

Scleroderma

Care and Research

Volume 3, Number 1
Autumn 2005

Journal of the
Scleroderma Clinical
Trials Consortium



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

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New Therapies for Pulmonary Arterial Hypertension Associated with Systemic Sclerosis

*Robert W. Simms, MD
Ariane L. Herrick, MD*

Mission Statement

Scleroderma Care and Research is an independent, biannual journal committed to elevating the standards of care in scleroderma and presenting new and useful information from ongoing clinical trials. It is the official journal of the Scleroderma Clinical Trials Consortium. The journal is distributed to rheumatologists in the United States and additional physicians internationally.

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Scleroderma Care and Research is circulated to the community of physicians caring for patients with scleroderma.

About the cover:

A new trial in the United States, the Scleroderma Cyclophosphamide or Transplant (SCOT) trial, approved by the FDA and supported by the NIH, has begun. Figure depicts logo of this trial. Schematic drawing depicts process of hematopoiesis that occurs in three successive cell compartments. Stem cells are pluripotent cells guaranteeing permanent production of blood cells. Precursor cells (or determined cells) are capable of only a limited number of divisions. Maturing cells constitute a transition between the preceding compartments and the bloodstream; cells in the bloodstream have identifiable morphologies. (Copyright, Photo Researchers, 2005.) SCOT logo and figure provided by Keith M. Sullivan, MD, Principal Investigator, NIH Contract Award, and the SCOT Investigators Steering Committee, without whose work and dedication this protocol would not have come to fruition.

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 (EMA) 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" regimens (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

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

M. E. Csuka, MD, Associate Professor of Medicine,
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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 preceded 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.²⁹ 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

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 No. N01-AI-25481 and N01-AI-05419.

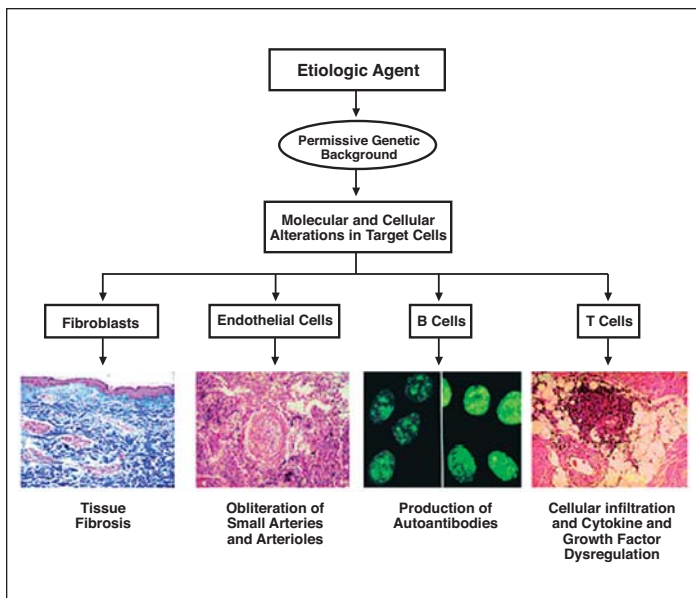


Figure 1. General overview of pathogenesis of systemic sclerosis. (Copyright © 2004, *Annals of Internal Medicine*. All rights reserved.)

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 up regulates 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

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

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+/CDI1b (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 CD+8 and γ/δ 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 CD+8 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 therapy.

(continued on page 8)

SEE
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 PAH³
- WHO recommends annual screening with echocardiogram⁴
- Only a right heart catheterization can confirm PAH diagnosis and assess precise hemodynamics^{3,5}

In Pulmonary Arterial Hypertension WHO Class III or IV

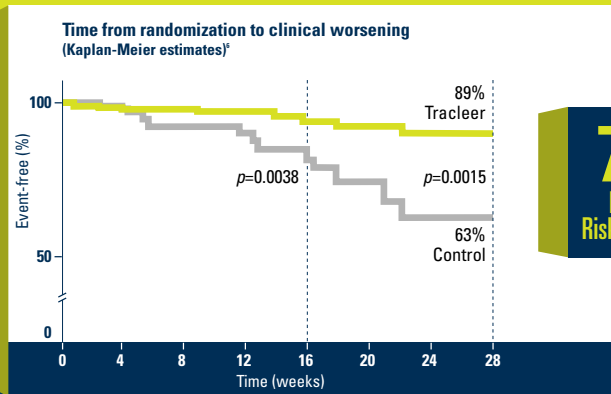


TREAT with Tracleer

The oral endothelin receptor antagonist backed by long-term data

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

Reduces risk of clinical worsening



71%
Relative Risk Reduction

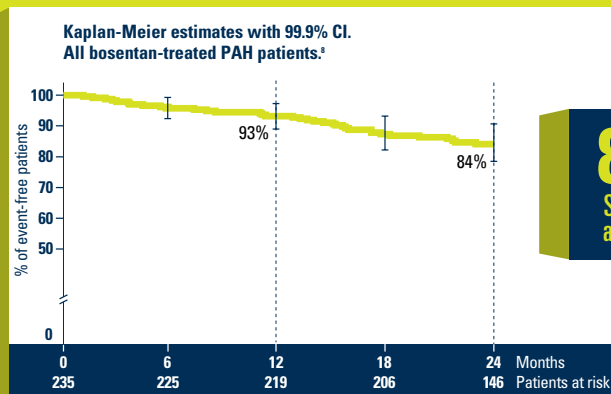
BREATHE-1 All patients (n=144 in the Tracleer group and n=69 in the control group) participated in the first 16 weeks. A subset of this population (n=35 in the Tracleer group and n=13 in the control group) continued for up to 28 weeks.

Tracleer significantly reduced risk of clinical worsening by 71% relative to control at week 28.⁶

- Clinical worsening defined as combined endpoint of death, hospitalization or discontinuation due to worsening PAH, or initiation of epoprostenol therapy⁶
- A statistically significant difference was apparent as early as week 16⁶
- 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 included⁷:
 - Vasodilators
 - Calcium channel blockers
 - ACE inhibitors
 - Digoxin
 - Diuretics
 - Anticoagulants

STAY with Tracleer

Long-term data for patients treated with Tracleer



84%
Still Alive at 2 Years

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

The Cornerstone of Oral Therapy



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



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62.5 mg and 125 mg film-coated tablets

Brief Summary: Please see package insert for full prescribing information.

Use of TRACLEER® requires attention to two significant concerns: 1) potential for serious liver injury, and 2) potential damage to a fetus.

WARNING: Potential Liver Injury. TRACLEER® causes at least 3-fold (upper limit of normal; ULN) elevation of liver aminotransferases (ALT and AST) in about 11% of patients, accompanied by elevated bilirubin in a small number of cases. Because these changes are a marker for potential serious liver injury, serum aminotransferase levels must be measured prior to initiation of treatment and then monthly (see WARNINGS: Potential Liver Injury and DOSAGE AND ADMINISTRATION). To date, in a setting of close monitoring, elevations have been reversible, within a few days to 9 weeks, either spontaneously or after dose reduction or discontinuation, and without sequelae. Elevations in aminotransferases require close attention (see DOSAGE AND ADMINISTRATION). TRACLEER® should generally be avoided in patients with elevated aminotransferases (> 3 x ULN) at baseline because monitoring liver injury may be more difficult. If liver aminotransferase elevations are accompanied by clinical symptoms of liver injury (such as nausea, vomiting, fever, abdominal pain, jaundice, or unusual lethargy or fatigue) or increases in bilirubin ≥ 2 x ULN, treatment should be stopped. There is no experience with the re-introduction of TRACLEER® in these circumstances.

