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A Primer with a Focus on Scleroderma**

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**Pulmonary Arterial Hypertension
in Systemic Sclerosis: Risk Factors and
Diagnosis**

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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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About the cover:

Elevated right ventricular pressure in scleroderma can result from arteriolar, capillary or postcapillary venular disease or from left ventricular dysfunction. Illustration courtesy of Michael McGoon, MD, Mayo College of Medicine, Rochester, Minnesota.

Editor's Memo

Although collagen deposition, vascular phenomena, and autoimmunity typify systemic sclerosis (SSc), our greatest treatment successes to date relate to successful management of several of the vascular complications—particularly renal crisis and pulmonary arterial hypertension. There are currently five medications approved by the Food and Drug Administration (FDA) for the management of pulmonary arterial hypertension: three prostenoids (epoprostenol, treprostinil, and iloprost), one endothelin-1A/B receptor inhibitor (bosentan) and one phosphodiesterase inhibitor (sildenafil). In addition several new medications are circulating in the FDA approval process, most notably sitaxsentan and ambrisentan (also endothelin-1 inhibitors). Although these are frequently effective, they are only partially effective in many cases. But that is the subject for another editorial.

In primary pulmonary arterial hypertension, the data suggest that once patients develop any elevation in pulmonary arterial pressures (with normal wedge pressures), they will most certainly worsen—the pressures will continue to rise and the patients will become very dyspneic and will die—unless treated with a pulmonary hypertension-specific agent. The data about the outcome of patients with the pulmonary arterial hypertension of systemic sclerosis, however, are not as clear and certain as they are in primary pulmonary hypertension. Echocardiographic screening of patients suggests that as many as a third to half of all SSc patients have at least mild elevations of right ventricular systolic pressure (RVSP, the echocardiographic equivalent of pulmonary arterial systolic pressure), but clinical experience suggests that only about 10% to 15% of SSc patients go on to develop critical, life-threatening pulmonary arterial hypertension. This presents a quandary. Which patients will go on to develop severe pulmonary arterial hypertension? Which patients need to be treated? How do we pick up early cases of pulmonary arterial hypertension? If we pick up mild cases, do we need to treat them? And when in the course do we treat them?

Unfortunately we know very little about the natural history of the pulmonary vascular disease that results in pulmonary arterial hypertension in SSc. The article by Virginia Steen, MD, in this issue lays out what we think we know about this natural history and proposes an approach for studying patients who might be at risk for developing clinically significant pulmonary arterial hypertension. She has developed a prospective study titled PHAROS (Pulmonary Hypertension Assessment Registry of Scleroderma) designed to evaluate and study patients who may be at risk. The three major entry criteria include SSc patients with diffusing capacity less than 55% of predicted, RVSP above 35 mmHg on echocardiography, and a ratio of forced vital capacity to diffusing capacity (%FVC/%DLCO) greater than 1.6. The rationale for using these criteria is presented and discussed in this issue. The article is aimed particularly at physicians who might see these patients and who might thus be interested in getting these patients entered into the PHAROS study (members of the Scleroderma Clinical Trials Consortium are participants). The purpose of PHAROS is to learn more about the early years of pulmonary vascular disease in SSc and to learn what the markers are that identify the patient likely to go on to significant pulmonary arterial hypertension. Contact the Consortium's Web site (www.scte-online.org) for a list of the sites and contact information for participation in PHAROS.

Although clinical trials in rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis have, for some time now, included questionnaires querying patients about their function and health-related quality of life, these tools are just now being included in clinical trials in SSc. In this issue Dinesh Khanna, MD, who has been at the leading edge of this area in scleroderma, discusses the available tools and instruments that measure function and quality of life in general and then illustrates how some of these tools can be, and have been, used in SSc studies. He also discusses data, derived from several treatment trials (some positive), that have shown that function and health-related quality of life change (better or worse) as the physiologic and objective data change by nature or in response to the treatment.

The clinical/scientific field studying function and health-related quality of life is in its infancy in SSc. Hopefully this article will improve the understanding of the importance of measuring function and health-related quality of life in SSc. It makes the argument that questionnaires assessing these areas should be included in future SSc trials—and maybe even office physicians should consider including them in their assessment of the SSc patient in the office.

Philip J. Clements, MD
Editor-in-Chief

Health-Related Quality of Life: A Primer with a Focus on Scleroderma

Dinesh Khanna, MD

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Chronic diseases often have a relapsing and remitting course with substantial impact on function and quality of life. For chronic illnesses where there is no cure, it is important to establish that therapy really makes people feel better. Thus, survival per se is no longer perceived to be the only end point; the goal is to improve, restore, or preserve functioning and well-being or health-related quality of life (HRQOL). In other words, HRQOL is “the extent to which one’s usual or expected physical, emotional, and social well-being are affected by a medical condition or its treatment.”¹ As exemplified by the definition, HRQOL incorporates multidimensionality and subjectivity. HRQOL, however, does not capture the quality of environment, income, housing, etc. The concept of HRQOL, therefore attempts to measure quality of life in the context of one’s health and illness (Figure 1).²

Scleroderma (systemic sclerosis, SSc) is an example of a disease in which patients must cope with pain, disfigurement, disability, and feelings of helplessness, each of which can affect their HRQOL and outlook on the present and the future.³ Despite the marked changes experienced by persons with SSc, this disease has received very little attention from the HRQOL perspective, compared with other rheumatic diseases.⁴

Assessing Health-Related Quality of Life

Work in HRQOL has originated from two fundamentally different approaches, as detailed by Tsevat and colleagues: health status and health value/preference/utility assessment (Table 1, Figure 2).⁵ In general, *health status* measures describe a person’s functioning in one or more domains (eg, physical functioning and mental well-being). Currently, one of the most commonly used generic health status instruments (ie, the concepts are not specific for any age, disease, or treatment group) is the SF-36, a 36-item measure encompassing eight domains—physical functioning, social functioning, mental health, role limitations due to physical problems, role limitations due to emotional problems, vitality (energy and fatigue), bodily pain, and general health perceptions—each of which is scored separately from 0 (worst) to 100 (best).⁶ The SF-36 domains can be summarized into physical component summa-

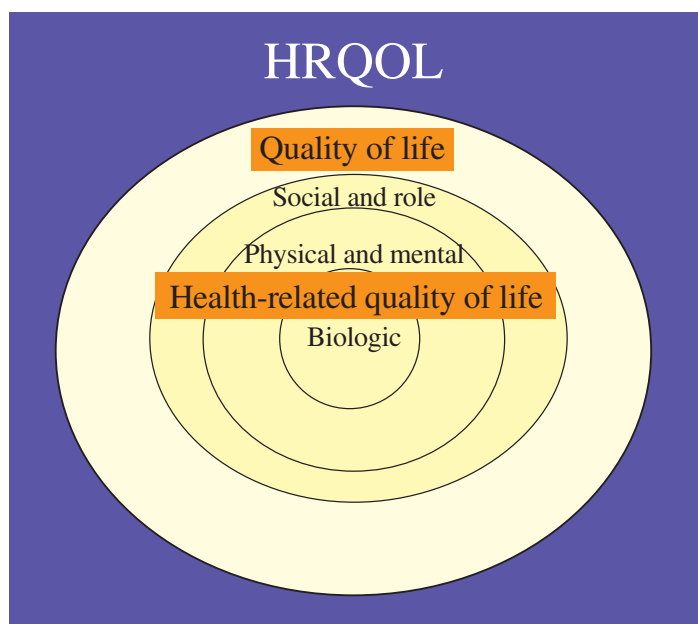


Figure 1. Health-related quality of life (HRQOL) is measured in the context of both health and illness. (Source: Ware and Dewey.²)

ry and mental component summary scores. In comparison, the most commonly used disease-specific instrument in SSc is the Health Assessment Questionnaire-Disability Index (HAQ-DI)—a self-administered 20-question instrument that assesses a patient’s level of functional ability and includes questions of fine movements of the upper extremity, locomotor activities of the lower extremity, and activities that involve both upper and lower extremities.⁷ The HAQ-DI score is determined by summing the highest item score in each of the eight domains and dividing the sum by 8, yielding a score ranging from 0 (no disability) to 3 (severe disability).

