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*M.E. Csuka, MD*

New Therapies for Pulmonary Arterial Hypertension Associated with Systemic Sclerosis

*Robert W. Simms, MD*
*Ariane L. Herrick, MD*
Editor’s Memo

Highlighting New Leadership for the SCTC, Its Journal, and New Clinical Trials for Systemic Sclerosis

The Scleroderma Clinical Trials Consortium (SCTC) has a new president, James Seibold, MD. That means it is time to bring in a new editor of Scleroderma Care and Research (SC&R). The SCTC has been very fortunate to have had Jim’s vigorous leadership during the development of SC&R. Jim helped found the journal and made it a standard-bearer for the organization. Change, however, is inevitable. As such, the Executive Committee has asked me to take on the role of editor, a role I hope I can take to the next level.

The Executive Committee has, in addition, proposed several changes to the format of SC&R. With this issue, therefore, we are instituting one of the changes recommended: brief evaluations of newer treatments for systemic sclerosis. In this issue Ariane L. Herrick, MD, and Robert W. Simms, MD, present brief evaluations of two of the newer drugs for systemic sclerosis-related pulmonary artery hypertension: treprostinil (Remodulin®) and inhaled iloprost (Ventavist™). A bit of perspective from the editor: Although the market for pulmonary hypertension is smaller than the systemic sclerosis market, there are already five therapies that are approved by the Food and Drug Administration (FDA) and/or the European Medicines Agency (EMEA) for pulmonary arterial hypertension, including the pulmonary arterial hypertension of the scleroderma-spectrum diseases. There are in addition several therapies still under investigation and at least one drug (sitaxsentan) is under review at the FDA for approval. This demonstrates that if we, as investigators, show that we can conduct trials that successfully demonstrate efficacy of at least one therapy, companies will become interested in our “little” orphan disease.

In this issue also is a review by M.E. Csuka, MD, of high-dose immunotherapy (HDIT) with autologous stem cell transplantation (SCT) as it is being conducted in patients with systemic sclerosis. Preliminary results from Europe and the United States have been cautiously optimistic enough to encourage the investigators to develop and conduct funded, randomized, controlled trials (RCTs). In Europe the RCT for HDIT with SCT is named ASTIS (Autologous Stem cell Transplantation International Scleroderma), and it already is well under way. In the United States the trial is named SCOT (Scleroderma Cyclophosphamide Or Transplant) and it is just now getting started. In the preliminary phases, as in the current phase, the investigators on both sides of the ocean have worked hard to interact in a mutually collaborative and supportive way. With the two current trials (RCTs), the investigators are conducting nearly identical trials, with only a few differences in design and conduct. Thus the entry criteria, the outcome variables, the “mobilization” and “conditioning” regimes (with one or two exceptions), the purification and purging of the stem cells (with one or two exceptions), the timing of visits, the length of trials, etc, are nearly uniform. When they are analyzed, it should be relatively easy to compare and contrast the results from the two trials. If the treatments are effective, efficacy will be confirmed. If one method of mobilizing or conditioning works better than the other, it should be easy to discern which is which. Because these two RCTs embody the spirit of the SCTC in their design, conduct, and analysis, the journal is happy to highlight the trials and bring them to everyone’s attention.

Philip J. Clements, MD
Editor-in-Chief
Systemic sclerosis is an autoimmune disease characterized by progressive vascular damage (Raynaud’s phenomenon and digital ulcers, hypertensive renal failure, cardiomyopathy, pulmonary hypertension) and organ fibrosis (skin thickening, pulmonary fibrosis, gastrointestinal dysmotility, myocardial fibrosis). Early in the disease process, signs of inflammation are frequently present (fatigue, edema, tendon friction rubs, arthritis, myositis, pericarditis). Two subtypes are defined by extent of skin involvement: limited cutaneous systemic sclerosis with skin thickening confined to the distal extremities and face often proceeded by years of Raynaud’s phenomenon and diffuse cutaneous systemic sclerosis with skin thickening involving the entire extremity and torso frequently associated with visceral organ involvements.1

The most severe cases are identified by rapid advancement of skin thickening and early internal organ damage during the first 5 years of onset. The 5- and 10-year survival rates for those with rapid onset of signs and symptoms is estimated to be 50% and 38%.2,3 Although pulmonary involvement may be documented in the majority of patients with systemic sclerosis (with either limited or diffuse skin thickening), progression to end stage lung disease is variable. In patients with early symptomatic pulmonary or cardiac involvement the 5-year survival is decreased to 33%.4

Until recently, systemic sclerosis was considered an untreatable disease.5 Pharmacotherapy focused on management of symptoms related to specific organ involvement, eg, calcium channel blockers and vasodilator therapy for Raynaud’s and proton pump inhibitors for esophageal reflux secondary to esophageal dysmotility. Angiotensin-converting enzyme (ACE) inhibitors were the first class of drug to demonstrate an improvement in mortality. Acute scleroderma hypertensive renal disease was nearly 100% fatal within 6 months before the development and use of ACE inhibitors to treat this complication.5,6 Pulmonary artery hypertension (PAH) is a rare but often fatal complication of systemic sclerosis, more commonly associated with the limited cutaneous subset. PAH is no longer considered an untreatable complication of systemic sclerosis as studies with prostaglandins (intravenous, subcutaneous, or inhaled), antiendothelial receptor blockers, and phosphodiesterase inhibitors have demonstrated improved quality of life, function, and survival in systemic sclerosis patients with PAH.7-13

Despite these successes most pharmacotherapeutic intervention to treat the disease remains empiric. Efforts to document efficacy have been disappointing when therapies are tested in controlled trials.14-28 Many of these trials were doomed to failure given the heterogeneous nature of disease expression and too often patients had late disease with established fibrosis that would not necessarily be amenable to the treatments tried. A multicenter Phase II clinical trial comparing oral Type I bovine collagen as a toleragen to placebo evaluating effect on the modified Rodnan skin score in diffuse cutaneous systemic sclerosis has completed enrollment though results have not yet been reported. Based on the up regulation of endothelin binding sites seen in systemic sclerosis lung fibrosis, the antiendothelin receptor bosentan is under evaluation in a double-blind, randomized, placebo-controlled, multicenter study. Information on these two novel therapies for treatment of systemic sclerosis manifestations (skin and lung) can be found on the Scleroderma Clinical Trials Consortium Web site: http://www.sctc-online.org.

Pathophysiology of Systemic Sclerosis

Lacking a specific etiology there is no unifying hypothesis to explain the varied clinical manifestations of systemic sclerosis. The development of systemic sclerosis is believed to be due to an interaction of an as yet unidentified environmental exposure(s) (infectious and/or noninfectious) in a genetically susceptible individual. Endothelial and immune activation cause endothelial damage, fibroblast proliferation and collagen synthesis resulting in dysfunction of various end organs. Abnormalities of three cell types: fibroblasts, endothelial cells, and cells of the immune system, especially T and B lymphocytes, have been identified as primal to the development of the clinical and pathologic expression of the disease. Further, the availability of anticyclic citrullinated peptide antibodies/resources and antidiagonal cDNA-derived sequences (CD-9) has suggested a genetic predisposition to the development of systemic sclerosis.30-33

High-Dose Immunosuppressive Therapy and Autologous Hematopoietic Stem Cell Transplantation for Treatment of Severe Systemic Sclerosis

M. E. Csuka, MD, Associate Professor of Medicine, Medical College of Wisconsin, Milwaukee, Wisconsin

Dr Csuka is a member of the Speakers Bureaus of Actelion, Merck, and Proctor and Gamble. The SCOT study is a research effort that has been funded in whole or in part with Federal funds from the National Institute of Allergy and Infectious Disease, National Institutes of Health, under Contracts Nos. N01-AI-25481 and N01-AI-05419.
of clinical disease (Figure 1).30 In diffuse cutaneous systemic sclerosis, organ fibrosis is the most characteristic clinical finding. However, fibrosis is considered a late manifestation and occurs as a consequence of immune activity and vascular injury. An initial immune-mediated process is hypothesized to trigger endothelial injury and fibroblast activation.