CONTRAINDICATION: Pregnancy. TRACLEER® (bosentan) is very likely to produce major birth defects if used by pregnant women, as this effect has been seen consistently when it is administered to animals (see CONTRAINDICATIONS). Therefore, pregnancy must be excluded before the start of treatment with TRACLEER® and prevented thereafter by the use of a reliable method of contraception. Hormonal contraceptives, including oral, injectable and implantable contraceptives should not be used as the sole means of contraception because these may not be effective in patients receiving TRACLEER® (see Precautions: Drug Interactions). Monthly pregnancy tests should be obtained.

Because of potential liver injury and an effort to make the chance of fetal exposure to TRACLEER® (bosentan) as small as possible, TRACLEER® may be prescribed only through the TRACLEER® Access Program by calling 1 866 228 3546. Adverse events can also be reported directly via this number.

INDICATIONS AND USAGE: TRACLEER® is indicated for the treatment of pulmonary arterial hypertension in patients with WHO Class III or IV symptoms, to improve exercise ability and decrease the rate of clinical worsening.

CONTRAINDICATIONS: TRACLEER® is contraindicated in pregnancy, with concomitant use of cyclosporine A, with co-administration of glyburide, and in patients who are hypersensitive to bosentan 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 knockout mice and in animals treated with other endothelin receptor antagonists indicates that teratogenicity is a class effect of these drugs. There are no data on the use of TRACLEER® in pregnant women. TRACLEER® should be started only in patients known not to be pregnant. For female patients of childbearing potential, a prescription for TRACLEER® should not be issued by the prescriber unless the patient assures the prescriber that she is not sexually active or provides negative results from a urine or serum pregnancy test performed during the first 5 days of a normal menstrual period and at least 11 days after the last unprotected act of sexual intercourse. Follow-up urine or serum pregnancy tests should be obtained monthly in women of childbearing potential taking TRACLEER®. The patient must be advised that if there is any delay in onset of menses or any other reason to suspect pregnancy, she must notify the physician immediately for pregnancy testing. If the pregnancy test is positive, the physician and patient must discuss the risk to the pregnancy and to the fetus.

WARNINGS: Potential Liver Injury. Elevations in ALT or AST by more than 3 x ULN were observed in 11% of bosentan-treated patients (N = 658) compared to 2% of placebo-treated patients (N = 280). The combination of hepatocellular injury (increases in aminotransferases of > 3 x ULN) and increases in total bilirubin (≥ 3 x ULN) is a marker for potential serious liver injury; Elevations of AST and/or ALT associated with bosentan are dose-dependent, occur both early and late in treatment, usually progress slowly, are typically asymptomatic, and to date have been reversible after treatment interruption or cessation. These aminotransferase elevations may reverse spontaneously while continuing treatment with TRACLEER®. Liver aminotransferase levels must be measured prior to initiation of treatment and then monthly. If elevated aminotransferase levels are seen, changes in monitoring and treatment must be initiated. If liver aminotransferase elevations are accompanied by clinical symptoms of liver injury (such as nausea, vomiting, fever, abdominal pain, jaundice, or unusual lethargy or fatigue) or increases in bilirubin ≥ 2 x ULN, treatment should be stopped. There is no experience with the re-introduction of TRACLEER® in these circumstances. *Pre-existing Liver Impairment:* TRACLEER® should generally be avoided in patients with moderate or severe liver impairment. In addition, TRACLEER® should generally be avoided in patients with elevated aminotransferases (> 3 x ULN) because monitoring liver injury in these patients may be more difficult.

PRECAUTIONS: Hematologic Changes: Treatment with TRACLEER® caused a dose-related decrease in hemoglobin and hematocrit. The overall mean decrease in hemoglobin concentration for bosentan-treated patients was 0.9 g/dl (change to end of treatment). Most of this decrease of hemoglobin concentration was detected during the first few weeks of bosentan treatment and hemoglobin levels stabilized by 4–12 weeks of bosentan treatment. In placebo-controlled studies of all uses of bosentan, marked decreases in hemoglobin (> 15% decrease from baseline resulting in values of < 11 g/dl) were observed in 6% of bosentan-treated patients and 3% of placebo-treated patients. In patients with pulmonary arterial hypertension treated with doses of 125 and 250 mg b.i.d., marked decreases in hemoglobin occurred in 3% compared to 1% in placebo-treated patients. A decrease in hemoglobin concentration by at least 1 g/dl was observed in 57% of bosentan-treated patients as compared to 29% of placebo-treated patients. In 80% of cases, the decrease occurred during the first 6 weeks of bosentan treatment. During the course of treatment the hemoglobin concentration remained within normal limits in 68% of bosentan-treated patients compared to 76% of placebo patients. The explanation for the change in hemoglobin is not known, but it does not appear to be hemorrhage or hemolysis. It is recommended that hemoglobin concentrations be checked after 1 and 3 months, and every 3 months thereafter. If a marked decrease in hemoglobin concentration occurs, further evaluation should be undertaken to determine the cause and need for specific treatment. *Fluid retention:* In a placebo-controlled trial of patients with severe chronic heart failure, there was an increased incidence of hospitalization for CHF associated with weight gain and increased leg edema during the first 4–8 weeks of treatment with TRACLEER®. In addition, there have been numerous post-marketing reports of fluid retention in patients with pulmonary hypertension, occurring within weeks after starting TRACLEER®. Patients required intervention with a diuretic, fluid management, or hospitalization for decompensating heart failure.

Information for Patients: Patients are advised to consult the TRACLEER® Medication Guide on the safe use of TRACLEER®. The physician should discuss with the patient the importance of monthly monitoring of serum aminotransferases and urine or serum pregnancy testing and of avoidance of pregnancy. The physician should discuss options for effective contraception and measures to prevent pregnancy with their female patients. Input from a gynecologist or similar expert on adequate contraception should be sought as needed.