Health value/preference/utility measures, in contrast, assess the *value* or *desirability* of a state of health against an external metric,⁸ are generic HRQOL measures, and summarize HRQOL in a single number. Health utilities can be determined either directly via face-to-face interview with a subject or indirectly based on

IN PAH, TAKE AIM AT ET-1 THROUGH ET_A SELECTIVITY

Circulating levels of ET-1, the most potent subtype of ET, have been associated with disease severity in PAH.¹ The deleterious effects of elevated ET-1 include cellular proliferation, vasoconstriction, and vascular remodeling.²⁻⁴

In pulmonary arterial hypertension (PAH), endothelin (ET-1) exerts its cardiovascular effects through 2 receptors: ET_A and ET_B. When ET-1 activates the ET_A receptor on the vascular smooth muscle, it leads to vasoconstriction and vascular remodeling.^{4,5} Endothelial ET_B receptors mediate the release of vasodilating nitric oxide (NO) and prostacyclin (PGI₂), while inhibiting and clearing ET-1 from circulation.^{5,6} Blockade of ET_B receptors may significantly impair the balance of endothelium-derived vasodilating substances.^{4,7}

Endothelial dysfunction has been shown to improve with selective ET_A blockade.⁸ Hence, preemptive targeting of ET-1 through selective ET_A receptor antagonism can slow the progression of PAH, and may even provide better overall outcomes.^{2,4,8}

TARGETED ET-1 TREATMENTS MAY PROVIDE BETTER OUTCOMES

Imbalances in the key endothelial cell-derived mediators NO, PGI₂, and specifically ET-1 are thought to be central to the pathogenesis of PAH.⁹ NO and PGI₂ are potent vasodilators with antiproliferative activity.¹⁰ ET-1 is a potent vasoconstrictor with proliferative activity.⁵ Chronically elevated levels of ET-1 are associated with pulmonary vascular resistance, excessive scar formation and cardiac remodeling, cellular proliferation, and cardiac hypertrophy.^{1,11-13}

A reduction of excess ET-1 levels may result in positive outcomes for patients with PAH. It has been shown that in patients with congestive heart failure, elevated ET-1 plasma

Figure 1: ET_A receptor pathway

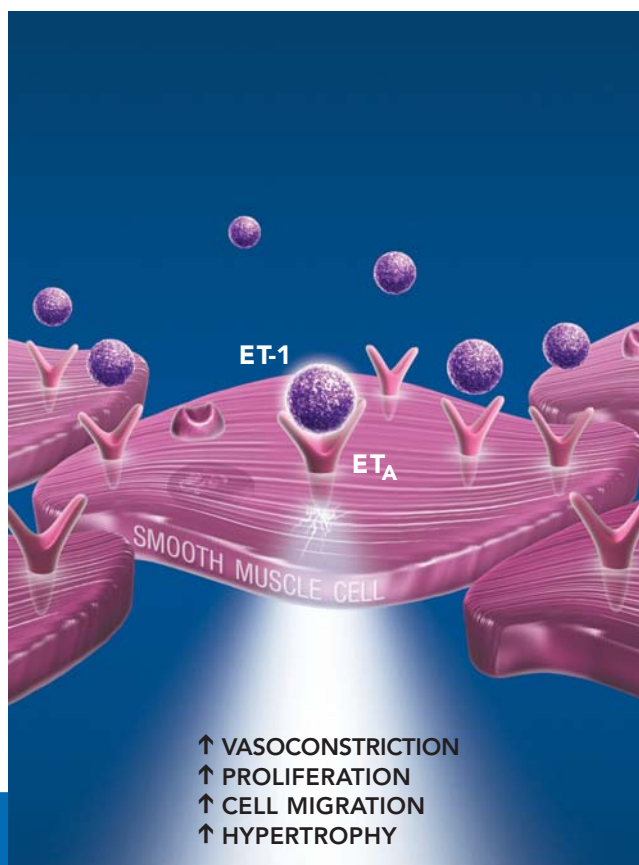
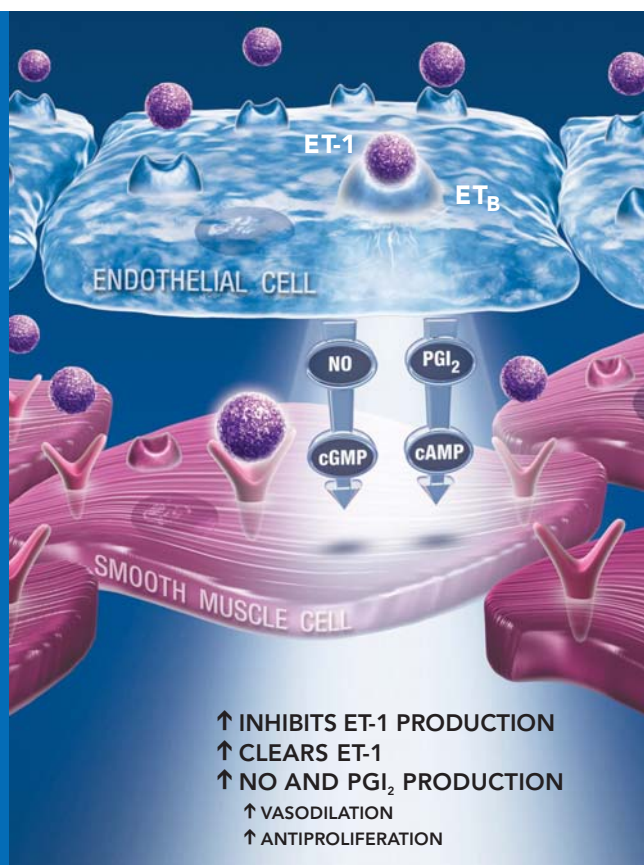


Figure 2: ET_B receptor pathway



levels are at least partly associated with impaired ET_B receptor-mediated clearance.¹³ Furthermore, the long-term administration of a selective ET_B receptor antagonist was found to have unfavorable effects on vascular remodeling.⁴ This is in sharp contrast to the benefits of selective ET_A antagonism.¹⁴

THE DIFFERENCE LIES IN ET_A SELECTIVITY

Vasoconstriction, cellular proliferation, and vascular remodeling are the hallmarks of PAH.¹² Studies have demonstrated that selective ET_A antagonists play a pivotal role in the regulation of ET-1 levels in PAH and have been beneficial for vascular remodeling.^{4,7,13}

ET-1 AND RECEPTOR-MEDIATED ACTIVITIES

Highly selective ET_A blockade maintains ET-1 clearance, NO and PGI₂ levels, and reduces or maintains circulating ET-1 levels, resulting in vasodilation, increased blood flow, and repair of remodeled vasculature compared to less selective agents.^{5-7,14} (See Figures 1,2)

HOW SELECTIVE TO ET_A SHOULD TREATMENT BE?