Vascular dysfunction occurs early and is characterized by vasomotor instability and impaired vasodilatation. As the disease progresses, proliferative intimal arterial lesions and eventual obliteration of vessels lead to chronic ischemia. Perivascular activated T cells are present in small blood vessels and secrete transforming growth factor-beta (TGF-beta), which injures endothelial cells inducing expression of MHC class I and II antigens and adhesion ligand intercellular adhesion molecule-1 (ICAM-1). TGF-beta also upregulates connective tissue growth factor, resulting in increased extracellular matrix components and platelet-derived growth factor. Endothelial cell injury may also result from cytotoxic factors present in serum,31,32 or by serum IgG antibodies causing antibody-dependent cell-mediated cytotoxicity.33,34

The evidence for autoimmune activity is supported by several observations, including the presence of systemic sclerosis findings in overlap syndromes characterized more clearly as autoimmune, such as systemic lupus erythematosus and the familial associations with other autoimmune connective tissue diseases. Additional recognition of an autoimmune process is supported by similarities of human graft-versus-host disease and the occurrence of scleroderma-like changes in experimental murine graft-versus-host disease.35 The presence of circulating autoantibodies to a variety of nuclear antigens is an obvious laboratory manifestation of autoimmunity. Although these antibodies are useful diagnostically, and can help predict the probable pattern of organ involvement, severity, and disease progression, they do not appear to be involved directly in pathogenesis.36,37

The presence of T cells in affected skin in early disease and the severity and progression of skin sclerosis correlates with the extent of lymphocytic infiltration. In the skin, the majority of the mononuclear cells are CD4+ T cells, express the activation marker MHC class II antigen DR, and appear to be oligoclonal, consistent with an antigen-driven response. These T cells produce cytokines that can stimulate fibroblast collagen production.

In the peripheral blood the proportions and absolute numbers of C4+CD45RA+ (suppressor-inducer T cells) and CD8+CD81b (suppressor T cells) are decreased consistent with impaired balance between immunoregulatory T cell populations. Peripheral blood T cells in systemic sclerosis express interleukin-2 receptor (IL-2R) on their membranes and serum from systemic sclerosis patients has higher levels of soluble IL-2R consistent with activation.38,39 Activated T cells express adhesion ligands that promote egress from the blood vessel to the tissues. The integrin lymphocyte function-associated antigen-1 (LFA-1) is one of the cell surface receptors with increased expression on T cells that promotes adhesion to fibroblasts by interaction with its counter receptor intercellular adhesion molecules ICAM-1, ICAM-2, and ICAM-3. T cells are also important in the pathogenesis of systemic sclerosis interstitial lung disease.40 Histologic examinations of lung tissue and bronchoalveolar lavage fluid confirm high levels of CD8+ and gamma/delta T cells. These cells are oligoclonal and have increased expression of type 2 (Th2) cytokines and IL-4 and IL-5 messenger RNA compared to normal controls. The production of these Th2 cytokines by CD8 cells in alveolar fluid predicts a greater decline in lung function.41

**Immunosuppressive Therapy as Treatment for Systemic Sclerosis**

The increasing recognition of systemic sclerosis as an autoimmune disorder (Table 1) is the basis for immunosuppressive therapy.35 Lung fibrosis without cardiac or renal disease is now identified as the most common cause of death in systemic sclerosis patients. Patients with diffuse cutaneous systemic sclerosis and symptomatic pulmonary involvement without cardiac or renal disease have a median survival of 78 months.42 The presence of inflammatory cells found in bronchoalveolar lavage fluid and from open lung biopsies has lent credence that treatment of “active” alveolitis may be amenable to immunosuppressive thera-

Table 1. Evidence for Autoimmune Activity in Systemic Sclerosis.

| Antibody-dependent cellular cytotoxicity against fibroblasts and endothelium |
| Activated endothelium in early disease moderates intracellular adhesion molecules and promotes immunological chemotaxis |
| Activated T cells in lung parenchyma and alveolar fluid |
| Activated T cells in skin in early disease |
| Activated fibroblasts |
| High prevalence of disease-specific antinuclear antibodies |
| Genetic array data |

(continued on page 8)
Scleroderma
SUSPECT
Pulmonary Arterial Hypertension (PAH)
WHO Class III or IV

- From <10%\(^1\) to 50%\(^2\) of scleroderma patients develop PAH
- Dyspnea in scleroderma can indicate PAH\(^3\)
- WHO recommends annual screening with echocardiogram\(^4\)
- Only a right heart catheterization can confirm PAH diagnosis and assess precise hemodynamics\(^5\)
TREAT with Tracleer

Reduces risk of clinical worsening

Tracleer significantly reduced risk of clinical worsening by 71% relative to control at week 28.¹

- Clinical worsening defined as combined end-point of death, hospitalization or discontinuation due to worsening PAH, or initiation of epoprostenol therapy

A statistically significant difference was apparent as early as week 16.⁶

Treatment effect was notable because both the Tracleer groups and the control groups could have received background therapy, which excluded IV epoprostenol but may have included:

- Vasodilators
- Calcium channel blockers
- ACE inhibitors
- Digoxin
- Diuretics
- Anticoagulants

In Pulmonary Arterial Hypertension WHO Class III or IV

TREAT with Tracleer

The oral endothelin receptor antagonist backed by long-term data

- Improves exercise ability
- Improves hemodynamics (CI, PAP, PVR, RAP)

In the 2 Tracleer pivotal trials and their open-label extensions (n=235), 93% and 84% of patients were still alive at 1 year and 2 years, respectively, after the start of treatment with Tracleer.⁷

- Without a control group, these data must be interpreted cautiously and cannot be interpreted as an improvement in survival⁷

These estimates may be influenced by the presence of epoprostenol treatment, which was administered to 43 of the 235 patients⁷

Patients in the Tracleer trials may have also been receiving vasodilators (calcium channel blockers or ACE inhibitors), digoxin, anticoagulants, and/or diuretics⁷

Liver and pregnancy warnings

- Requires attention to two significant concerns
  — Potential for serious liver injury: Liver monitoring of all patients is essential prior to initiation of treatment and monthly thereafter
  — High potential for major birth defects: Pregnancy must be excluded and prevented by two forms of birth control; monthly pregnancy tests should be obtained
- Contraindicated for use with cyclosporine A and glyburide

For additional information about Tracleer or to report any adverse events, please call T.A.P. at 1-866-228-3546.

To learn more: Call 1-866-228-3546 or visit www.TRACLEER.com

STAY with Tracleer

Long-term data for patients treated with Tracleer

In the 2 Tracleer pivotal trials and their open-label extensions (n=235), 93% and 84% of patients were still alive at 1 year and 2 years, respectively, after the start of treatment with Tracleer.⁷

- Without a control group, these data must be interpreted cautiously and cannot be interpreted as an improvement in survival⁷

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The Cornerstone of Oral Therapy

Please see brief summary of prescribing information and full reference list on following page.

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Use of TRACLEER® requires attention to two significant concerns: 1) potential for serious liver injury, and 2) potential development of endogenous anion exchange.  