Drug Interactions: Bosentan is metabolized by CYP2C9 and CYP3A4. Inhibition of these isoenzymes may increase the plasma concentration of bosentan. Bosentan is an inducer of CYP3A4 and CYP2C9. Consequently, plasma concentrations of drugs metabolized by these two isoenzymes will be decreased when TRACLEER® is co-administered. Contraceptives: Specific interaction studies have not been performed to evaluate the effect of co-administration of bosentan and hormonal contraceptives, including oral, injectable or implantable contraceptives. Since many of these drugs are metabolized by CYP3A4, there is a possibility of failure of contraception when TRACLEER® is co-administered. Women should not rely on hormonal contraception alone when taking TRACLEER®. Cyclosporine A: During the first day of concomitant administration, trough concentrations of bosentan were increased by about 30-fold. Steady-state bosentan plasma concentrations were 3- to 4-fold higher than in the absence of cyclosporine A (see CONTRAINDICATIONS). Tacrolimus: Co-administration of tacrolimus and bosentan has not been studied in man. Co-administration of tacrolimus and bosentan resulted in markedly increased plasma concentrations of bosentan in animals. Caution should be exercised if tacrolimus and bosentan are used together. Glyburide: An increased risk of elevated liver aminotransferases was observed in patients receiving concomitant therapy with glyburide (see CONTRAINDICATIONS). Alternative hypoglycemic agents should be considered. Bosentan is also expected to reduce plasma concentrations of other oral hypoglycemic agents that are predominantly metabolized by CYP2C9 or CYP3A4. The possibility of worsened glucose control in patients using these agents should be considered. Ketoconazole: Co-administration of bosentan 125 mg b.i.d. and ketoconazole, a potent CYP3A4 inhibitor, increased the plasma concentrations of bosentan by approximately 2-fold. No dose adjustment of bosentan is necessary, but increased effects of bosentan should be considered. Simvastatin and Other Statins: Co-administration of bosentan decreased the plasma concentrations of simvastatin (a CYP3A4 substrate), and its active β-hydroxy acid metabolite, by approximately 50%. The plasma concentrations of bosentan were not affected. Bosentan is also expected to reduce plasma concentrations of other statins that have significant metabolism by CYP3A4, eg, lovastatin and atorvastatin. The possibility of reduced statin efficacy should be considered. Patients using CYP3A4 metabolized statins should have cholesterol levels monitored after TRACLEER® is initiated to see whether the statin dose needs adjustment. Warfarin: Co-administration of bosentan 500 mg b.i.d. for 6 days decreased the plasma concentrations of both S-warfarin (a CYP2C9 substrate) and R-warfarin (a CYP3A4 substrate) by 29 and 38%, respectively. Clinical experience with concomitant administration of bosentan and warfarin in patients with pulmonary arterial hypertension did not show clinically relevant changes in INR or warfarin dose (baseline vs. end of the clinical studies), and the need to change the warfarin dose during the trials due to changes in INR or due to adverse events was similar among bosentan- and placebo-treated patients. Digoxin, Nimodipine and Losartan: Bosentan has been shown to have no pharmacokinetic interactions with digoxin and nimodipine, and losartan has no effect on plasma levels of bosentan.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Two years of dietary administration of bosentan to mice produced an increased incidence of hepatocellular adenomas and carcinomas in males at doses about 8 times the maximum recommended human dose (MRHD) of 125 mg b.i.d., on a mg/m² basis. In the same study, doses greater than about 32 times the MRHD were associated with an increased incidence of colon adenomas in both males and females. In rats, dietary administration of bosentan for two years was associated with an increased incidence of brain astrocytomas in males at doses about 16 times the MRHD. **Impairment of Fertility/Testicular Function:** Many endothelin receptor antagonists have profound effects on the histology and function of the testes in animals. These drugs have been shown to induce atrophy of the seminiferous tubules of the testes and to reduce sperm counts and male fertility in rats when administered for longer than 10 weeks. Where studied, testicular tubular atrophy and decreases in male fertility observed with endothelin receptor antagonists appear irreversible. In fertility studies in which male and female rats were treated with bosentan at oral doses up to 50 times the MRHD on a mg/m² basis, no effects on sperm count, sperm motility, mating performance or fertility were observed. An increased incidence of testicular tubular atrophy was observed in rats given bosentan orally at doses as low as about 4 times the MRHD for two years but not at doses as high as about 50 times the MRHD for 6 months. An increased incidence of tubular atrophy was not observed in mice treated for 2 years at doses up to about 75 times the MRHD or in dogs treated up to 12 months at doses up to about 50 times the MRHD. There are no data on the effects of bosentan or other endothelin receptor antagonists on testicular function in man.

Pregnancy, Teratogenic Effects: Category X

SPECIAL POPULATIONS: Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, breastfeeding while taking TRACLEER® is not recommended. Pediatric Use: Safety and efficacy in pediatric patients have not been established. Use in Elderly Patients: Clinical experience with TRACLEER® in subjects aged 65 or older has not included a sufficient number of such subjects to identify a difference in response between elderly and younger patients.

ADVERSE REACTIONS: Safety data on bosentan were obtained from 12 clinical studies (8 placebo-controlled and 4 open-label) in 777 patients with pulmonary arterial hypertension, and other diseases. Treatment discontinuations due to adverse events other than those related to pulmonary hypertension during the clinical trials in patients with pulmonary arterial hypertension were more frequent on bosentan (5%; 8/165 patients) than on placebo (3%; 2/80 patients). In this database the only cause of discontinuations > 1%, and occurring more often on bosentan was abnormal liver function. In placebo-controlled studies of bosentan in pulmonary arterial hypertension and for other diseases (primarily chronic heart failure), a total of 677 patients were treated with bosentan at daily doses ranging from 100 mg to 2000 mg and 288 patients were treated with placebo. The duration of treatment ranged from 4 weeks to 6 months. For the adverse drug reactions that occurred in ≥ 3% of bosentan-treated patients, the only ones that occurred more frequently on bosentan than on placebo (≥ 2% difference) were headache (16% vs. 13%), flushing (7% vs. 2%), abnormal hepatic function (6% vs. 2%), leg edema (5% vs. 1%), and anemia (3% vs. 1%). Additional adverse reactions that occurred in > 3% of bosentan-treated pulmonary arterial hypertension patients were: nasopharyngitis (11% vs. 8%), hypotension (7% vs. 4%), palpitations (5% vs. 1%), dyspepsia (4% vs. 0%), edema (4% vs. 3%), fatigue (4% vs. 1%), and pruritus (4% vs. 0%).

Long-term Treatment: The long-term follow-up of the patients who were treated with TRACLEER® in the two pivotal studies and their open-label extensions (N=235) shows that 93% and 84% of patients were still alive at 1 and 2 years, respectively, after the start of treatment with TRACLEER®. These estimates may be influenced by the presence of eoprostenol treatment, which was administered to 43/235 patients. Without a control group, these data must be interpreted cautiously and cannot be interpreted as an improvement in survival.

Special Considerations: Patients with Congestive Heart Failure (CHF): Based on the results of a pair of studies with 1613 subjects, bosentan is not effective in the treatment of CHF with left ventricular dysfunction.

OVERDOSSAGE: Bosentan has been given as a single dose of up to 2400 mg in normal volunteers, or up to 2000 mg/day for 2 months in patients, without any major clinical consequences. The most common side effect was headache of mild to moderate intensity. In the cyclosporine A interaction study, in which doses of 500 and 1000 mg b.i.d. of bosentan were given concomitantly with cyclosporine A, trough plasma concentrations of bosentan increased 30-fold, resulting in severe headache, nausea, and vomiting, but no serious adverse events. Mild decreases in blood pressure and increases in heart rate were observed. There is no specific experience of overdose with bosentan beyond the doses described above. Massive overdose may result in pronounced hypotension requiring active cardiovascular support.

DOSAGE AND ADMINISTRATION: TRACLEER® treatment should be initiated at a dose of 62.5 mg b.i.d. for 4 weeks and then increased to the maintenance dose of 125 mg b.i.d. Doses above 125 mg b.i.d. did not appear to confer additional benefit sufficient to offset the increased risk of liver injury. Tablets should be administered morning and evening with or without food.

Dosage Adjustment and Monitoring in Patients Developing Aminotransferase Abnormalities

ALT/AST levels	Treatment and monitoring recommendations
> 3 and ≤ 5 x ULN	Confirm by another aminotransferase test; if confirmed, reduce the daily dose or interrupt treatment, and monitor aminotransferase levels at least every 2 weeks. If the aminotransferase levels return to pre-treatment values, continue or re-introduce the treatment as appropriate (see below).
> 5 and ≤ 8 x ULN	Confirm by another aminotransferase test; if confirmed, stop treatment and monitor aminotransferase levels at least every 2 weeks. Once the aminotransferase levels return to pre-treatment values, consider re-introduction of the treatment (see below).
> 8 x ULN	Treatment should be stopped and reintroduction of TRACLEER® should not be considered. There is no experience with re-introduction of TRACLEER® in these circumstances.