The more selective, the better. One should always be aware of the varying degrees of selectivity, as they equate to differences in blockade of the ET_A and ET_B receptors and resulting levels of ET-1.^{8,15,16} Figure 3 illustrates the difference between a less selective agent and highly selective agents. These in vitro selectivity ratios demonstrate the stark differences in ET_A selectivity. Figure 4 depicts how agents with low selectivity of the ET_A receptor (<2400) increase ET-1 levels whereas highly selective ET_A receptor (>2400) antagonists have been shown to

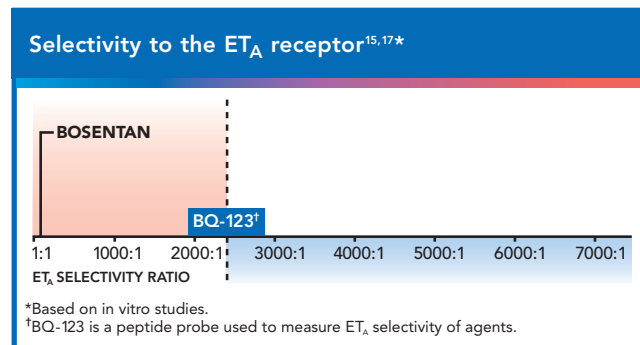


Figure 3

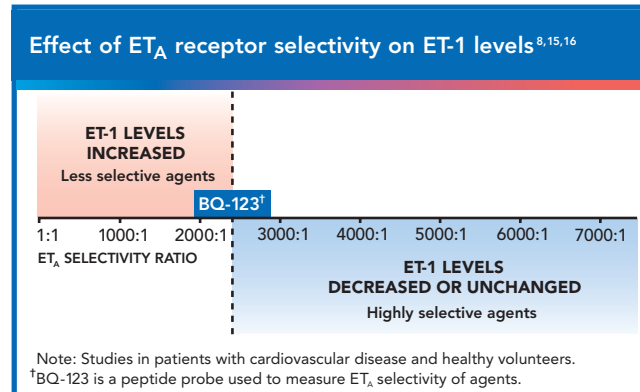


Figure 4

decrease ET-1 levels or leave them unchanged.^{6,8,15} The benefits of ET_A selectivity are being recognized.

TOWARD BETTER OUTCOMES IN PAH

Currently, there are no highly selective ET_A antagonists available for the treatment of PAH. In vivo studies have shown that highly selective ET_A antagonism may lead to better overall outcomes.^{7,8,12}

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Table 1. Health Status and Health Utility Measures

	Uses	Advantages	Disadvantages
Generic Health Status Measures (eg, SF-36)	Informing and monitoring outcomes in clinical encounters	Can be used across diseases and populations	May not be as sensitive to change compared to disease-specific measure in disease symptoms
	Monitoring population health	Allows comparison across diseases, levels of health, and age ranges on the same metric	
	Estimating the burden of different conditions	Can be self-administered	Does not provide a single health-related quality-of-life (HRQOL) number
	As end points in clinical trials ⁵	Provides detailed information about different domains	
		Can detect unexpected side-effects	
Disease-Specific Health Status Measures (eg, HAQ-DI)		More sensitive to smaller differences and smaller changes over time	Applicable only to certain diseases or conditions
		More face validity to the population under study	
		Can be self-administered	
Health Utility Measures (eg, time tradeoff)	As global HRQOL measures in clinical trials ⁵	Provides a single HRQOL number	May not be as sensitive to change in disease symptoms
	Guiding decision-making under uncertainty or resource constraints ^{5,43}		Requires face-to-face interview (except for indirect utility measures)
	Serving as “quality-adjustment factors” for calculating quality-adjusted life years (QALYs) in decision and cost-effectiveness analyses		Concepts may be difficult to comprehend for some subjects
	Aiding in individual-level decision-making regarding testing, treatment, and procedures so that decisions are made from the perspective of the patient’s own value system ^{36,37}		May depend on patient’s attitude toward money, risk, or time

Adapted from King et al.⁴²

an individual’s responses to a health status questionnaire (eg, the SF-6D that can be assessed from the SF-36), with face-to-face computer-assisted administration being the state of the art. There are two major families of utilities: direct and indirect (or multiattribute).

Direct Health Utilities

The most common health utilities are the standard gamble, the time tradeoff, and the rating scale.⁹⁻¹¹ The standard gamble determines the risk of (usually) death that one would be willing to take to improve a state of health. The time tradeoff technique asks how many months or years of life one would be willing to give up in exchange for a better health state. Scores on the standard gamble and time tradeoff can range from 0.0 to 1.0, where 0.0 usually rep-

resents death and 1.0 excellent or perfect health. The rating scale, perhaps the simplest of the three (although not a true measure of utility in a strict sense because it doesn’t involve comparison against an external metric, such as risk or time), asks subjects to rate their health on a scale, eg, from 0 to 100, where 0 usually represents death and 100 perfect health. Another utility measure commonly used by health economists is the willingness to pay.¹² Willingness to pay measures the value of an improvement in health or a decrease in health risk by the maximum amount of money a person would willingly exchange for it. Willingness to pay depends on ability to pay, including an individual’s wealth and competing demands for the resources.

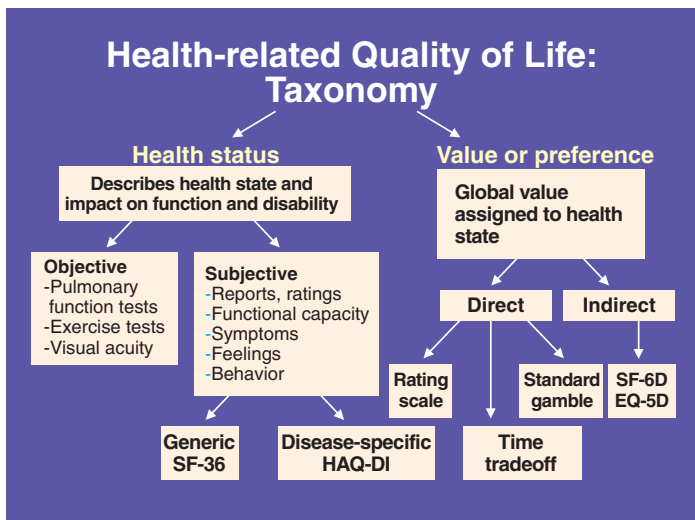


Figure 2. Two approaches to measuring health-related quality of life: health status and health value or preference. (Source: Tsevat et al.⁵)

Indirect Health Utilities

Indirect health utilities use a utility scoring system to provide utility scores for a particular health state from the health status instruments. Because of their ease of administration (self-administered), these indirect measures can be used in national epidemiological mail-in questionnaires and are commonly used as the source of quality weightings in economic evaluations. Two measures, the EuroQoL (EQ-5D) and the SF-6D, have been used based on their ease and inclusion of domains applicable to arthritides.¹³ The EQ-5D has five domains: mobility, usual activities, self-care, pain, and anxiety, with three levels of function for each domain.¹⁴ The score range is from -0.59 to 1.00, with -0.59 (worse than death) to 1.0 (perfect health). In rheumatoid arthritis, the EQ-5D has been found to be reliable and valid.¹³ Normative data are available for the US population to make valid comparisons.¹⁵ The SF-6D¹⁶ derives preference-based scores from the SF-36. The SF-6D revised the SF-36 into a six-dimensional health state classifications system: physical function, role limitation, social function, pain, mental health, and vitality. The boundaries of the SF-6D utility scores are from 0.30 to 1.00 with a score of 1.00 indicative of perfect or full health. Some of the other commonly used indirect utilities include the Quality of Well Being Scale and the Health Utilities Index (reviewed in Kopeck and Willison¹⁷).

