longer have a neural supply, erythromycin 250 mg three times a day is useful because it directly stimulates smooth muscle. It loses effectiveness late in the disease, however, when the smooth muscle is completely replaced by fibrosis.

**Treat chronic diarrhea with antibiotics**

Tetracycline is an inexpensive and effective treatment for patients with diarrhea, weight loss, and bloating. Once treated, patients who have suffered from diarrhea for many months often quickly regain weight. Because the clinical picture is straightforward, there is no need to test for bacterial overgrowth.

**Treat gastric ectasia with laser ablation**

Another serious gastrointestinal complication is gastric ectasia, the appearance of which is similar to the telangiectasia typically seen on the lips of scleroderma patients. It gives the stomach a watermelon appearance as seen by endoscopy.

Gastric ectasia causes recurrent bleeding, leading some patients to require infusion with several units of blood each week. Fortunately, it can now be effectively treated with argon laser ablation, and as a result, few people die of this complication anymore.

**■ CARDIAC DISEASE IS DIFFICULT TO MANAGE**

Myocardial fibrosis with arrhythmias, sometimes referred to as “scleroderma heart,” is caused by vascular occlusion, local ischemia, and microinfarcts. Coronary arteries are spared; only the microvasculature in the heart is affected. ACE inhibitors may be effective, but no data are available to confirm this. Treatment of established disease remains a difficult challenge.

**■ SKIN TREATMENTS ON HORIZON**

No good treatment for scleroderma’s skin changes has yet been found, despite trials with more than a dozen agents. Once fibrosis occurs, with the resultant loss of architecture, it is irreversible. Loss of hair follicles, sweat glands, and nerves accompanies the changes. Hair may regrow, but the skin does not return to normal.

More than a dozen agents have been tried to treat sclerodermal skin disease: Potaba, colchicine, D-penicillamine, methotrexate, 5-fluorouracil, chlorambucil, interferons alpha and gamma, cyclophosphamide, bone marrow ablation with stem cell reconstitution,



antithymocyte globulin, cyclofenil, photopheresis, and relaxin. Trials of anti-TGF beta, oral collagen (as a toleragen), and interferon beta are in progress. Trials of other promising biologic agents, including those directed at adhesion molecules, immune cells, and cytokines, are planned. New medications should be available within a few years.

### ■ TARGETING FIBROSIS

Fibrosis is a complex process that suggests many potential targets for therapy. It occurs in the lungs, around joints, in the gastrointestinal tract, and around blood vessels. It may be immune-driven, involving immune cytokines, injury-repair mechanisms, hypoxia, or a metabolic defect.

According to our current understanding, scleroderma is a vascular disease early on. At first it is functional, with vasoconstriction causing decreased flow. Later on it becomes a structural problem, with proliferation of endothelial cells, smooth muscle cells, and cytokines, which turn on fibroblasts to make matrix proteins. The fibroblasts somehow become autonomous, no longer depending on immune cells as a trigger: fibroblasts removed from the body continue to overproduce matrix proteins. The matrix proteins, in turn, lead to cutaneous and visceral fibrosis.

This model offers many targets for therapy. We can try to intervene at the level of the immune cells or of the blood vessels. We can potentially disrupt growth factors, intercellular signaling, gene transcription, and collagen and matrix synthesis pathways.

Early attempts to use interferon gamma to reduce collagen production were unsuccessful in improving scleroderma. Although interferon gamma blocks collagen synthesis, it unfortunately also turns on macrophage function and promotes the immune arm of scleroderma.

Another tack was to destroy the immune system by bone marrow ablation and stem cell reconstitution in the hope that the patient would regenerate a normal immune system. Some scleroderma patients improved with this risky procedure, but the disease recurred within a year in many patients.

### ■ OTHER RESEARCH DIRECTIONS

Some researchers have targeted a specific cytokine—TGF beta—which stimulates matrix genes and causes vascular damage. Mice treated with TGF beta get kidney disease similar to that seen in scleroderma patients. In addition, normal fibroblasts treated with TGF beta resemble the abnormal fibroblasts seen in scleroderma. In the future, TGF beta inhibitors may prove to be an effective weapon against the disease.<sup>9</sup>

It may also be worthwhile to examine gene expression profiles of patients with scleroderma to find the genes that cause the disease for clues for future interventions.

Other potential agents that are either currently undergoing or about to undergo clinical trials against scleroderma include another growth factor, connective tissue growth factor; endothelin receptor antagonists; signaling pathway inhibitors; PD5 inhibitors; better sildenafil-like agents; thalidomide (Thalomid); and halofuginone, a collagen type-1 inhibitor.



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ADDRESS: Joseph H. Korn, MD, Chief, Rheumatology Section, Boston University Medical Center, 80 East Concord Street, Boston, MA 02118.