If TRACLEER® is re-introduced it should be at the starting dose; aminotransferase levels should be checked within 3 days and thereafter according to the recommendations above. If liver aminotransferase elevations are accompanied by clinical symptoms of liver injury (such as nausea, vomiting, fever, abdominal pain, jaundice, or unusual lethargy or fatigue) or increases in bilirubin ≥ 2 x ULN, treatment should be stopped. There is no experience with the re-introduction of TRACLEER® in these circumstances. Use in Women of Child-bearing Potential: TRACLEER® treatment should only be initiated in women of child-bearing potential following a negative pregnancy test and only in those who practice adequate contraception that does not rely solely upon hormonal contraceptives, including oral, injectable or implantable contraceptives. Input from a gynecologist or similar expert on adequate contraception should be sought as needed. Urine or serum pregnancy tests should be obtained monthly in women of childbearing potential taking TRACLEER®. **Dosage Adjustment in Renally Impaired Patients:** The effect of renal impairment on the pharmacokinetics of bosentan is small and does not require dosing adjustment. **Dosage Adjustment in Geriatric Patients:** Clinical studies of TRACLEER® did not include sufficient numbers of subjects aged 65 and older to determine whether they respond differently from younger subjects. In general, caution should be exercised in dose selection for elderly patients given the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy in this age group. **Dosage Adjustment in Hepatically Impaired Patients:** The influence of liver impairment on the pharmacokinetics of TRACLEER® has not been evaluated. Because there is *in vivo* and *in vitro* evidence that the main route of excretion of TRACLEER® is biliary, liver impairment would be expected to increase exposure to bosentan. There are no specific data on dose dosing in hepatically impaired patients; caution should be exercised in patients with mildly impaired liver function. TRACLEER® should generally be avoided in patients with moderate or severe liver impairment. **Dosage Adjustment in Children:** Safety and efficacy in pediatric patients have not been established. **Dosage Adjustment in Patients with Low Body Weight:** In patients with a body weight below 40 kg but who are over 12 years of age the recommended initial and maintenance dose is 62.5 mg b.i.d. **Discontinuation of Treatment:** There is limited experience with abrupt discontinuation of TRACLEER®. No evidence for acute rebound has been observed. Nevertheless, to avoid the potential for clinical deterioration, gradual dose reduction (62.5 mg b.i.d. for 3 to 7 days) should be considered.

HOW SUPPLIED: 62.5 mg film-coated, round, biconvex, orange-white tablets, embossed with identification marking "62.5"; NDC 66215-101-06: Bottle containing 60 tablets. 125 mg film-coated, oval, biconvex, orange-white tablets, embossed with identification marking "125"; NDC 66215-102-06: Bottle containing 60 tablets.

Rx only.

STORAGE: Store at 20°C – 25°C (68°F – 77°F). Excursions are permitted between 15°C and 30°C (59°F and 86°F). [See USP Controlled Room Temperature].

Reference this page: 1. Zimmerman HJ. *Hepatotoxicity - The adverse effects of drugs and other chemicals on the liver*. Second ed. Philadelphia: Lippincott, 1999. **References for previous page:** 1. Braunwald E, Fauci AS, Kasper DL, Hauser SL, Longo DL, Jameson JL, eds. *Harrison's Principles of Internal Medicine*. Vol. 2. 15th ed. New York: McGraw-Hill; 2001:1942. 2. Mirani OA, Dweik RA, Arroliga AC. Manifestations of scleroderma pulmonary disease. *Clin Chest Med*. 1996;19:713–731, viii–ix. Review. 3. Gaine SP, Rubin LJ. Primary pulmonary hypertension. *Lancet*. 1998;352:719–725. 4. Rich S, ed. Primary pulmonary hypertension: executive summary. *World Symposium—Primary Pulmonary Hypertension 1998*. Evian, France; September 8–10, 1998. 5. Braunwald E, Zipes DP, Libby P, eds. *Heart Disease*. 2 vols. 6th ed. Philadelphia, Pa: WB Saunders Co; 2001:1921, 1918, 1919. 6. Rubin LJ, Badesch DB, Barst RJ, et al. Bosentan therapy for pulmonary arterial hypertension. *N Engl J Med*. 2002;346:996–903. 7. Tracleer (bosentan) full prescribing information. Actelion Pharmaceuticals, Inc. 2003. 8. Data on file, Actelion Pharmaceuticals.

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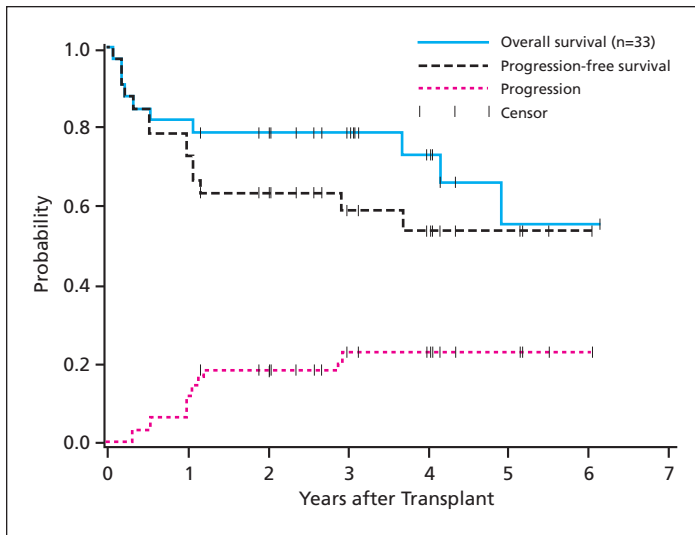


Figure 2. Summary of survival in Fred Hutchinson Cancer Research Center (FHCRC) Protocol 1019.

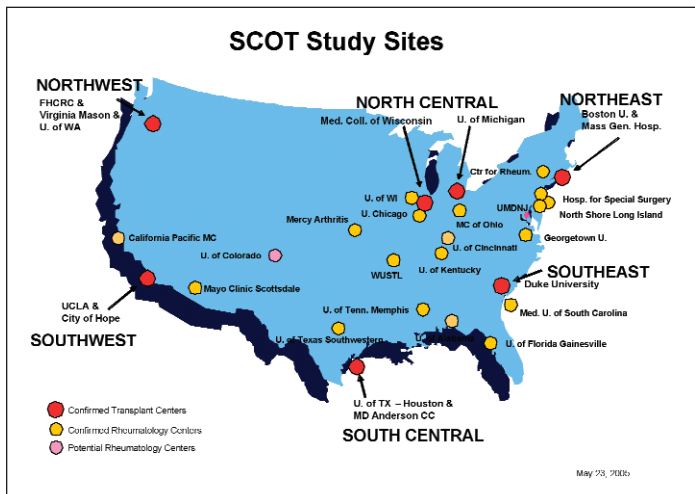


Figure 3. Scleroderma Cyclophosphamide or Transplant (SCOT) trial transplant and rheumatology study sites.

py. 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.²⁰ Improvement of alveolitis and stabilization of lung function have been demonstrated in uncontrolled trials with cyclophosphamide.⁴³⁻⁵¹ 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.

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.⁵² 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.⁵³ 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.⁵⁴

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.^{55,56} 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.⁵⁷

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.^{58,59} 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

Table 2. Overview of Scleroderma Cyclophosphamide or Transplant (SCOT) Trial.

Primary study end point

- “Event-free” survival at 44 months after randomization; events are defined as:
 - Death
 - Respiratory failure
 - Chronic renal dialysis
 - Cardiomyopathy (NYHA heart failure class III or IV) or left ventricular ejection fraction <30% by echocardiography sustained for 3 months
-

Eligibility criteria

- Subjects with poor prognosis systemic sclerosis characterized by extensive skin involvement (modified Rodnan skin score ≥ 16) and early internal organ involvement will be recruited to participate
-

Inclusion criteria

- Age 18 to 65 years
 - Systemic sclerosis as defined by American College of Rheumatology criteria
 - Modified Rodnan skin score ≥ 16 verified on two separate occasions ≥ 1 day and < 28 days apart
 - Duration of systemic sclerosis ≤ 4 years from onset of first non-Raynaud’s symptom
 - One of following two: (1) systemic sclerosis-related pulmonary disease with forced vital capacity or hemoglobin-adjusted diffusing capacity of carbon monoxide $< 70\%$ and evidence of alveolitis by high-resolution chest CT scan or bronchoalveolar lavage; or (2) history of systemic sclerosis-related renal crisis or disease, not active at time of screening
-

Exclusion criteria

(more fully detailed at <http://www.sclerodermatrial.org>)