Both generic (health status and health utility) and disease-specific measures complement each other and both should be incorporated in clinical trials as measures of HRQOL. **Table 1** summarizes the clinical use, advantages, and disadvantages of generic versus disease-specific measures.

Minimally Important Differences

An important advance in HRQOL research is the concept of minimally important differences, defined as the smallest difference in score of an HRQOL (or measure of interest) instrument that patients perceive as beneficial and that would mandate, in the absence of troublesome side-effects and excessive cost, a change in the patient's management.¹⁸ For example, an average change

of 0.15 points on the HAQ-DI may be statistically significant for a new treatment in a clinic trial, but may not be perceived as beneficial by the subjects. Thus, differences in scores smaller than the minimally important differences are considered unimportant, regardless of whether statistical significance is reached. Minimally important difference estimates of HRQOL measures have propelled new drug development in different arthritides and successful design of controlled studies to improve HRQOL.¹⁹ An improvement of 0.22 or greater in the HAQ-DI in rheumatoid arthritis^{20,21} and improvements of 2.5 to 5.0 in SF-36 summary scores and 5.0 to 10.0 points in SF-36 individual domain scores represent minimally important differences in various arthritides.²¹⁻²³ For the indirect health utilities, an improvement of 0.01 to 0.10 represents minimally important differences.²⁴ In the next section, the above-mentioned concepts will be illustrated using published data in patients with SSc. Where published data in SSc are currently unavailable, data from other arthritides were used.

Applicability of HRQOL Instruments

Estimate Burdens of Different Diseases

The HRQOL instruments can be used to assess impact of different diseases on HRQOL. An example is the Scleroderma Lung Study—a double blind, placebo-controlled, multicenter, randomized clinical trial evaluating the safety and efficacy of oral cyclophosphamide versus placebo for rapidly progressive active pulmonary alveolitis associated with SSc.²⁵ The study was for 1 year with an additional year of follow-up without any treatment. The mean SF-36 scores in each domain were compared to mean SF-36 scores for the published healthy US and chronic obstructive pulmonary disease (COPD) populations.²⁶ Patients with SSc reported impairment across multiple domains of functioning compared to the normal US population and similar impairment to that reported by patients with COPD (**Figure 3**).²⁷ This information is vital; it helps researchers compare the impact of scleroderma lung disease to a much more common lung disease, COPD. This information can also help researchers argue funding for a disease that has achieved very little attention.

Use as an End Point in Clinical Trials

The first step in the incorporation of HRQOL in clinical trials is to assess its responsiveness to change, ie, whether the HRQOL scores change in the right direction and are of greater magnitude when the underlying construct it is measuring changes compared to the no-change group. For example, for HAQ-DI to be a valuable HRQOL measure, it should improve (rather than worsen) when skin score and patient global score improve in patients with SSc. In addition, the improvement in the HAQ-DI scores should be greater in the improved group compared to the no-change group. The SF-36 and the HAQ-DI have been found to be responsive to change in a diffuse SSc clinical trial²⁸ and are included in different SSc clinical trials. In the Scleroderma Lung Study,²⁵ the course of forced vital capacity (FVC, the primary outcome) was significantly better in the cyclophosphamide group compared to the placebo group ($P < .05$). The change in three HRQOL measures—the Mahler's Dyspnea Index (a measure of breathlessness—the primary symptom of SSc lung disease), the SF-36, and

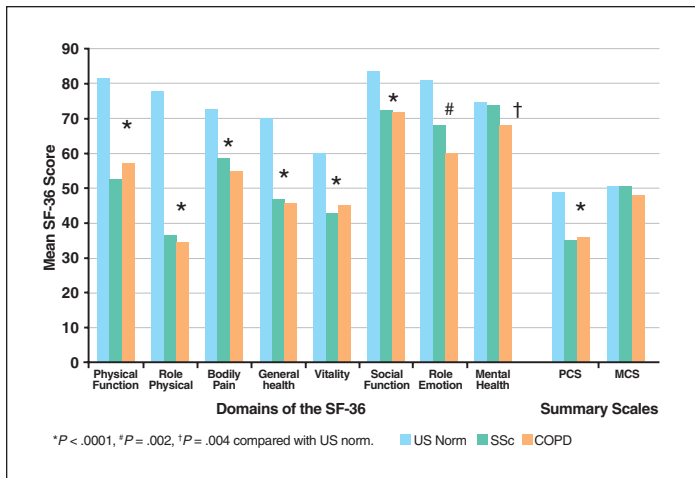


Figure 3. Comparison of health-related quality of life in the normal US population, in patients with systemic sclerosis and lung disease, and in patients with chronic obstructive pulmonary disease. (Source: Khanna et al.²⁷)

the HAQ-DI, all favored cyclophosphamide. Cyclophosphamide had a positive effect on physical functioning (as assessed by the HAQ-DI); vitality (assessed by the SF-36); and dyspnea (assessed by Mahler’s Transitional Dyspnea Index, or TDI) ($P < .05$ for all analyses). In addition the placebo-corrected differences between the response in the cyclophosphamide and the placebo groups were 0.16 for HAQ-DI, 7.99 for vitality (SF-26), and 2.9 units for TDI, which are near or greater than the minimally important difference scores for HAQ-DI (0.22 or greater in rheumatoid arthritis), for vitality (5 to 10 units), and for TDI (greater than 1 unit in lung diseases).²⁵ This study also confirms the previous observations that a disease-specific measure (HAQ-DI here) may be more sensitive to change than a generic measure (the SF-36 physical functioning domain did not differ between the two groups). Incorporation of HRQOL provided confidence in the results of this clinical trial; both objective and subjective measures favored cyclophosphamide.

Monitor Outcomes in Clinical Practice

HRQOL measures can be used in day-to-day practice. Extensive research in rheumatoid arthritis has shown that HAQ-DI is the most powerful predictor of mortality after adjusting for sociodemographic and clinical features.²⁹ In SSc, researchers have shown that an HAQ-DI score of 1.0 or greater at baseline correlates with morbidity and mortality (at 4 years)³⁰ in people with diffuse SSc (Figure 4). In the D-penicillamine study, an improvement in HAQ-DI was associated with an improvement in skin score (Figure 5), pulmonary function tests (%FVC and %DLCO predicted), and acute-phase reactants.³⁰

Special Note on Health Utilities

Data on health utility measures are sparse in SSc. In a recent study assessing health utilities in 107 patients with SSc, our group³¹ found that the median (25th to 75th percentile) rating scale score was 62 (50, 80) indicating the patients rated their current health as 62.0% of perfect health. The median standard gamble score was 0.83 (0.63, 0.94), which indicates a willingness to accept up to a