INDICATIONS AND USAGE: TRACLEER® is indicated for the treatment of pulmonary arterial hypertension in patients with WHO Heart Failure Classification (New York Heart Association (NYHA) Functional Class III or IV) with pulmonary hypertension associated with HIV infection and in patients with connective tissue disease with pulmonary arterial hypertension. Endothelin receptor antagonists indicate that teratogenicity is a class effect of these drugs. There are no data on the use of TRACLEER® in conditions that are an indication for the use of one of the available methods of contraception. Hormonal contraceptives, including oral, implantable and injectable contraceptives, are not considered as the sole means of contraception because they may not be effective in patients receiving TRACLEER® (see Precautions: Drug Interactions). Monthly pregnancy tests should be obtained. Because of potential liver injury and in an effort to make the chance of total fetal loss to TRACLEER® besotted on as small as possible, efforts should be made during the use of TRACLEER®. Pregnancy Category X. TRACLEER® is expected to cause fetal harm if administered to pregnant women. The similarity of malformations induced by bosentan and those observed in endothelin-1 (endothelin) mice and rats treated with other endothelin receptor antagonists supports the hypothesis that bosentan has a teratogenic potential. Because bosentan has been shown to be embryotoxic and teratogenic in animals, women of childbearing potential should be warned of the potential for harm to the fetus. TRACLEER® should be given to a pregnant woman only if clearly needed. Medication Guide: Use of TRACLEER® requires attention to two significant concerns: 1) potential for serious liver injury, and 2) potential development of endogenous anion exchange.

TRACLEER® is contraindicated in pregnancy, concurrent use of cyclosporine A, with co-administration of glyburide, and in patients with known hepatic or renal impairment or any component of the medication.

Pregnancy Category X. TRACLEER® is expected to cause fetal harm if administered to pregnant women. The similarity of malformations induced by bosentan and those observed in endothelin-1 (endothelin) mice and rats treated with other endothelin receptor antagonists supports the hypothesis that bosentan has a teratogenic potential. Because bosentan has been shown to be embryotoxic and teratogenic in animals, women of childbearing potential should be warned of the potential for harm to the fetus. TRACLEER® should be given to a pregnant woman only if clearly needed. Medication Guide: Use of TRACLEER® requires attention to two significant concerns: 1) potential for serious liver injury, and 2) potential development of endogenous anion exchange.
A trial of total lymphoid irradiation did not prove sustained benefit when 12 patients were equally randomized to treatment versus observation. However, neither was irradiation found to be excessively toxic in the active treatment arm. Improvement of alveolitis and stabilization of lung function have been demonstrated in uncontrolled trials with cyclophosphamide. Preliminary data from the Scleroderma Lung Study were presented at the International Conference of the American Thoracic Society in San Diego on May 25, 2005. Systemic scleroderma patients with active alveolitis were randomized to receive either oral cyclophosphamide or placebo for one year. For the first time a small but statistically significant stabilization of lung function was found, as was an improved quality of life at one year. A European trial evaluating monthly intravenous cyclophosphamide for treatment of active alveolitis in systemic sclerosis patients with interstitial lung disease completed its first year and at the same American Thoracic Society meeting in June 2005 one of the investigators reported benefits on forced vital capacity by cyclophosphamide compared to placebo.

Figure 2. Summary of survival in Fred Hutchinson Cancer Research Center (FHCRC) Protocol 1019.

Figure 3. Scleroderma Cyclophosphamide or Transplant (SCOT) trial transplant and rheumatology study sites.

Immunoablation and Stem Cell Transplantation in Severe Autoimmune Disease

The concept of resetting the autoimmunostat for treating severe autoimmune disease has evolved over the past decade. That bone marrow transplantation may be effective against human autoimmune disease was noted in aplastic anemia, a hematologic autoimmune disease caused by immunological suppression of the bone marrow. HLA-identical marrow transplantations are now routine practice in transplantations centers since the 1980s. Preclinical studies of high-dose immunosuppressive therapy followed by allogeneic and later autologous hematopoietic stem cell transplantation (HSCT) in antigen-induced animal models of autoimmune disease encouraged application of this therapy to human autoimmune disease. In contrast, syngeneic bone marrow transplantation in autoimmune animal models that develop generalized autoimmunity (eg, the model of systemic lupus erythematosus in NZBxNZW F1 mice) or organ-specific autoimmunity (eg, the model of diabetes mellitus in NOD mice) did not prevent disease expression. The effectiveness of allogeneic transplantation in such models suggests that the hematopoietic stem cells are the source of the autoimmunity in that animal model.

If development of clinical autoimmune disease was purely based on genetic make-up, predisposition would reside in hematopoietic stem cells and autologous HSCT would provide at best temporary antiinflammatory benefit from immunosuppression as seen in autoimmune-prone animal models. Most theories of the development of autoimmune disease in genetically susceptible individuals include exposure to an unidentified environmental trigger, infectious or noninfectious. The difficulty of identifying the environmental trigger is consistent with a latent period between exposure and expression of clinical disease. The rationale for high-dose immunosuppressive therapy with autologous HSCT is to “time shift” the course of the clinical autoimmune disease to an earlier period, thereby restoring self-tolerance. To be successful, this rationale assumes that response to repeat exposure to even self-antigens will differ and not result in reexpression of clinical autoimmunity.

Low-dose immunosuppressive therapy has demonstrated some benefit, although it is often the absence of progression rather than improvement that is considered the positive outcome. Evidence that intensive chemoradiotherapy followed by immune reconstitution with “naïve” stem cells is beneficial in patients with severe autoimmune disease was observed when patients with pre-existing autoimmune disease received allogeneic bone marrow transplantation for marrow failure or malignancy. The need for HLA-identical matched donor stem cells and the risk of graft-versus-host disease have limited the role of allogeneic stem cell transplantation in autoimmune diseases. The rationale for autologous HSCT relies on the effect of high-dose immunosuppressive therapy on T cell recovery. Non-T cell immune recovery is more rapid than T cell recovery. Three months after high-dose immunosuppressive therapy, CD3 cells normalize while the numbers of CD4 cells remain reduced and an inverted CD4/CD8 cell ratio persists for 12 months. There is a predominance of CD45RO+ cells, a deficiency of naïve CD45RA+ cells, and restriction of the T cell repertoire in adult patients. With experience, protocols of
HSCT in autoimmune disease have now come to use CD34+ cell selection and antithymocyte globulin therapy at the time of stem cell reinfusion, for an even greater degree of immunosuppression.57

**High-Dose Immunosuppressive Therapy and Autologous HSCT**

More patients with systemic sclerosis have undergone autologous HSCT than have patients with rheumatoid arthritis or systemic lupus erythematosus. This reflects the poor prognosis for an identifiable subset of systemic sclerosis patients and the absence of effective therapy. Initial case reports of benefit have been substantiated by cumulative experience in the European Bone Marrow Transplantation (EBMT) registry,60 the French multicenter trial,61 and the Fred Hutchinson Cancer Research Center (FHCRC) Protocol 1019.62 In contrast to patients with hematologic malignancies undergoing HSCT, eligible systemic sclerosis patients by definition have underlying organ damage that poses increased risk for transplant-related mortality.