- Pulmonary, cardiac, hepatic, or renal impairment of degree that would limit therapy and compromise survival
 - Active gastric antral vascular ectasia (GAVE, “watermelon stomach”)
 - Previous treatment with cyclophosphamide
 - Steroid therapy: > 10 mg/day prednisone or equivalent within 30 days prior to randomization
 - Unwilling or unable to discontinue disease-modifying antirheumatic drugs for treatment of systemic sclerosis
 - History or presence of overlap syndrome
 - Active uncontrolled infection
 - Positive serology for hepatitis B or C or HIV
 - Absolute neutrophil count < 1500 cells/ μ L, platelets $< 120,000$ cells/ μ L, hematocrit $< 27\%$, or hemoglobin < 9.0 g/dL
 - Malignancy within previous 2 years, excluding treated skin cancer and carcinoma *in situ*
 - Myelodysplasia
 - Comorbid illnesses with estimated median life expectancy < 5 years
 - Uncontrolled hypertension
 - History of hypersensitivity to murine or *E. coli* proteins
 - Pregnancy or unwilling to use contraceptive methods for at least 15 months after starting treatment
 - History of substance abuse within last 5 years
-

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 (FHRC) Protocol 1019.⁶² In contrast to patients with hemato-

logic 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-

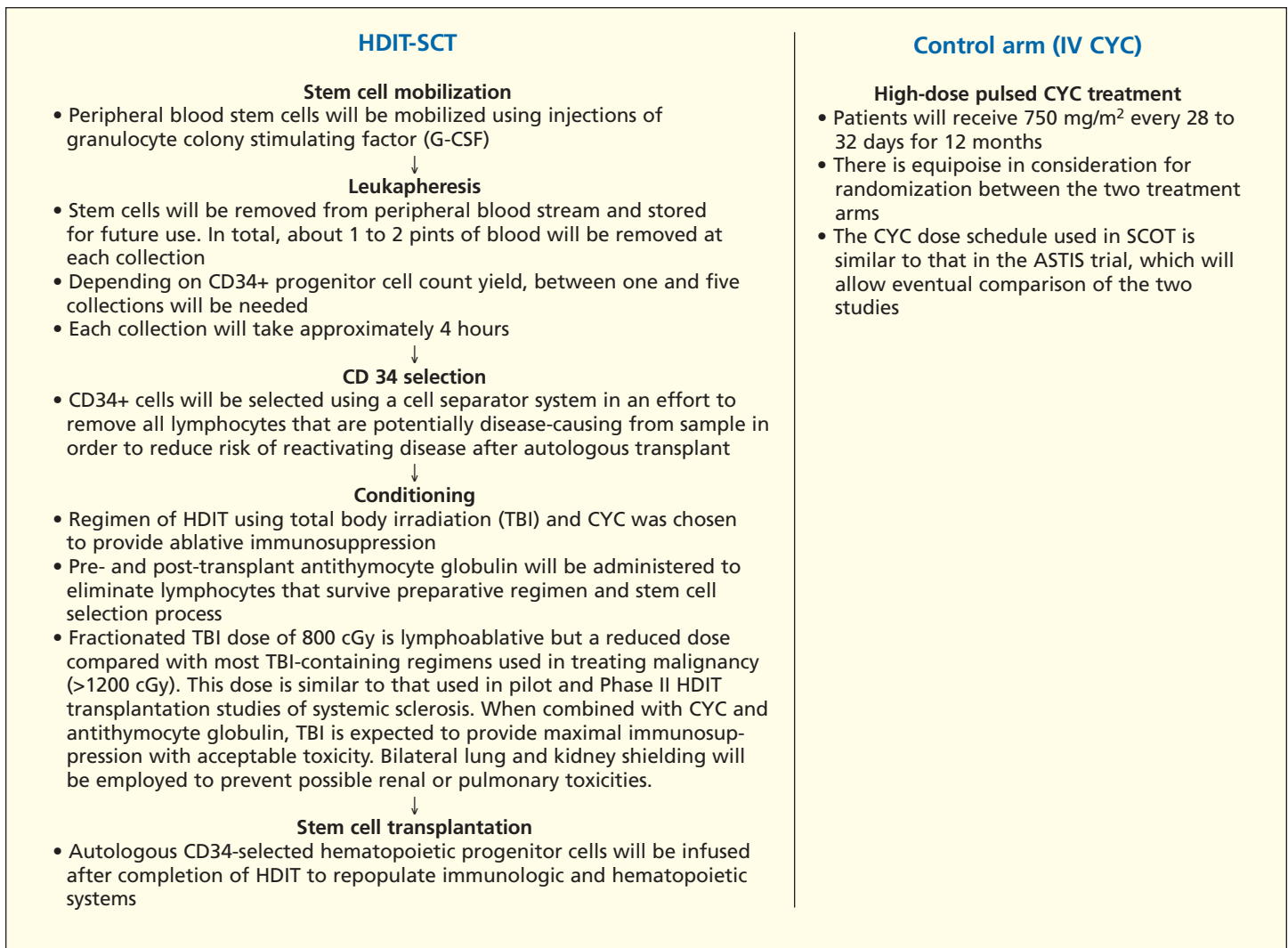


Figure 4. High-dose immunotherapy with stem cell transplant (HDIT-SCT) vs control (intravenous cyclophosphamide, IV CYC).

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.⁶⁴ 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.astis-trial.com>) is being



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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.sclerodermatrial.org>. Study contact numbers are listed on the Web site.

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New Therapies for Pulmonary Arterial Hypertension Associated with Systemic Sclerosis

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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%).¹ Additional predictors of PAH in systemic sclerosis include a decreasing diffusion capacity of carbon monoxide, later disease onset, and male sex.¹ 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.² 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.¹ 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.³

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 1976.⁴ Epoprostenol, a synthetic analogue of prostacyclin was initially described in 1980 to treat a patient with idiopathic pulmonary hypertension.⁵ Subsequently, its efficacy by continuous intravenous infusion was established in idiopathic PAH. In 1996, the first randomized controlled trial of intravenous poprostenol showed improved physical capacity and survival compared to controls.⁶ Another randomized controlled trial in patients with scleroderma-spectrum disease showed that poprostenol therapy was associated with improved physical capacity but failed to show an improvement in survival.⁷ Subsequent long-term studies have established the long-term survival benefit of intravenous poprostenol in both idiopathic and scleroderma-associated pulmonary hypertension.^{8,9}

Other than poprostenol, three other prostacyclin analogues have been developed for treatment of pulmonary hypertension:

(continued on page 17)

Dr Simms is a Consultant for Encysive and a funded researcher with Actelion and Encysive; Dr Herrick reports no conflicts of interest.

Important: Correction of Information about Remodulin[®] (treprostinil sodium) Injection

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, unsubstantiated effectiveness 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 infusion) for the treatment of pulmonary arterial hypertension in patients with NYHA Class II-IV symptoms to diminish symptoms associated with exercise.

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.

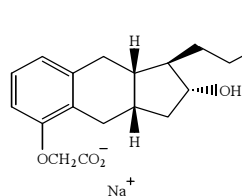
REMOLDILIN® (treprostinil sodium) Injection

BRIEF SUMMARY

The following is a brief summary of the full prescribing information on Remodulin (treprostinil sodium) Injection. Please review the full prescribing information prior to prescribing Remodulin.

DESCRIPTION

Remodulin® (treprostinil sodium) Injection is a sterile sodium salt formulated for subcutaneous or intravenous administration. Remodulin is supplied in 20 mL multi-use vials in four strengths, containing 1 mg/mL, 2.5 mg/mL, 5 mg/mL or 10 mg/mL of treprostinil. Each mL also contains 5.3 mg sodium chloride (except for the 10 mg/mL strength which contains 4.0 mg sodium chloride), 3.0 mg metacresol, 6.3 mg sodium citrate, and water for injection.