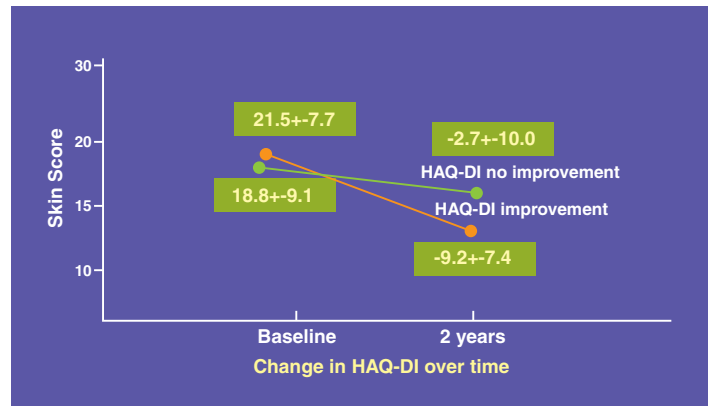


Figure 4. Improvement in Health Assessment Questionnaire-Disability Index (HAQ-DI) predicts improvement in skin score in a D-penicillamine trial. (Source: Clements et al.³⁰)

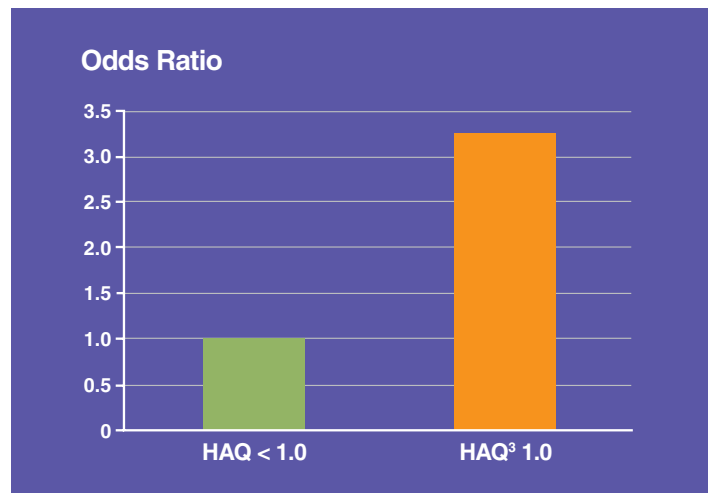


Figure 5. Baseline HAQ-DI predicts mortality at 4 years in diffuse systemic sclerosis in a D-penicillamine trial. (Source: Clements et al.³⁰)

17% risk of immediate death in exchange for perfect health. The median time tradeoff score was 0.88 (0.63, 0.94), indicating a willingness to give up a median of 12% of one’s life expectancy in exchange for perfect health. These data are similar to those seen in other arthritides.³²⁻³⁴ These scores serve as “quality-adjustment factors” for calculating quality-adjusted life-years (QALYs) in decision and cost-effectiveness analyses that are used in resource allocation. A QALY takes into account both quantity and the quality of life generated by healthcare interventions.³⁵ It is the arithmetic product of life expectancy and a measure of the quality of the remaining life-years. A QALY places a weight on time in different health states—a year of perfect health is worth 1 QALY, a year of less than perfect health life expectancy is worth less than 1 QALY, and death is considered equivalent to 0 QALY. Based on the data shown above, the QALY for one patient with SSc ranges from 0.62 for rating scale to 0.88 for time tradeoff.

On a more microscopic scale, one’s utilities may be used to help individual-level decision-making regarding testing, treatment, and procedures so that decisions are made from the perspective of the patient’s own value system. Because medical decision-making inherently involves consideration of multiple uncertain

(continues on page 11, under the fold)

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.

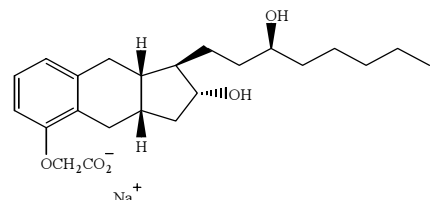
REMODULIN® (treprostinil sodium) Injection

BRIEF SUMMARY

The following is a brief summary of the full prescribing information on Remodulin (treprostinil sodium) Injection. Please refer 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-hydroxyethyl side chain (HU2) and subsequent additional oxidation (HU3) or dehydration (HU4). Based on the results of in vitro human cytochrome P450 studies, Remodulin does not inhibit CYP-1A2, C2C9, C2C19, 2D6, 2E1, or 3A. 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 AUC₀₋₁₂₀ 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, 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 prostanacyclin therapy, 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 Tracleer® (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%), Hypotension (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 patient's 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 interruption 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 ±6% 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.

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Rx only

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outcomes, this approach of valuing health states has been proposed to be particularly relevant in healthcare.^{36,37}

The indirect health utilities such as EQ-5D and SF-6D have not been assessed in SSc. SF-6D was assessed in a 12-month, randomized, controlled trial in patients with rheumatoid arthritis receiving a background methotrexate therapy for active disease.³⁸ The baseline SF-6D scores in the placebo and methotrexate group and the abatacept and methotrexate group were 0.55 and 0.56, respectively. The combination therapy of the abatacept and methotrexate led to an improvement of 0.05 in the SF-6D compared to no change in the placebo group, a difference that is both statistically significant and greater than the published minimally important difference estimate for the SF-6D (0.041).²⁴ This can be interpreted as treatment of 100 patients with rheumatoid arthritis with abatacept and methotrexate will result in a gain of 0.05 x 100 = 5 QALY, in other words, 5 more patients per 100 treated will be in perfect health for one year compared to the patients receiving methotrexate.³⁸ From a societal perspective, \$50,000/QALY gained has become a de facto standard (although some have upped it to \$100,000/QALY). The historical standard used for setting this threshold has been hemodialysis for chronic renal failure. The abatacept example signifies that a cost of approximately \$2,500 to \$5,000 per year for each patient treated with abatacept (5 QALY x \$50,000 to \$100,000/100 patients with rheumatoid arthritis = \$2,500 to \$5,000) will be cost-effective.

Apart from their use in clinical trials and health policy, health utilities can be used in clinical encounters.⁵ Consider a 50-year-old woman with recently diagnosed diffuse SSc, active alveolitis, and worsening shortness of breath. She is given a treatment choice of undergoing stem cell transplantation versus intravenous pulse cyclophosphamide, both of which may offer her similar chances of survival. She wants to be involved actively in decision-making and reviews the short- and long-term effects of each option on her other aspects of health. A standard gamble question might give more insight on her attitude toward risky treatments, and reflection on a time tradeoff question might uncover her attitude regarding quality versus length of life. Incorporating her preference for either treatment would also enhance the acceptability of patient care guidelines. In this case scenario the patient may realize, using her “internal” values, that she is risk-averse and does not want to take a 5% to 10% mortality risk during the stem cell transplantation. With this in mind, it is easier for her physician to make a decision that incorporates the patient’s preference.