In the EBMT registry, initial transplant-related mortality was high. With experience, protocol modifications (addition of cyclophosphamide 4 g/m² to G-CSF for mobilization, CD34+ purging, and conditioning regimens of cyclophosphamide plus anti-T cell antibodies) and better patient selection, transplant-related mortality improved from 27% to 8.7%.63 Of the 57 systemic sclerosis patients entered into this prospective registry, 19 were available for 24-month assessment. Fifteen (79%) had a >25% decline in initial modified Rodnan skin score. Pulmonary function, as measured by diffusing capacity of carbon monoxide and forced vital capacity, remained stable in a majority. There were no instances of systemic sclerosis renal crisis. Although either complete or partial remission as assessed by local investi-
HDIT-SCT

Stem cell mobilization
• Peripheral blood stem cells will be mobilized using injections of granulocyte colony stimulating factor (G-CSF)

Leukapheresis
• Stem cells will be removed from peripheral blood stream and stored for future use. In total, about 1 to 2 pints of blood will be removed at each collection
• Depending on CD34+ progenitor cell count yield, between one and five collections will be needed
• Each collection will take approximately 4 hours

CD 34 selection
• CD34+ cells will be selected using a cell separator system in an effort to remove all lymphocytes that are potentially disease-causing from sample in order to reduce risk of reactivating disease after autologous transplant

Conditioning
• Regimen of HDIT using total body irradiation (TBI) and CYC was chosen to provide ablative immunosuppression
• Pre- and post-transplant antithymocyte globulin will be administered to eliminate lymphocytes that survive preparative regimen and stem cell selection process
• Fractionated TBI dose of 800 cGy is lymphoablative but a reduced dose compared with most TBI-containing regimens used in treating malignancy (>1200 cGy). This dose is similar to that used in pilot and Phase II HDIT transplantation studies of systemic sclerosis. When combined with CYC and antithymocyte globulin, TBI is expected to provide maximal immunosuppression with acceptable toxicity. Bilateral lung and kidney shielding will be employed to prevent possible renal or pulmonary toxicities.

Stem cell transplantation
• Autologous CD34-selected hematopoietic progenitor cells will be infused after completion of HDIT to repopulate immunologic and hematopoietic systems

Control arm (IV CYC)

High-dose pulsed CYC treatment
• Patients will receive 750 mg/m² every 28 to 32 days for 12 months
• There is equipoise in consideration for randomization between the two treatment arms
• The CYC dose schedule used in SCOT is similar to that in the ASTIS trial, which will allow eventual comparison of the two studies

Figure 4. High-dose immunotherapy with stem cell transplant (HDIT-SCT) vs control (intravenous cyclophosphamide, IV CYC).

gators was seen in 92% of patients, a 35% relapse rate was seen within 1 year. Eight (14%) of the 57 died of disease progression. Transplant-related mortality reported at 8.7% included death from sepsis in two, one CNS bleed, one with interstitial pneumonitis, and one from diffuse alveolar hemorrhage. Death from disease progression, transplant-related causes, or relapse was 23% at a mean of 12 months. Overall two thirds of the patients experienced an initial clinical response not previously seen for any other therapeutic intervention in severe systemic sclerosis.

In the United States, a parallel Phase II study was conducted and results were recently published. In contrast to the EBMT registry, patients received total-body irradiation prior to transplant to promote maximum immunosuppression in addition to G-CSF for mobilization, CD 34 purging, and cyclophosphamide 120 mg/kg, and antithymocyte globulin. The safety of total-body irradiation has improved as lung and kidney shielding has become standard. The 3-year summary experience reported improvement in modified Rodnan skin score by a median of 49% (n = 24) at 12 months and a median of 79% (n = 10) at 36 months post transplant. Functional improvement as measured by the modified Health Assessment Questionnaire Disability Index improved by a median of 57.6% at 12 months and 72.8% at 36 months. Lung function (diffusing capacity of carbon monoxide and forced vital capacity), left ventricular ejection fraction, and serum creatinine remained stable. Transplant-related mortality was 8.7% after lung shielding, with no irradiation mortality noted in the 25 patients who received lung shielding. One death was due to Epstein-Barr virus-related lymphoproliferative disorder. By 3 years, a 23% mortality rate was reported from either transplant-related mortality or disease progression. Fifteen percent was attributed to disease progression (Figure 2).

In comparing the European regimen, which used higher doses of cyclophosphamide, and the US regimen, which used less cyclophosphamide but included total-body irradiation with lung shielding, there were no striking differences in mortality. The reported mortality rates following stem cell transplantation compare favorably to the projected 5-year mortality rate of approximately 50% for patients with early diffuse systemic sclerosis with renal and/or lung involvement who are left untreated. Encouraged by these results, a Phase III, prospective, randomized, controlled trial, the Autologous Stem cell Transplantation International Scleroderma (ASTIS) trial (http://www.astistrial.com) is being
conducted under the auspices of the European League Against Rheumatism (EULAR) and EBMT. Results of the ASTIS trial are not expected until 2009.

In the United States the Scleroderma Cyclophosphamide or Transplant (SCOT) trial, a prospective, randomized, clinical trial approved by the FDA and supported by the NIH has begun. Enrollment of 226 subjects randomly assigned to either high-dose immunosuppressive therapy with autologous stem cell transplantation or monthly pulsed intravenous cyclophosphamide is planned over the next 3 years. A map of transplant centers and participating rheumatology centers is found in Figure 3 and an overview of the study protocol is provided in Table 2 and Figure 4. Although early experiences with stem cell transplantation in systemic sclerosis showed a higher than expected transplant-related mortality, more stringent eligibility requirements and modification of treatment regimens are anticipated to reduce mortality risk and improve outcome overall.

Both the ASTIS and SCOT trials have similar inclusion and exclusion criteria with nearly identical follow-up and end points. In both trials patients will be randomized to the transplant arm or the control arm (monthly intravenous cyclophosphamide for one year). The dose of 750 mg/m² for 12 monthly cycles is approximately twice the dose of cyclophosphamide given as part of the HSCT arm and was chosen to strengthen equipoise between the two regimens. The results of these parallel studies will provide sound clinical data to evaluate the optimal treatment regimen for high-dose immunosuppressive therapy with autologous HSCT as well as to assess the efficacy of high-dose immunosuppressive therapy without HSCT in patients with early severe systemic sclerosis when immunomanipulation is proposed to be most effective.

Finally, the SCOT trial represents a unique opportunity to broaden our understanding of the pathogenesis of systemic sclerosis and its response to high-dose immunosuppressive therapy. Several mechanistic studies are proposed to improve understanding of the role of T cells in systemic sclerosis with lung disease, the molecular mechanisms of fibrosis and the role of circulating endothelial progenitor cells. Additional information on this pivotal study for patients and physicians can be found at http://www.sclerodermarxresearch.org. Study contact numbers are listed on the Web site.

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Pulmonary arterial hypertension (PAH) associated with scleroderma is a potentially life-threatening complication of the disease. Treatment of PAH in scleroderma has undergone revolutionary change within the past decade and now includes analogues of prostacyclin (prostanoids), phosphodiesterase inhibitors, and endothelin receptor antagonists. This review will focus on two new therapies, namely treprostinil and inhaled iloprost.