CLINICAL PHARMACOLOGY

General: The major pharmacologic actions of treprostinil are direct vasodilation of pulmonary and systemic arterial vascular beds and inhibition of platelet aggregation. In animals, the vasodilatory effects reduce right and left ventricular afterload and increase cardiac output and stroke volume. Other studies have shown that treprostinil causes a dose-related negative inotropic and lusitropic effect. No major effects on cardiac conduction have been observed.

Pharmacokinetics:

The pharmacokinetics of continuous subcutaneous Remodulin are linear over the dose range of 1.25 to 22.5 ng/kg/min (corresponding to plasma concentrations of about 0.03 to 8 mcg/L) and can be described by a two-compartment model. Dose proportionality at infusion rates greater than 22.5 ng/kg/min has not been studied. Subcutaneous and intravenous administration of Remodulin demonstrated bioequivalence at steady state at a dose of 10 ng/kg/min.

Absorption: Remodulin is relatively rapidly and completely absorbed after subcutaneous infusion, with an absolute bioavailability approximating 100%. Steady-state concentrations occurred in approximately 10 hours. Concentrations in patients treated with an average dose of 9.3 ng/kg/min were approximately 2 mcg/L.

Distribution: The volume of distribution of the drug in the central compartment is approximately 14L/70 kg ideal body weight. Remodulin at in vitro concentrations ranging from 330-10,000 mcg/L was 91% bound to human plasma protein.

Metabolism: Remodulin is substantially metabolized by the liver, but the precise enzymes responsible are unknown. Five metabolites have been described (HU1 through HU5). The biological activity and metabolic fate of these metabolites are unknown. The chemical structure of HU1 is unknown. HU5 is the glucuronide conjugate of treprostinil. The other metabolites are formed by oxidation of the 3-hydroxyoctyl side chain (HU2) and subsequent additional oxidation (HU3) or dehydration (HU4). Based on the results of in vitro human hepatic cytochrome P450 studies, Remodulin does not inhibit CYP-1A2, 2C9, 2C19, 2D6, 2E1, or 3A4. Whether Remodulin induces these enzymes has not been studied.

Excretion: The elimination of Remodulin is biphasic, with a terminal half-life of approximately 4 hours. Approximately 79% of an administered dose is excreted in the urine as unchanged drug (4%) and as the identified metabolites (64%). Approximately 13% of a dose is excreted in the feces. Systemic clearance is approximately 30 liters/hr for a 70 kg ideal body weight person.

Special Populations

Hepatic Insufficiency: In patients with portopulmonary hypertension and mild (n=4) or moderate (n=5) hepatic insufficiency, Remodulin at a subcutaneous dose of 10 ng/kg/min for 150 minutes had a C_{max} that was increased 2-fold and 4-fold, respectively, and an AUC₀₋₁₂ that was increased 3-fold and 5-fold, respectively, compared to healthy subjects. Clearance in patients with hepatic insufficiency was reduced by up to 80% compared to healthy adults. In patients with mild or moderate hepatic insufficiency, the initial dose of Remodulin should be decreased to 0.625 ng/kg/min ideal body weight and should be increased cautiously. Remodulin has not been studied in patients with severe hepatic insufficiency.

Renal Insufficiency: No studies have been performed in patients with renal insufficiency, so no specific advice about dosing in such patients can be given. Although only 4% of the administered dose is excreted unchanged in the urine, the five identified metabolites are all excreted in the urine.

Effect of Other Drugs on Remodulin: In vitro studies: Remodulin did not significantly affect the plasma protein binding of normally observed concentrations of digoxin or warfarin. In vivo studies: Acetaminophen - Analgesic doses of acetaminophen, 1000 mg every 6 hours for seven doses, did not affect the pharmacokinetics of Remodulin, at a subcutaneous infusion rate of 15 ng/kg/min.

Clinical Trials in Pulmonary Arterial Hypertension (PAH)

Two 12-week, multicenter, randomized, double-blind studies compared continuous subcutaneous infusion of Remodulin to placebo in a total of 470 patients with NYHA Class II-IV pulmonary arterial hypertension (PAH). PAH was primary in 58% of patients, associated with collagen vascular disease in 19%, and the result of congenital left to right shunts in 23%. The mean age was 45 (range 9 to 75 years). About 81% were female and 84% were Caucasian. Pulmonary hypertension had been diagnosed for a mean of 3.8 years. The primary endpoint of the studies was change in 6-minute walking distance, a standard measure of exercise capacity. There were many assessments of symptoms related to heart failure, but local discomfort and pain associated with Remodulin may have substantially unblinded those assessments. The 6-minute walking distance and an associated subjective measurement of shortness of breath during the walk (Borg dyspnea score) were administered by a person not participating in other aspects of the study. Remodulin was administered as a subcutaneous infusion, described in DOSAGE AND ADMINISTRATION, and the dose averaged 9.3 ng/kg/min at Week 12. Few subjects received doses > 40 ng/kg/min. Background therapy, determined by the investigators, could include anticoagulants, oral vasodilators, diuretics, digoxin, and oxygen but not an endothelin receptor antagonist or epoprostenol. The two studies were identical in design and conducted simultaneously, and the results were analyzed both pooled and individually.

Hemodynamic Effects:

Chronic therapy with Remodulin resulted in small hemodynamic changes consistent with pulmonary and systemic vasodilation.

Clinical Effects

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. Remodulin also consistently improved indices of dyspnea, fatigue and signs and symptoms of pulmonary hypertension, but these indices were difficult to interpret in the context of incomplete blinding to treatment assignment resulting from infusion site symptoms.

INDICATIONS AND USAGE

Remodulin® is indicated as a continuous subcutaneous infusion or intravenous infusion (for those not able to tolerate a subcutaneous infusion) for the treatment of pulmonary arterial hypertension in patients with NYHA Class II-IV symptoms (see CLINICAL PHARMACOLOGY: Clinical Effects) to diminish symptoms associated with exercise.

CONTRAINDICATIONS

Remodulin is contraindicated in patients with known hypersensitivity to the drug or to 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. Remodulin is a potent pulmonary and systemic vasodilator. Initiation of Remodulin must be performed in a setting with adequate personnel and equipment for physiological monitoring and emergency care. Therapy with Remodulin may be used for prolonged periods, and the patient's ability to administer Remodulin and care for an infusion system should be carefully considered. Dose should be increased for lack of improvement in, or worsening of, symptoms and it should be decreased for excessive pharmacologic effects or for unacceptable infusion site symptoms. Abrupt withdrawal or sudden large reductions in dosage of Remodulin may result in worsening of PAH symptoms and should be avoided.

Information for Patients

Patients receiving Remodulin should be given the following information: Remodulin is infused continuously through a subcutaneous or surgically placed indwelling central venous catheter, via an infusion pump. Therapy with Remodulin will be needed for prolonged periods, possibly years, and the patient's ability to accept and care for a catheter and to use an infusion pump should be carefully considered. In order to reduce the risk of infection, aseptic technique must be used in the preparation and administration of Remodulin. Additionally, patients should be aware that subsequent disease management may require the initiation of an alternative intravenous prostaticylin drug, Flolan® (epoprostenol sodium).

Drug Interactions:

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. During clinical trials, Remodulin was used concurrently with anticoagulants, diuretics, cardiac glycosides, calcium channel blockers, analgesics, antiplatelets, nonsteroidal anti-inflammatories, opioids, corticosteroids, and other medications. Remodulin has not been studied in conjunction with Flolan or Tracleor® (bosentan).

Effect of Other Drugs on Remodulin:

In vivo studies: Acetaminophen - Analgesic doses of acetaminophen, 1000 mg every 6 hours for seven doses, did not affect the pharmacokinetics of Remodulin, at a subcutaneous infusion rate of 15 ng/kg/min.