Minimally Important Differences in Scleroderma

Our group recently assessed the minimally important differences for modified Rodnan Skin Score and HAQ-DI in a D-penicillamine clinical trial.³⁹ At 6, 12, 18, and 24 months, the investigator was asked to rate the change in the patient’s health since entering the study: *markedly worsened*, *moderately worsened*, *slightly worsened*, *unchanged*, *slightly improved*, *moderately improved*, or *markedly improved*. Patients who were rated as *slightly improved* were defined as the minimally changed subgroup. The minimally important difference estimates for the skin score improvement ranged from 3.2 to 5.3 and for the HAQ-DI from 0.10 to 0.14. A word of caution must be added—the minimally important differ-

Table 2. Items Proposed for Quality of Life by Members of the Scleroderma Clinical Trial Consortium in a Recent Delphi Exercise

Type or Measure	Have Met OMERACT Filters in Systemic Sclerosis
Health Status	
Scleroderma Health Assessment Questionnaire	No
Health Assessment Questionnaire-Disability Index	Yes
Visual Analog Scale Pain Scale from HAQ	No
SF-12	Yes
SF-36	Yes
UK Hand Function Questionnaire	No
Arthritis Impact Measurement Scale-2	No
ACR Functional Status	No
WHO Functional Status	Yes
Self-administered scleroderma questionnaire (SYSQ)	No
Health Utilities (Indirect)	
SF-6D	No
EuroQol (EQ-5D)	No
Health Utility Index (HUI)	No
Quality of Well Being	No
Health Utilities (Direct)	
Time trade-off	No
Standard gamble	No
Rating scale	No
Quality adjusted life year (QALY)	No
Sexual Function	
Female Sexual Function Inventory	No
Measure of erectile dysfunction, loss of libido	No
Fatigue	
Functional Assessment of Chronic Illness Therapy-Fatigue Questionnaire	No
Psychosocial	
Psychological Adjustment to Illness Scale (PAIS)	No
Appearance-related issues—disease-related changes and perceptions of changes	No
Disease-related coping	No
Multidimensional Health Locus of Control scales	No
Positive and Negative Affect Scale	No
Sense of Coherence Scale	No
McGill Pain Questionnaire	No
Multidimensional Scale of Social Support	No
Beck’s Depression Inventory	No
Center for Epidemiologic Studies Depression Scale	No
Satisfaction with Life Scale	No
Satisfaction with Appearance Scale	No

* Yes indicates that the item is feasible, reliable, valid, and sensitive to change in SSc. No indicates that the instrument is not ready to be used in clinical trials as an outcome measure; it may be incorporated for exploratory purposes; more information is needed on the feasibility, reliability, validity, and/or sensitivity to change.

ences were assessed using investigators' rather than patients' assessment of their health (they were not assessed in the clinical trial); the HAQ-DI parameters should be considered preliminary before these are confirmed in other studies.

Scleroderma Clinical Trials Consortium: Current Work

Table 2 provides a summary of the first phase of a recent Delphi exercise involving members of the Scleroderma Clinical Trials Consortium. Among other things, the members were asked to provide a listing of quality-of-life measure(s) that could be used in the development of scleroderma response criteria; 52 researchers provided more than 30 unique items. These are summarized according to different domains and whether they meet the OMERACT filters of truth, discrimination, and feasibility.⁴⁰

Conclusion

This review attempts to provide a comprehensive overview of HRQOL with a focus on SSc. HRQOL is considered an important outcome in arthritis clinical trials and the Food and Drug Administration (FDA) requires a sustained improvement in the HRQOL scores to file for an "improvement in HRQOL" claim. The FDA acknowledges: "not enough information is available on the performance of general HRQOL measures in longer term arthritis trials (and) the incorporation of such measures in planned trials is encouraged."⁴¹ Secondary analyses from ongoing and recently completed SSc trials will provide much information on reliability, validity, and responsiveness to change of HRQOL measures. The members of the consortium have shown a very strong commitment to further the field of scleroderma research and clinical trials.

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Pulmonary Arterial Hypertension in Systemic Sclerosis: Risk Factors and Diagnosis

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Introduction

Over the past 25 years there has been an overall improvement in survival as well as a shift in the causes of death in systemic sclerosis (SSc) (**Figure 1**).¹ Prior to the advent of ACE inhibitors, renal crisis accounted for 25% of SSc-related deaths. Renal crisis, now, accounts for only 7% to 10% and pulmonary fibrosis and pulmonary arterial hypertension are the primary causes of SSc-related deaths. More than half of all SSc-related deaths are now from lung disease: 27% from pulmonary arterial hypertension and 25% from pulmonary fibrosis. Thus the lung is the major focus of interest in the diagnosis and management of SSc.

Pulmonary arterial hypertension, resulting from pulmonary vascular disease, is one of the most deadly complications in all of rheumatology. Until recently, there was a 50% 2-year survival and it was almost uniformly fatal within 5 years for patients with severe pulmonary hypertension with right heart failure.² Fortunately, earlier diagnosis, coupled with a number of new drugs for pulmonary arterial hypertension, is changing the treatment and long-term outcome of this serious problem. It is critical that there is prompt diagnosis, referral, and treatment before end stage heart failure occurs. As in renal crisis, early intervention is our best chance to change the course of this deadly complication. This paper will discuss several risk factors and the ways of identifying patients who are likely to have or develop pulmonary arterial hypertension.

Historical Review of Pulmonary Arterial Hypertension in SSc

The initial description of pulmonary arterial hypertension as a specific entity in limited cutaneous SSc was made by Salerni et al in the 1970s.³ These patients had long-standing limited cutaneous SSc, no or minimal interstitial lung disease and a very bad prognosis. Later, a larger group of SSc patients with isolated pulmonary hypertension, also from Pittsburgh, was reported by Stupi et al.⁴ They also were patients with long-standing limited disease, with little to no parenchymal lung disease, and frequently had anti-centromere antibody. Their forced vital capacity (FVC) was usually normal (mean 85% predicted) and there was only minimal evidence of interstitial lung disease present on radiography. The most striking finding in this group of patients was that they uniformly had a marked decrease in the diffusing capacity of the lung for carbon monoxide (DLCO), a mean of 39% predicted, at the time of diagnosis of pulmonary arterial hypertension. All of the 20

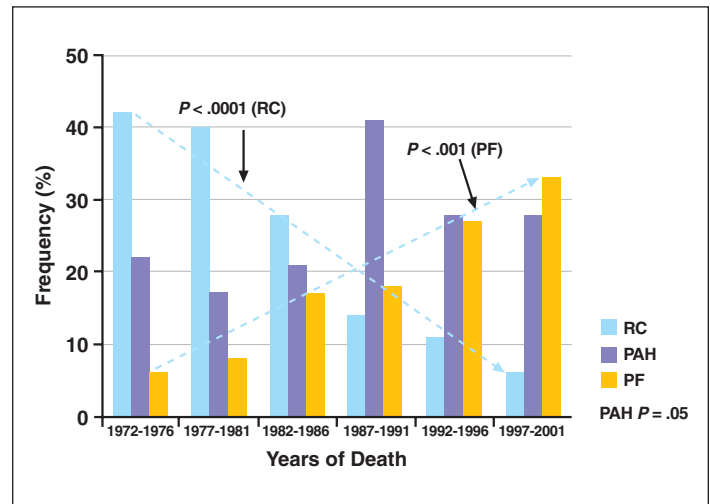


Figure 1. Changes in causes of systemic sclerosis-related deaths over time. PAH = pulmonary arterial hypertension, PF = pulmonary fibrosis, RC = renal crisis.

patients who underwent cardiac catheterization had elevated pulmonary arterial pressures (mean pulmonary artery pressure of 50 mmHg). They had a 2-year 50% survival; autopsies showed that there indeed was severe vasculopathy similar to that of idiopathic pulmonary arterial hypertension,⁵ in the absence of significant interstitial disease.