Pulmonary Hypertension in Scleroderma

PAH is a relatively late, but potentially lethal complication primarily of the limited form of the disease (limited cutaneous systemic sclerosis, lcSSc). PAH occurs in approximately 10% to 15% of all patients with lcSSc, but much less frequently in patients with the diffuse form, or dcSSc (prevalence <5%). Additional predictors of PAH in systemic sclerosis include a decreasing diffusion capacity of carbon monoxide, later disease onset, and male sex. Prevalence estimates of PAH vary with the study and the mode of diagnosis, but are exclusively derived from retrospective studies. With echocardiography the prevalence (approximately 40% to 50%) is estimated to be higher than with right heart catheterization, which is approximately 12% to 15%. Echocardiography appears to overestimate the prevalence, especially at lower pressures. At Boston University, we found that echo overestimated the prevalence of pulmonary hypertension in approximately 20% to 25% of patients whose pulmonary artery pressures were between 25 and 35 mm Hg on right heart catheterization. Estimates of disease duration prior to the development of PAH have varied in the literature from as little as 5 years from the first non-Raynaud’s symptom onset to 14 years and appear to depend on how pulmonary hypertension is defined. For example, Steen and Medsger found that the mean lcSSc disease duration preceding the diagnosis was 14.4 years. Pulmonary hypertension in this series was defined as: 1) pulmonary artery systolic pressure (PASP) >30 mm Hg on echocardiography with 2) mild to moderate dyspnea on exertion and 3) at least one additional clinical finding of right heart failure (eg, peripheral edema, ascites, or right heart abnormalities on electrocardiography). Bolster and colleagues used a less restrictive definition of PAH (with only PASP >30 mm Hg and no requirement of symptoms or signs of right heart failure) and found that disease duration varied between 5.8 years for African-American patients and 8.5 years for Caucasians.

PAH in systemic sclerosis is frequently confounded by left ventricular dysfunction (often diastolic in nature) that may become evident only when patients exert themselves. It is therefore important to distinguish PAH from pulmonary hypertension secondary to left ventricular dysfunction before beginning treatment for PAH. Because prostanoid therapy is contraindicated in patients with significant left ventricular dysfunction, this situation may require right heart catheterization with exercise, which often induces a rise in wedge pressure that might have been normal at rest.

Prostanoids

Prostacyclin is a vasodilatory and antithrombotic substance derived from vascular endothelium which was discovered in 1976. Epoprostenol, a synthetic analogue of prostacyclin was initially described in 1980 to treat a patient with idiopathic pulmonary hypertension. Subsequently, its efficacy by continuous intravenous infusion was established in idiopathic PAH. In 1996, the first randomized controlled trial of intravenous epoprostenol showed improved physical capacity and survival compared to controls. Another randomized controlled trial in patients with scleroderma-spectrum disease showed that epoprostenol therapy was associated with improved physical capacity but failed to show an improvement in survival. Subsequent long-term studies have established the long-term survival benefit of intravenous epoprostenol in both idiopathic and scleroderma-associated pulmonary hypertension.

Other than epoprostenol, three other prostacyclin analogues have been developed for treatment of pulmonary hypertension:
Dear Health Care Provider:

This letter provides important information about Remodulin relating to the treatment of pulmonary arterial hypertension. We are notifying you that United Therapeutics Corporation recently received a Warning Letter from the Food and Drug Administration (FDA) concerning the promotion of Remodulin® (treprostinil sodium) Injection. The Warning Letter concluded that United Therapeutics disseminated an advertisement and a promotional booklet that contained unsubstantiated comparative claims, omitted material facts, and minimized risks relating to the use of Remodulin.

This letter provides accurate information about Remodulin and corrects certain information from our promotional materials.

Specifically, the FDA letter stated that these promotional materials contained misleading comparative claims about the benefits of Remodulin administration versus Flolan (epoprostenol sodium) because the booklet did not also disclose other comparative information that Flolan has a proven effect on walking distance and survival in the indicated patient population, while Remodulin has not demonstrated these benefits. Additionally, the promotional materials suggested that patients can successfully switch from Flolan to Remodulin therapy, but the FDA stated there was insufficient clinical experience to support this statement.

FDA also stated that these promotional materials contained unsubstantiated effectiveness claims by implying that Remodulin had a dose-response effect on walk distance, a statistically significant effect on walk distance, and that the effect on walk distance exceeded 10 meters. FDA concluded that these claims were not supported by substantial evidence.

These promotional materials also contained statements minimizing the risks of the infusion site reactions and pain associated with the subcutaneous administration of Remodulin. The FDA considered these statements as misleading because they did not include the incidence rates for severe reactions and pain from our clinical trials. In clinical trials, severe infusion site reactions occurred in 38% of subjects and severe pain occurred in 39% of subjects treated with Remodulin.

The FDA approved Remodulin as a continuous subcutaneous or intravenous infusion (for those not able to tolerate a subcutaneous dose) and led to the discontinuation of treatment in 7% of Remodulin treated patients. Other adverse events included headache (27%), infusion site reaction (83%). Subcutaneous infusion site pain required the use of narcotics in 32% of Remodulin treated patients and led to the discontinuation of treatment in 7% of Remodulin treated patients. Other adverse events included headache (27%), diarrhea (25%), nausea (22%), rash (14%), jaw pain (13%), vasodilatation (11%), dizziness (9%), edema (9%), pruritus (8%) and hypotension (4%). In controlled studies of Remodulin administered subcutaneously, there were no reports of infection related to the drug delivery system. There were 187 infusion system complications reported in 28% of patients (23% Remodulin, 33% placebo); 173 (93%) were pump related and 14 (7%) related to the infusion set. There are no controlled clinical studies with Remodulin administered intravenously. Among patients (n=38) treated for twelve weeks with intravenous Remodulin in an open-label study, two patients experienced either line infections or sepsis. Other events potentially related to intravenous dosing of Remodulin include arm swelling, paresthesias, hematoma and pain. Remodulin is a potent pulmonary and systemic vasodilator and should be used only by clinicians experienced in the diagnosis and treatment of pulmonary arterial hypertension. Abrupt withdrawal or sudden large reductions in dosage of Remodulin may result in worsening of PAH symptoms and should be avoided. Reduction in blood pressure caused by Remodulin may be exacerbated by drugs that by themselves alter blood pressure, such as diuretics, antihypertensive agents, or vasodilators. Since Remodulin inhibits platelet aggregation, there is also a potential for increased risk of bleeding, particularly among patients maintained on anticoagulants. Remodulin should be used with caution in patients with hepatic or renal impairment. Remodulin has not been studied in conjunction with Flolan® or Tracleer® (bosentan).

The Clinical Effects section of the Remodulin PI states:

“The effect of Remodulin on 6-minute walk, the primary end point of the studies, was small and did not achieve conventional levels of statistical significance. For the combined populations, the median change from baseline on Remodulin was 10 meters and the median change from baseline on placebo was 0 meters. Although it was not the primary endpoint of the study, the Borg dyspnea score was significantly improved by Remodulin during the 6-minute walk, and Remodulin also had a significant effect, compared with placebo, on an assessment that combined walking distance with the Borg dyspnea score.”

Important Safety Information

In clinical trials, the most common side effects reported with subcutaneous Remodulin therapy included infusion site pain (85%) and infusion site reaction (83%). Subcutaneous infusion site pain required the use of narcotics in 32% of Remodulin treated patients and led to the discontinuation of treatment in 7% of Remodulin treated patients. Other adverse events included headache (27%), diarrhea (25%), nausea (22%), rash (14%), jaw pain (13%), vasodilatation (11%), dizziness (9%), edema (9%), pruritus (8%) and hypotension (4%). In controlled studies of Remodulin administered subcutaneously, there were no reports of infection related to the drug delivery system. There were 187 infusion system complications reported in 28% of patients (23% Remodulin, 33% placebo); 173 (93%) were pump related and 14 (7%) related to the infusion set. There are no controlled clinical studies with Remodulin administered intravenously. Among patients (n=38) treated for twelve weeks with intravenous Remodulin in an open-label study, two patients experienced either line infections or sepsis. Other events potentially related to intravenous dosing of Remodulin include arm swelling, paresthesias, hematoma and pain. Remodulin is a potent pulmonary and systemic vasodilator and should be used only by clinicians experienced in the diagnosis and treatment of pulmonary arterial hypertension. Abrupt withdrawal or sudden large reductions in dosage of Remodulin may result in worsening of PAH symptoms and should be avoided. Reduction in blood pressure caused by Remodulin may be exacerbated by drugs that by themselves alter blood pressure, such as diuretics, antihypertensive agents, or vasodilators. Since Remodulin inhibits platelet aggregation, there is also a potential for increased risk of bleeding, particularly among patients maintained on anticoagulants. Remodulin should be used with caution in patients with hepatic or renal impairment. Remodulin has not been studied in conjunction with Flolan® or Tracleer® (bosentan).