Effect of Remodulin on Other Drugs:

In vitro studies: Remodulin did not significantly affect the plasma protein binding of normally observed concentrations of digoxin or warfarin.

In vivo studies: Warfarin - Remodulin does not affect the pharmacokinetics or pharmacodynamics of warfarin. The pharmacokinetics of R- and S- warfarin and the INR in healthy subjects given a single 25 mg dose of warfarin were unaffected by continuous subcutaneous Remodulin at an infusion rate of 10 ng/kg/min.

Hepatic and Renal Impairment

Caution should be used in patients with hepatic or renal impairment (see Special Populations).

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies have not been performed to evaluate the carcinogenic potential of treprostinil. In vitro and in vivo genetic toxicology studies did not demonstrate any mutagenic or clastogenic effects of treprostinil. Treprostinil sodium did not affect fertility or mating performance of male or female rats given continuous subcutaneous infusions at rates of up to 450 ng treprostinil/kg/min [about 59 times the recommended starting human rate of infusion (1.25 ng/kg/min) and about 8 times the average rate (9.3 ng/kg/min) achieved in clinical trials, on a ng/m2 basis]. In this study, males were dosed from 10 weeks prior to mating and through the 2-week mating period. Females were dosed from 2 weeks prior to mating until gestational day 6.

Pregnancy

Pregnancy Category B - In pregnant rats, continuous subcutaneous infusions of treprostinil sodium during the period of organogenesis and late gestational development, at rates as high as 900 ng treprostinil/kg/min (about 117 times the starting human rate of infusion, on a ng/m2 basis) and about 16 times the average rate achieved in clinical trials, resulted in no evidence of harm to the fetus. In pregnant rabbits, effects of continuous subcutaneous infusions of treprostinil during organogenesis were limited to an increased incidence of fetal skeletal variations (bilateral full rib or right rudimentary rib on lumbar 1) associated with maternal toxicity (reduction in body weight and food consumption) at an infusion rate of 150 ng treprostinil/kg/min (about 41 times the starting human rate of infusion, on a ng/m2 basis, and 5 times the average rate used in clinical trials). In rats, continuous subcutaneous infusion of treprostinil from implantation to the end of lactation, at rates of up to 450 ng treprostinil/kg/min, did not affect the growth and development of offspring. Because animal reproduction studies are not always predictive of human response, Remodulin should be used during pregnancy only if clearly needed.

Labor and delivery

No treprostinil sodium treatment-related effects on labor and delivery were seen in animal studies. The effect of treprostinil sodium on labor and delivery in humans is unknown.

Nursing mothers

It is not known whether treprostinil is excreted in human milk or absorbed systemically after ingestion. Because many drugs are excreted in human milk, caution should be exercised when Remodulin is administered to nursing women.

Pediatric use

Safety and effectiveness in pediatric patients have not been established. Clinical studies of Remodulin did not include sufficient numbers of patients aged <16 years to determine whether they respond differently from older patients. In general, dose selection should be cautious.

Geriatric use

Clinical studies of Remodulin did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

Patients receiving Remodulin as a subcutaneous infusion reported a wide range of adverse events, many potentially related to the underlying disease (dyspnea, fatigue, chest pain, right ventricular heart failure, and pallor). During clinical trials with subcutaneous infusion of Remodulin, infusion site pain and reaction were the most common adverse events among those treated with Remodulin. Infusion site reaction was defined as any local adverse event other than pain or bleeding/bruising at the infusion site and included symptoms such as erythema, induration or rash. Infusion site reactions were sometimes severe and could lead to discontinuation of treatment.

Other adverse events included diarrhea, jaw pain, edema, vasodilatation and nausea, and these are generally considered to be related to the pharmacologic effects of Remodulin, whether administered subcutaneously or intravenously.

Percentages of subjects reporting subcutaneous infusion site adverse events:

	Reaction		Pain	
	Placebo	Remodulin	Placebo	Remodulin
Severe	1	38	2	39
Requiring narcotics*	NA**	NA**	1	32
Leading to discontinuation	0	3	0	7

* based on prescriptions for narcotics, not actual use

** medications used to treat infusion site pain were not distinguished from those used to treat site reactions

Adverse Events During Chronic Dosing:

The following adverse events occurred at a rate of at least 3% and were more frequent in patients treated with subcutaneous Remodulin than with placebo in controlled trials in PAH. Not included are those too general to be informative, and those not plausibly attributable to the use of the drug, because they were associated with the condition being treated or are very common in the treated population.

Adverse events reported include (Remodulin/Placebo, respectively): Infusion Site Pain (85%/27%), Infusion Site Reaction (83%/27%), Headache (27%/23%), Diarrhea (25%/16%), Nausea (22%/18%), Rash (14%/11%), Jaw Pain 13%/5%), Vasodilatation (11%/5%), Dizziness (9%/8%), Edema (9%/3%), Pruritus (8%/6%), Hypertension (4%/2%).

Adverse Events Attributable to the Drug Delivery System

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. Eight of these patients (4 Remodulin, 4 Placebo) reported non-serious adverse events resulting from infusion system complications. Adverse events resulting from problems with the delivery systems were typically related to either symptoms of excess Remodulin (e.g., nausea) or return of PAH symptoms (e.g., dyspnea). These events were generally resolved by correcting the delivery system pump or infusion set problem such as replacing the syringe or battery, reprogramming the pump, straightening a crimped infusion line. Adverse events resulting from problems with the delivery system did not lead to clinical instability or rapid deterioration.

There are no controlled clinical studies with Remodulin administered intravenously. Among the subjects (n=38) treated for 12-weeks in an open-label study, 2 patients had either line infections or sepsis. Other events potentially related to the mode of infusion include arm swelling, paresthesias, hematoma and pain.

OVERDOSAGE

Signs and symptoms of overdose with Remodulin during clinical trials are extensions of its dose-limiting pharmacologic effects and include flushing, headache, hypotension, nausea, vomiting, and diarrhea. Most events were self-limiting and resolved with reduction or withholding of Remodulin.

In controlled clinical trials, seven patients received some level of overdose and in open-label follow-on treatment seven additional patients received an overdose; these occurrences resulted from accidental bolus administration of Remodulin, errors in pump programmed rate of administration, and prescription of an incorrect dose. In only two cases did excess delivery of Remodulin produce an event of substantial hemodynamic concern (hypotension, near-syncope).

DOSAGE AND ADMINISTRATION

Remodulin® is supplied in 20 mL vials in concentrations of 1 mg/mL, 2.5 mg/mL, 5 mg/mL and 10 mg/mL. Remodulin can be administered as supplied or diluted for intravenous infusion with Sterile Water for Injection or 0.9% Sodium Chloride Injection prior to administration.

Initial Dose

Remodulin is administered by continuous infusion. Remodulin is preferably infused subcutaneously, but can be administered by a central intravenous line if the subcutaneous route is not tolerated, because of severe site pain or reaction. The infusion rate is initiated at 1.25 ng/kg/min. If this initial dose cannot be tolerated because of systemic effects, the infusion rate should be reduced to 0.625 ng/kg/min.

Dosage Adjustments

The goal of chronic dosage adjustments is to establish a dose at which PAH symptoms are improved, while minimizing excessive pharmacologic effects of Remodulin (headache, nausea, emesis, restlessness, anxiety and infusion site pain or reaction). The infusion rate should be increased in increments of no more than 1.25 ng/kg/min per week for the first four weeks and then no more than 2.5 ng/kg/min per week for the remaining duration of infusion, depending on clinical response. There is little experience with doses >40 ng/kg/min. Abrupt cessation of infusion should be avoided (see PRECAUTIONS).