Another large series of SSc-pulmonary hypertension patients from the Pittsburgh Scleroderma database was evaluated and matched to SSc controls from the database with similar demographic features including race, sex, scleroderma subtype (limited, diffuse), and disease duration at the time of first visit.² The 106 cases were similar to the earlier described patients in that they had long-standing Raynaud phenomenon (for a mean 14.7 years at time of diagnosis of pulmonary hypertension) and severe pulmonary hypertension, with a mean pulmonary arterial pressure of 80 mmHg. The FVC was 80% of predicted at the time of diagnosis, both in the pulmonary arterial hypertension cases and the matched controls. However, at the time of diagnosis the DLCO was 40% of predicted in the cases as compared with 80% in the controls. Five years prior to the diagnosis of pulmonary hypertension, the DLCO in the cases was 52% of predicted, compared with 81% in controls.

There was a subgroup of patients who had serial pulmonary function tests during each of four 5-year periods prior to and at the

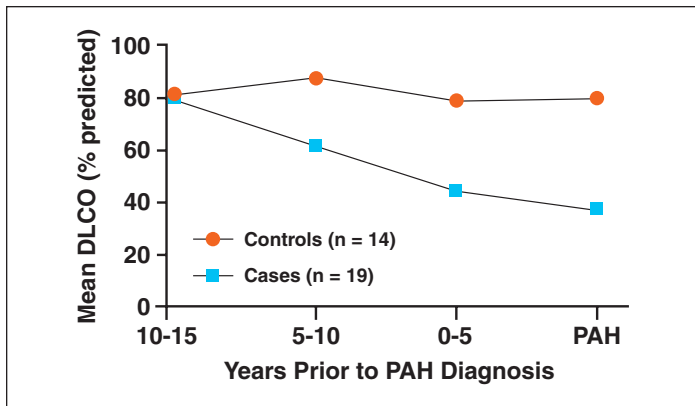


Figure 2. Change in diffusing capacity of the lung for carbon monoxide (DLCO) in pulmonary arterial hypertension (PAH) cases and controls over 15 years prior to diagnosis of PAH.

time of the diagnosis of pulmonary hypertension (**Figure 2**). Both the cases and the controls had a DLCO of 80% of predicted at the onset of that 10-to-15-year period. The controls had no change in their diffusing capacity during the 15 years, remaining around 80% of predicted. However, the cases had an almost linear decrease in the DLCO over the 15-year period, beginning at 80% and decreasing to 40% at the time of diagnosis of pulmonary arterial hypertension. Thus the development of this vasculopathy clearly began early in the course of limited SSc but, like other aspects of limited SSc, it took a long time to become severe enough to cause significant end organ damage (right heart failure and death in this case). The FVC%/ DLCO% ratio was very high in these patients, usually greater than 1.6, which led to this ratio being a good marker and predictor of future pulmonary arterial hypertension.

Defining Pulmonary Arterial Hypertension

Right heart catheterization, and not echocardiography, is the “gold standard” procedure for determining pulmonary arterial hypertension, be it primary or secondary. The diagnosis rests on finding a mean pulmonary arterial pressure (PAP) of 25 mmHg or greater at rest with a wedge pressure of less than 16 mmHg. To be certain that the elevated PAP or pulmonary arterial systolic pressure (PASP) is really from pulmonary arterial hypertension, it is important to rule out cardiac disease (left ventricular disease, especially) that might spill over into the pulmonary circulation and right ventricle. In SSc the left ventricular involvement is frequently subclinical and becomes manifest only when the heart is stressed (ie, during exercise).

Pathology of Pulmonary Arterial Hypertension

Blood vessels of SSc patients who die of pulmonary arterial show severe intimal proliferation and luminal occlusion.^{5,6} These changes are similar to those seen in idiopathic pulmonary arterial hypertension and to the vascular changes seen in the digital and renal arteries in SSc (**Figure 3**). Autopsy studies also showed that the SSc patients who died of causes other than pulmonary arterial hypertension had very abnormal pulmonary arteries. Morphometric studies have shown that the degree of arterial narrowing and luminal occlusion correlates with the disease dura-

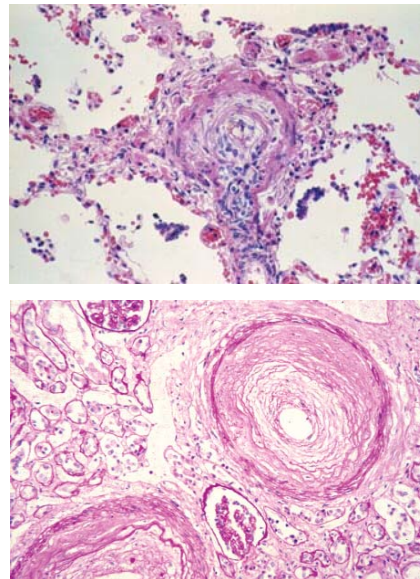


Figure 3. Intimal proliferation and luminal occlusion in systemic sclerosis with pulmonary arterial hypertension. Upper panel: pulmonary artery. Lower panel: renal artery.

tion.⁵ Thus, pulmonary vasculopathy develops early and progresses over a long time before the patient develops pulmonary arterial hypertension, as shown both by anatomic and physiologic data.

Types of Lung Disease in SSc

Basically there are three types of lung disease in SSc: 1) interstitial lung disease, 2) pulmonary vascular disease (culminating in pulmonary arterial hypertension), and 3) a combination of both (mixed ILD-PAH). Chang and Wigley looked at 600 patients with SSc who had simultaneous pulmonary function tests and echocardiography (**Figure 4**).⁷ A majority of these patients either had normal studies (40%) or only pulmonary fibrosis (23%) or pulmonary hypertension (19%). However, 18% had both pulmonary hypertension and pulmonary fibrosis. This latter group is likely to include two different subsets of patients: One group likely includes patients with severe parenchymal lung disease (with or without anti-topoisomerase antibody) who have chronic hypoxia from parenchymal destruction and who then develop secondary pulmonary arterial hypertension. The second group includes patient with some degree of interstitial lung disease but who develop severe pulmonary hypertension out of proportion to the degree of fibrosis.

The group with severe pulmonary fibrosis, unlike the isolated pulmonary arterial hypertension patients, usually has a FVC/DLCO ratio that is close to 1.0 because as the FVC decreases the DLCO decreases to a similar degree. In the group with severe pulmonary arterial hypertension, but no or mild fibrosis, the FVC/DLCO ratio is typically greater than 1.6. In the group with mixed ILD-PAH, the FVC may be moderately decreased (approximately 60% of predicted) but the DLCO will still be much lower (approximately 30% of predicted). The ratio then is greater than 1.6, also similar to that seen in the vasculopathy patients. In this mixed group the fibrosis usually occurs early. Once the fibrosis has stabilized (FVC remains stable), the DLCO may continue to decrease. In that case the patient’s dyspnea may be the result of acute, severe pulmonary arterial hypertension with

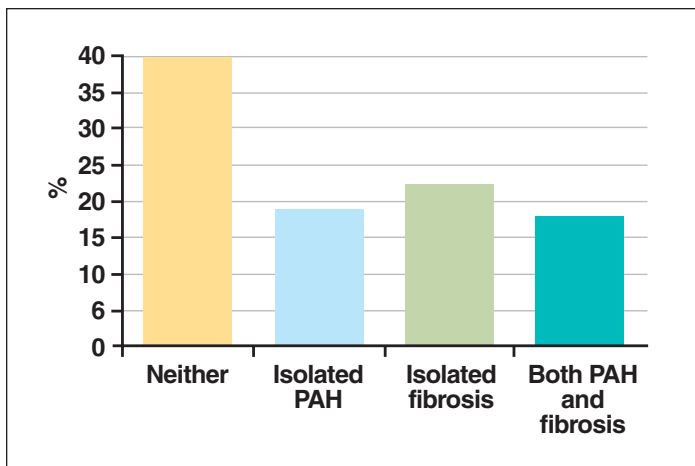


Figure 4. Frequency of pulmonary arterial hypertension (PAH) and pulmonary fibrosis in patients (n = 619) with scleroderma. Adapted from Chang et al.⁷

or without right heart failure, rather than from worsening interstitial disease.