If you have any questions regarding this important corrective information, please contact United Therapeutics Corporation at 919-485-8350. Please refer to the full prescribing information for Remodulin.

United Therapeutics Corporation
INDICATIONS AND USAGE
Remodulin® is indicated for subcutaneous infusion or intravenous infusion (for those not able to tolerate a subcutaneous infusion) for the treatment of pulmonary arterial hypertension (PAH), including pulmonary hypertension associated with repair or transplantation of the left ventricle (see CLINICAL PHARMACOLOGY: Clinical Effects) to diminish symptoms and improve functional status.

CONTRAINDICATIONS
Remodulin is contraindicated in patients with known hypersensitivity to the drug or to its structurally related compounds.

WARNINGS
Remodulin is indicated for subcutaneous or intravenous use only.

PRECAUTIONS
General
Remodulin should be used only by clinicians experienced in the diagnosis and treatment of PAH. Prior to the initiation of Remodulin, vasodilator-induced hypotension should be assessed. Initiation of Remodulin must be performed in a setting with adequate personnel and equipment for physiological monitoring and emergency care.

Pregnancy
Teratogenic Effects:
Remodulin has not been studied in pregnant women. In rats, subcutaneous infusions at rates of up to 450 ng treprostinil/kg/min (about 59 times the average rate used in clinical trials), resulted in no evidence of harm to the fetus. In rabbits, administration of Remodulin at an infusion rate of 0.524 ng/kg/min (6.0 times the rate achieved in clinical trials), resulted in no evidence of harm to the fetus. In both species, adverse effects on the mother were observed at all concentrations tested. In both species, the effects were more severe in the mother as the concentration was increased. There are no adequate and well-controlled studies in pregnant women. Use of Remodulin during pregnancy should be avoided.

Labor and Delivery
If Remodulin use is necessary during labor and delivery, the effects on the baby should be weighed against the potential benefit as a single bolus or by subcutaneous infusion. A prophylactic dose should not be used. Infusion, on a mg/m² basis, and 5 times the average rate used in clinical trials). In rabbits, the effects of Remodulin on the baby were reported only at a single dose (1.1 mg/kg). In both species, effects on the mother were observed at all concentrations tested. In both species, the effects were more severe in the mother as the concentration was increased. There are no adequate and well-controlled studies in pregnant women. Use of Remodulin during pregnancy should be avoided.

Usage in Labor
If Remodulin use is necessary during labor and delivery, the effects on the baby should be weighed against the potential benefit.

Infusion Studies:
Continuous subcutaneous Remodulin infusions rates of up to 450 ng treprostinil/kg/min (about 59 times the average rate used in clinical trials) resulted in no evidence of harm to the fetus. In rabbits, administration of Remodulin at an infusion rate of 0.524 ng/kg/min (6.0 times the rate achieved in clinical trials), resulted in no evidence of harm to the fetus. In both species, effects on the mother were observed at all concentrations tested. In both species, the effects were more severe in the mother as the concentration was increased. There are no adequate and well-controlled studies in pregnant women. Use of Remodulin during pregnancy should be avoided.

Do not administer Remodulin to women who are or may become pregnant, or to men who may father a child while they are receiving Remodulin. Use of Remodulin in women of childbearing potential requires that effective contraception be utilized during treatment with Remodulin. Women of childbearing potential must have a negative pregnancy test prior to the initiation of therapy and regularly during therapy with Remodulin. Women of childbearing potential who are receiving Remodulin should use effective contraceptive methods that have a high degree of effectiveness and are appropriate for their particular situation. Women of childbearing potential who are receiving Remodulin must be advised to avoid becoming pregnant during their treatment with Remodulin.

Fertility Tests
Fertility studies in rats and rabbits were done with subcutaneous infusions of Remodulin at levels that were toxic to the mother. In rats, subcutaneous infusions at rates of up to 450 ng treprostinil/kg/min (about 59 times the average rate used in clinical trials) resulted in no evidence of harm to the fetus. In rabbits, administration of Remodulin at an infusion rate of 0.524 ng/kg/min (6.0 times the rate achieved in clinical trials), resulted in no evidence of harm to the fetus. In both species, effects on the mother were observed at all concentrations tested. In both species, the effects were more severe in the mother as the concentration was increased. There are no adequate and well-controlled studies in pregnant women. Use of Remodulin during pregnancy should be avoided.

Pediatric Use
The safety and effectiveness of Remodulin in pediatric patients have not been established. Use of Remodulin in pediatric patients is not recommended.

Geriatric Use
There were no substantial differences in the adverse effects or in any other clinically important difference between elderly and younger patients. Use of Remodulin in elderly patients is not recommended.

OVERDOSAGE
Signs and symptoms of overdose with Remodulin during clinical trials are extensions of its dose-limiting pharmacologic effects and include flushing, headache, hypotension, and syncope. Reactions were generally limited and resolved with reduction or withholding of Remodulin. In controlled studies Remodulin was administered to patients aged 16 years or older. In an open-label follow-up treatment study, 2 patients had either life-threatening or severe PAH reactions. These events were generally limited and resolved with reduction or withholding of Remodulin. There are no controlled studies with Remodulin administered intravenously to patients aged less than 16 years. In an open-label follow-up treatment study, 2 patients had either life-threatening or severe PAH reactions. These events were generally limited and resolved with reduction or withholding of Remodulin. There are no controlled studies with Remodulin administered intravenously to patients aged less than 16 years. 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treprostinil, beraprost, and iloprost. The prostanoids as a group possess similar pharmacological and pharmacodynamic properties. While they are potent pulmonary vasodilators, most patients with pulmonary hypertension have relatively minor acute hemodynamic responses, but develop much more vasodilation during long-term use. It has been hypothesized that this long-term effect is due to reversal of the endothelial remodeling that characterizes the pathology of chronic pulmonary arterial hypertension, although there is no direct evidence that remodeling reversal occurs.

Treprostinil (Remodulin®)

Pharmacology

Treprostinil was initially developed as a continuous subcutaneous infusion to avoid the risks associated with intravenously administered therapy, especially catheter-related infections, thrombosis, and infusion interruption due to catheter dislodgment. Treprostinil is rapidly and completely absorbed after subcutaneous infusion with an absolute bioavailability approaching 100%. The drug is metabolized by the liver and predominately excreted in the urine. In contrast to epoprostenol, which has a very short half-life, treprostinil has a half-life of 2 to 4 hours when administered via subcutaneous infusion. Its short-term hemodynamic effects are very similar to epoprostenol, and like epoprostenol, treprostinil is contraindicated in the face of reduced left ventricular function. In contrast to epoprostenol, treprostinil is stable at room temperature and does not require the use of ice packs during the infusion. Remodulin is available in Europe and in the United States via United Therapeutics (www.unither.com). In the United States the total cost for 12 months of therapy with Remodulin is approximately $100,000.