Administration

Subcutaneous

Remodulin is administered subcutaneously by continuous infusion, via a self-inserted subcutaneous catheter, using an infusion pump designed for subcutaneous drug delivery. To avoid potential interruptions in drug delivery, the patient must have immediate access to a backup infusion pump and subcutaneous infusion sets. For subcutaneous infusion, Remodulin is delivered without further dilution at a calculated Subcutaneous Infusion Rate (mL/hr) based on a patients Dose (ng/kg/min), Weight (kg), and the Vial Strength (mg/mL) of Remodulin being used. During use, a single reservoir (syringe) of undiluted Remodulin can be administered up to 72 hours at 37°C.

Intravenous Infusion

Remodulin must be diluted with either Sterile Water for injection or 0.9% Sodium Chloride Injection and is administered intravenously by continuous infusion, via a surgically placed indwelling central venous catheter, using an infusion pump designed for intravenous drug delivery. To avoid potential interruptions in drug delivery, the patient must have immediate access to a backup infusion pump and infusion sets. The ambulatory infusion pump used to administer Remodulin should: (1) be small and lightweight, (2) have occlusion/no delivery, low battery, programming error and motor malfunction alarms, (3) have delivery accuracy of ±5% or better of the hourly dose, and (4) be positive pressure driven. The reservoir should be made of polyvinyl chloride, polypropylene or glass. Diluted Remodulin has been shown to be stable at ambient temperature for up to 48 hours at concentrations as low as 0.004 mg/mL (4,000 ng/mL) when using an appropriate infusion pump and reservoir, a predetermined intravenous infusion rate should first be selected to allow for a desired infusion period length of up to 48 hours between system changeovers. Typical intravenous infusion system reservoirs have volumes of 50 or 100 mL.

HOW SUPPLIED - Refer to Full Package Insert for Complete Information

Remodulin® is supplied in 20 mL multi-use vials at concentrations of 1 mg/mL, 2.5 mg/mL, 5 mg/mL, and 10 mg/mL treprostinil, as sterile solutions in water for injection, individually packaged in a carton. Unopened vials of Remodulin are stable until the date indicated when stored at 15 to 25°C (59 to 77°F). Store at 25°C (77°F), with excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

During use, a single reservoir (syringe) of undiluted Remodulin can be administered up to 72 hours at 37°C. Diluted Remodulin Solution can be administered up to 48 hours at 37°C when diluted to concentrations as low as 0.004 mg/mL in Sterile Water for Injection or 0.9% Sodium Chloride Injection. A single vial of Remodulin should be used for no more than 30 days after the initial introduction into the vial.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. If either particulate matter or discoloration is noted, Remodulin should not be administered.

United Therapeutics Corp., Research Triangle Park, NC 27709

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Rx only

November 2004

treprostinil, beraprost, and iloprost. The prostanoids as a group possess similar pharmacological and pharmacodynamic properties.⁴ 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.⁴

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.⁴ 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.⁴ 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.⁹ 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 base line 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.¹⁰

A retrospective subgroup analysis of the above study focused on patients with PAH associated with connective tissue diseases (CTD).¹¹ This subgroup included systemic lupus erythematosus

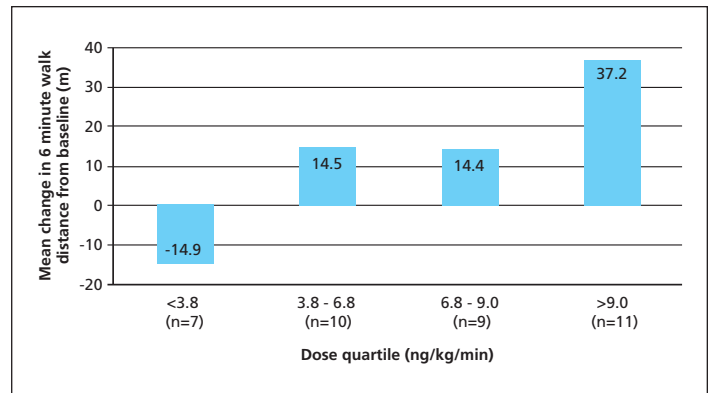


Figure 1. Mean change in 6-minute walk distance from baseline to week 12 as a function of week 12 treprostinil dose quartile. (Reprinted from Oudiz.¹¹)

(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.¹¹

For patients unable to tolerate intravenous epoprostenol it appears that safe transition to subcutaneous treprostinil can be accomplished. Vachery 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.¹² 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.

Adverse Events

Dose-limiting adverse events in the treprostinil group in the Oudiz study of patients with PAH associated with connective tissue diseases¹¹ 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.¹³ 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

Inhaled 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.^{14,15} Prostacyclin and its analogues are not only vasodilators but also have antiplatelet and antiproliferative effects. In PAH there is dysregulation of endogenous prostacyclin production; hence the rationale for exogenous administration.¹⁶ While epoprostenol confers benefit in patients with severe PAH, its administration is complex, and its half-life is short,

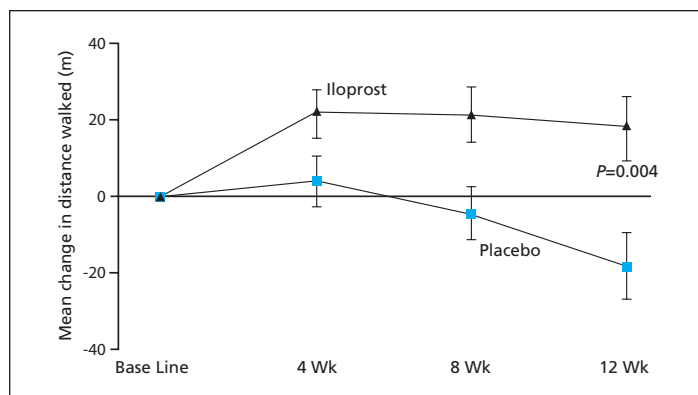


Figure 2. Effect of inhaled iloprost and placebo on the mean (\pm SE) change from base line in the distance walked in 6 minutes, according to an intention-to-treat analysis. The P value was obtained with Wilcoxon's test for two independent samples. (Reprinted from Olschewski.¹⁹)

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.¹⁷ 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.^{14,15} 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 μ g over 4 to 10 minutes, six to nine times daily.

Therapeutic Efficacy

Following a number of open-label, uncontrolled studies,¹⁸ efficacy was investigated in a double-blind, placebo-controlled, clinical trial of 203 patients with PAH.¹⁹ 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 μ g a day, six or nine times daily, median dose 30 μ g 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.

WHY I SPEAK UP ABOUT SCLERODERMA

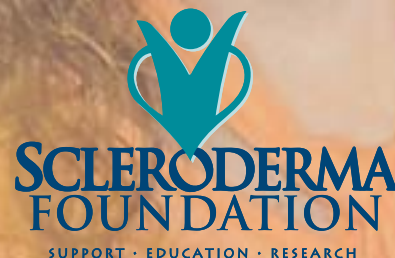
“It’s my goal to be an ambassador to people with scleroderma. Scleroderma changes lives and I hope to show them they can still enjoy their life. I also want to be an ambassador to unknowing Tennesseans and educate them about what we live through and why we need to raise money to find a cure. I hope to be alive when they find a cure for scleroderma, but in the meantime I want to use what time God has given me to make a difference for people who suffer from this disease.”

April Simpkins
Nashville, Tennessee
Scleroderma Patient

The Scleroderma Foundation is working to stimulate and support research to improve treatment and, ultimately, find a cure for scleroderma and diseases related to it. Will you join April and the Scleroderma Foundation and speak up about scleroderma?

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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.¹⁹ 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 patients¹⁹ 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.

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NATIONAL REGISTRY FOR CHILDHOOD ONSET SCLERODERMA

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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:jablonj@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
 - idiopathic 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.

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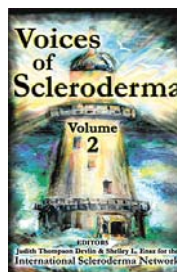
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