Therapeutic Efficacy

The efficacy of subcutaneously administered treprostinil was established in a large multicenter, double-blind, placebo-controlled, 12-week trial in 470 patients with PAH who were randomized to receive a continuous subcutaneous infusion of treprostinil or placebo. Inclusion criteria were: NYHA functional class II, III or IV despite treatment with conventional therapy, mean pulmonary artery pressure (PAPm) ≥25 mm Hg, pulmonary capillary wedge pressure or left ventricular end diastolic pressure ≤15 mm Hg, pulmonary vascular resistance ≥3 Wood units, and baseline 6-minute walk distance (6MWD) between 50 and 450 m. Exclusion criteria included significant parenchymal lung disease or total lung capacity <60% predicted. Improvement in 6MWD had a low overall mean of 16 m (placebo-controlled difference), but was greater in patients with more severe disease and was dose related. In patients tolerating more than 13.8 ng/kg/min, it was 36 m. Most patients (85%) reported infusion site pain, primarily due to skin reactions at the infusion site and 8% discontinued their study medication due to intolerable site pain. Small but significant improvements occurred in pulmonary hemodynamics and in the Borg dyspnea index.

A retrospective subgroup analysis of the above study focused on patients with PAH associated with connective tissue diseases (CTD). This subgroup included systemic lupus erythematosus (n = 25), diffuse scleroderma (n = 25), limited scleroderma (n = 20), and mixed CTD/overlap syndrome (n = 20). Forty-nine received placebo and 41 received treprostinil. After 12 weeks, the 6MWD for treprostinil-treated patients was 305±16 m, a mean difference of 24±12 m compared to baseline. The distance achieved by placebo-treated patients by comparison was 303±14 m, a mean difference of 3±8 m compared to baseline. Those patients (n = 11) in the highest dose quartile (>9 ng/Kg/min) achieved the largest increase in 6MWD compared to baseline (Figure 1). Using a post hoc combined outcome measure of 6MWD and Borg dyspnea score (‘Borg walk effect’), treprostinil-treated patients experienced greater improvement compared to placebo (P = .02). Treprostinil-treated patients showed a trend toward improvement in PAPm and mean right atrial pressure and significant improvement in cardiac index (P = .007) and pulmonary vascular resistance index (P = .006). Patients receiving treprostinil experienced a trend toward improvement in a quality of life measure (Minnesota Living with Heart Failure Questionnaire) compared with patients in the placebo group. Dose-limiting adverse events in the treprostinil group included infusion site pain and local reactions, diarrhea, headache, nausea, jaw pain, chest pain, backache, and restlessness. The authors noted that the relatively modest increase in 6MWD after 3 months of continuous subcutaneous infusion of treprostinil may have been due to the relatively low dose of treprostinil (≤9 ng/Kg/min) achieved in 26 of the 37 who completed the trial, perhaps due to limitation in up-titration because of dose-related infusion site pain.

For patients unable to tolerate intravenous epoprostenol it appears that safe transition to subcutaneous treprostinil can be accomplished. Vachiery et al reported 8 patients with PAH who developed severe complications of intravenous epoprostenol delivery including recurrent central venous catheter sepsis in 5 patients, severe headache, jaw pain, abdominal cramping, and diarrhea preventing dose escalation in one patient, recurrent cerebral air emboli with residual left paralysis in one patient, and several episodes of syncope due to accidental disconnections of the intravenous line in one patient. All patients were successfully transitioned to subcutaneous treprostinil with a mean follow-up period of 4 to 11 months, although all reported infusion site pain.

Figure 1. Mean change in 6-minute walk distance from baseline to week 12 as a function of week 12 treprostinil dose quartile. (Reprinted from Oudiz.11)
Dose-limiting adverse events in the treprostinil group in the Oudiz study of patients with PAH associated with connective tissue diseases included infusion site pain and local reactions, diarrhea, headache, nausea, jaw pain, chest pain, backache, and restlessness. Of the 90 patients, 7 discontinued therapy prematurely: 3 treprostinil-treated patients reported intolerable site pain and 4 patients died (1 in the treprostinil group and 3 in the placebo group; not a statistically significant difference).

**Intravenous Preparation**
The bioavailability and pharmacokinetics of intravenous treprostinil have been recently compared to the subcutaneously administered route. Fifty one subjects were administered both intravenous and subcutaneous treprostinil for 72 hours by each route. Pharmacokinetic assessments confirmed the comparability of the two routes at steady state. Recently the FDA has approved the intravenous route for treatment of PAH, although to date, there are no clinical trials of intravenous treprostinil in PAH with or without scleroderma.

**Conclusions**
Treprostinil is an effective prostanoid for treatment of PAH associated with scleroderma. When administered by the subcutaneous route, it is capable of producing improvement in physical function and symptoms of PAH, in addition to modest improvements in pulmonary hemodynamics and quality of life. For patients with severe PAH who are unable to tolerate epoprostenol or its intravenous administration, subcutaneously administered treprostinil may provide an effective alternative. The principal limitation of treprostinil, however, is infusion site pain during subcutaneous administration. Infusion site reactions may be helped by moving the infusion site every 3 days, local application of hot and cold packs, and topical or oral analgesics. Given the bioequivalence of the intravenous route, continuous infusion intravenous treprostinil may also be considered.

**Inhaled Iloprost (Ventavist™)**
Inhaled iloprost was approved in the United States in December 2004 for the treatment of PAH in patients with New York Heart Association (NYHA) functional class III or IV symptoms. It is also licensed in Europe. Iloprost is a stable analogue of prostacyclin; this increased stability allows it to be administered by the inhaled route. Labeling for registration includes PAH associated with collagen vascular disease, including scleroderma.

**Pharmacology**
Iloprost is a pulmonary vasodilator; in patients with PAH it reduces pulmonary artery pressure and pulmonary vascular resistance and increases cardiac output, with minimal effects on systemic arterial pressure. Prostacyclin and its analogues are not only vasodilators but also have antplatelet and antiproliferative effects. In PAH there is dysregulation of endogenous prostacyclin production; hence the rationale for exogenous administration. While epoprostenol confers benefit in patients with severe PAH, its administration is complex, and its half-life is short, necessitating intravenous infusion: potential problems include line sepsis, hemodynamic decompensation on abrupt discontinuation, and the need for refrigeration and daily mixing. Thus other routes of delivery have been examined. An attraction of inhaled iloprost is its preferential pulmonary (as opposed to systemic) vasodilatory effect, as well as the avoidance of the problems of intravenous therapy.

Serum concentrations peak at the end of the inhalation or within the next 5 minutes. While the elimination half-life of inhaled iloprost in plasma is 6.5 to 9.4 minutes, the half-life of its pharmacodynamic effect is on the order of 20 minutes. The duration of action is on the order of 60 minutes, necessitating frequent inhalations per day. Inhaled iloprost is administered by nebulizer in a dose of 2.5 or 5 µg over 4 to 10 minutes, six to nine times daily.

**Therapeutic Efficacy**
Following a number of open-label, uncontrolled studies, efficacy was investigated in a double-blind, placebo-controlled, clinical trial of 203 patients with PAH. One hundred two patients had primary pulmonary hypertension and 101 had secondary pulmonary hypertension. All had NYHA functional class III or IV status. Thirty-five patients (17% of the total cohort) had collagen vascular disease. The treatment period was 12 weeks. One hundred one patients were randomized to inhaled iloprost (2.5 or 5 µg a day, six or nine times daily, median dose 30 µg a day) and 102 to placebo. The primary end point (a combination of an improvement in 6-minute walk time of at least 10% plus an improvement in NYHA functional class in the absence of clinical deterioration) was achieved by 16.8% of iloprost- and 4.9% of placebo-treated patients ($P = .007$). 6MWD (Figure 2), NYHA functional class, dyspnea score, and quality of life all improved in the iloprost group. There was stabilization of hemodynamic parameters in the iloprost group. There were fewer noncompleters in the iloprost group (4.0%) than in the placebo group (13.7%). During the 12 week study, 1 patient in the iloprost group and 4 in the placebo group died (not significant). Acute hemodynamic responses to inhaled iloprost at 12 weeks did not differ between active and placebo groups, suggesting that tolerance did not develop over 12 weeks.
Benefits were conferred in both primary and secondary pulmonary hypertension groups, and so it is likely that inhaled iloprost is effective in systemic sclerosis-related PAH, although numbers of recruited patients with collagen vascular disease were small. The mean inhaled dose of iloprost was equivalent to 0.37 ng/kg/min, substantially lower than the effective intravenous or subcutaneous dose.

Adverse Events
In the trial of 203 patients there were similar numbers of patients with serious adverse effects in both the iloprost and the placebo groups. The most common side effects in iloprost-treated patients were increased cough, headache, flushing, and flulike symptoms. Flushing and jaw pain occurred significantly more often in the active treatment group. Although the number of syncopal attacks was similar in both groups, severe syncope was more commonly observed in the iloprost group. It is recommended that therapy with inhaled iloprost should not be initiated if the systolic blood pressure is less than 85 mm Hg.

Further Information
Inhaled iloprost is available in the United States through CoTherix’s (the manufacturer of iloprost in the United States) specialty pharmacy partners to patients (http://cotherix.com/ct/vepep). In the United Kingdom inhaled iloprost can be ordered through Schering Healthcare (http://www.schering.co.uk).

Conclusions
Inhaled iloprost has beneficial effects in PAH (albeit mild) and therefore clinicians caring for patients with systemic sclerosis need to be aware of its indications and safety profile. A disadvantage is the need for multiple administrations each day (six to nine administrations, each lasting 4 to 10 minutes). A number of studies have investigated or are investigating its use in combination with other pulmonary vasodilators. The treatment of PAH is a rapidly evolving field and further clarification of the roles of the different pulmonary vasodilators, singly and in combination, is likely to emerge over the next few years.

References
The goals of the Registry are to perform serum autoantibody profiles and to identify associations of specific autoantibodies with clinical and laboratory manifestations and prognosis.

We hope to stimulate future research on childhood onset scleroderma by having a large compilation of data and specimens available. Investigators may apply for access to de-identified clinical data, serum, peripheral blood mononuclear cells, and DNA from Registry subjects; and may use the Registry as a vehicle to make their projects known to this subject population.

We have thus far enrolled 18 patients with systemic sclerosis and 61 with localized scleroderma. We expect to have 75 systemic and 200 localized patients in the Registry by the end of 2004.

For further information please contact Jennifer Jablon, the Study Coordinator, at 412-383-8674 or HYPERLINK “mailto:jablondj@msx.dept-med.pitt.edu” jablonj@msx.dept-med.pitt.edu
New National Institutes of Health Study Entitled:

Pathogenic Studies in Families With Twins or Siblings Discordant for Systemic Rheumatic Disorders

A new unit of the National Institute of Environmental Health Sciences, called the Environmental Autoimmunity Group (EAG), has been established in Bethesda, Maryland, at the National Institutes of Health (NIH) in the US Department of Health and Human Services to conduct pioneering research in understanding the genetic and environmental risk factors that may result in autoimmune diseases.

The EAG is currently enrolling families in which an adult or child meets criteria for systemic sclerosis (scleroderma), rheumatoid arthritis/juvenile rheumatoid arthritis, systemic lupus erythematosus, or Myositis and in which a twin or sibling of the same gender, who is within 4 years of age, does not have any one of these four illnesses or another autoimmune disease. Subjects may enroll at the NIH Clinical Center in Bethesda, Maryland, or in their local doctors’ offices. Patients remain under the care of their personal physicians while participating in the study. There is no charge for study-related evaluations and medical tests at the NIH. Compensation is available to both physicians and subjects for enrollment.

For information about the NIH Twin-Sibs study, please call the persons below, or visit the Web site: http://dir.niehs.nih.gov/direag/

Call Drs. Frederick Miller, Lisa Rider or Mark Gourley at (301) 451-6280 or toll-free at 1-888-271-3207

Overview of the Study

- The goal of the study is to understand the genetic and environmental factors that may result in systemic rheumatic diseases.
- The study will perform evaluations to assess why one twin or sibling developed disease and why the other brother or sister did not.
- Subjects may enroll at the NIH Clinical Center in Bethesda, Maryland or their local doctors’ offices.
- A letter from a referring physician is required.
- Twins or siblings as well as their biological parents will be enrolled.
- 400 pairs of twins or siblings, in which one has disease and one does not, will be enrolled.
- Medical records, questionnaires and blood and urine samples will be collected at enrollment and at the end of the study after 5 years.
- For each subject, annual questionnaire follow-ups will be collected by mail.
- Subjects who develop new autoimmune diseases during the study will be reevaluated.

Subject Eligibility

- Families are eligible when an adult or child member meets criteria for:
  - Systemic sclerosis (SSc, scleroderma)
  - Rheumatoid arthritis (RA) or
  - Juvenile Rheumatoid Arthritis (JRA) or
  - Systemic lupus erythematosus (SLE) or
  - Diopathic inflammatory myopathy (IIM, meaning any form of adult or juvenile dermatomyositis, polymyositis or inclusion body myositis)
And when a twin or brother or sister of the same gender, and within 4 years of age, does not have rheumatic or autoimmune disease.
- The diagnosis of SSc, RA, SLE or IIM has to be within 4 years of enrollment.
- Affected and unaffected brothers or sisters must be of the same gender (both male or both female) and be offspring of the same parents.
- Normal healthy volunteers, who do not have a blood relative with a rheumatic or autoimmune disease, and who are matched to enrolled patients, are also eligible to enroll in the study.
Our focus may be on the heart & lungs...

but our commitment is full of heart & soul.

At Encysive Pharmaceuticals our goal is to be a leader in the discovery and development of small molecule drugs that will make a big impact on improving survival and the quality of life for people with life-threatening diseases, such as Pulmonary Arterial Hypertension.

The critical nature of PAH reinforces our sense of urgency to bring an effective therapy to market. We have the science, expertise and resources to make a difference…but most importantly we have the heart & soul.

Encysive Pharmaceuticals
www.encysive.com
What is the most important thing in the world you need to know about scleroderma?

www.sclero.org
1,000+ Web pages in 18 languages

Quality information for you:
- Scleroderma Care and Research Journal online
- Daily Scleroderma Medical News
- Excellent reference resource

Support for those you care for:
- Online Moderated Support Groups
- Worldwide Support Group Listings

As featured in EULAR 2004 Abstract SL0003 Internet as a Tool for Patient Support Groups to Provide quality Information. M. Dziadzio et al

International Scleroderma Network
7455 France Ave So #266
Edina, MN 55435 USA

ISN’s Voices of Scleroderma
Volume 2 book features
Professor Carol Black and Dr. Christopher Denton of Royal Free Hospital. Sound medical information and support!

Introduction by Dr. James R. Seibold, Chair of ISN Medical Advisory Board.

International Scleroderma Network (ISN)
Toll Free Phone: 1-800-564-7099
Email: medical@sclero.org

www.sclero.org
The most important thing in the world you need to know about scleroderma.