Frequency and Course of Pulmonary Arterial Hypertension in SSc

Many cross-sectional studies have looked at the frequency of elevated right ventricular systolic pressure (RVSP), as an estimate of PASP, in various groups of SSc patients.⁸⁻¹² Depending on the subset of patients and the definition of an elevated RVSP, the frequency ranges from 10% to 40% of predicted. Generally, it is felt that 20% to 30% of unselected SSc patients may have an elevation in the RVSP on echocardiography. This, however, does not mean that all of these patients have, or will develop, severe progressive pulmonary arterial hypertension, as assessed by right heart catheterization.

Two recent longitudinal studies have looked at serial echocardiograms in SSc patients.^{9,13} In the Macgregor et al study⁹ about 62% of patients with mild or moderately increased RVSP (30 to 60 mmHg) continued to have mild to moderately elevated RVSP at 2- to 3-year follow-up. Similarly, in the Chang et al¹³ study, 65% of these patients continued to have mild to moderately elevated RVSP (36 to 55 mmHg) at 2 years without going on to severe pulmonary arterial hypertension. In both Chang's and Macgregor's study about 20% of patients developed severe pulmonary arterial hypertension, many of whom died, over 3.2 years. Both studies suggested that the increases in RVSP were usually abrupt and rapid when they did occur. It appears that while the DLCO decreases gradually over a long period, the elevations in pulmonary pressures occur more acutely. Of the patients who developed and died of pulmonary arterial hypertension, many had a normal or near normal RVSP within 6 to 12 months prior to developing severe pulmonary arterial hypertension.

Autoantibodies

Another way to look at lung disease in scleroderma is to focus on the autoantibodies. We grouped our lung disease patients (interstitial lung disease and pulmonary arterial hypertension) by their antibodies: anticentromere, antinucleolar, and antitopoisomerase

Table 1. Patients with Pulmonary Hypertension by Autoantibody Subsets

Feature	ACA (n = 68)	AnoA (n = 48)	A-SCL-70 (n = 53)
C X-ray (fibrosis)	32%	53%	100%
FVC%/DLCO%	81 / 40	73 / 41	53 / 50
FVC/DLCO ratio	2.0	1.8	1.1
Mean PSAP mmHg) by right heart catheterization/echocardiography	75	74	55

ACA = anticentromere, AnoA = antinucleolar antibody, A-SCL-70 = anti SCL-70 antibody (antitopoisomerase). Adapted from Steen.¹⁵

(anti-SCL-70) antibodies (Table 1).^{14,15} The patients with a nucleolar pattern on routine antinuclear antibody testing were often positive for Th/To, PM-Scl, or anti-U3-RNP antibody but not for antitopoisomerase or antiRNA polymerase III antibodies. The degree of fibrosis was least in the anticentromere patients and was worst for antitopoisomerase. The nucleolar antibody patients were somewhere in between.

The ratio of the FVC/DLCO helps to identify the groups with predominantly a vasculopathy, which causes the most severe pulmonary hypertension. In our study, patients with anticentromere had FVC%/DLCO% ratios greater than 1.6 and had a high PASP of approximately 70 to 75 mmHg.¹⁴ However, the FVC%/DLCO% ratio in the topoisomerase patients with pulmonary arterial hypertension had a ratio very close to 1 and their pulmonary hypertension was less severe (mean PASP of only approximately 55 mmHg). Patients with an antinucleolar pattern had an FVC%/DLCO% ratio of greater than 1.6 and severe pulmonary arterial hypertension with a PASP of 74 mmHg.

Antinucleolar antibodies include three unique and different antibodies, whose assays unfortunately are not commercially available. One is U3 RNP antibody, which is associated with diffuse scleroderma, interstitial lung disease, and pulmonary arterial hypertension and is commonly seen in African-Americans. Another nucleolar antibody, anti-Th/To antibody, occurs in patients who are usually white and have limited scleroderma, but they also have both interstitial fibrosis and pulmonary arterial hypertension. It is unusual for anti-PM-SCL antibody-positive patients to develop significant interstitial lung disease or pulmonary arterial hypertension. Overall the nucleolar antibody pattern is likely to be an important marker for the combination of interstitial lung disease and pulmonary arterial hypertension.

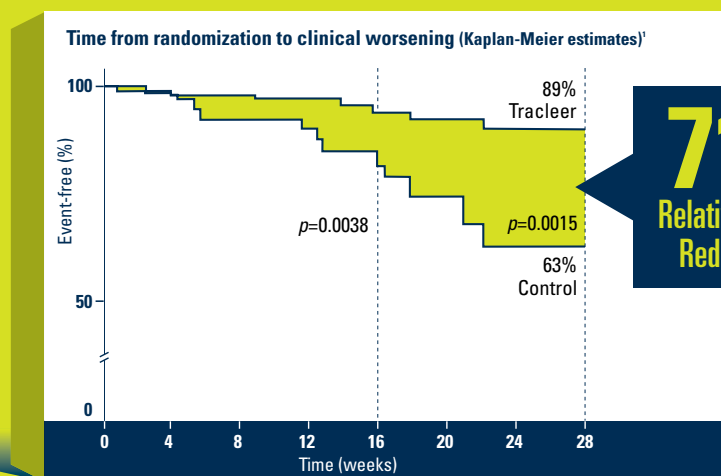
How to Diagnose Pulmonary Arterial Hypertension Symptoms

We cannot depend on or wait for patients to complain of symptoms. SSc patients often have difficulty in determining the degree of or the change in the amount of shortness of breath that they

In pulmonary arterial hypertension (PAH) WHO Class III or IV secondary to scleroderma, identify and treat early.



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Requires attention to two significant concerns: Potential for serious liver injury (including very rare cases of unexplained hepatic cirrhosis after prolonged treatment)—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.

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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). In the post-marketing period, in the setting of close monitoring, rare cases of unexplained hepatic cirrhosis were reported after prolonged (> 12 months) therapy with TRACLEER® in patients with multiple co-morbidities and drug therapies. There have also been rare reports of liver failure. The contribution of TRACLEER® in these cases could not be excluded.

In at least one case the initial presentation (after > 20 months of treatment) included pronounced elevations in aminotransferases and bilirubin levels accompanied by non-specific symptoms, all of which resolved slowly over time after discontinuation of TRACLEER®. This case reinforces the importance of strict adherence to the monthly monitoring schedule for the duration of treatment and the treatment algorithm, which includes stopping TRACLEER® with a rise of aminotransferases accompanied by signs or symptoms of liver dysfunction. (see DOSAGE AND ADMINISTRATION).

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 $\geq 2 \times$ 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, transdermal, 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). Therefore, effective contraception through additional forms of contraception must be practiced. Monthly pregnancy tests should be obtained.

Because of potential liver injury and in an effort to make the chance of fetal exposure to TRACLEER® (bosentan) as small as possible, TRACLEER® may be prescribed only through 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 (WHO Group I) 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 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 3x 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 ($\geq 3 \times$ 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 $\geq 2 \times$ 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 will likely 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:** Co-administration of bosentan and the oral hormonal contraceptive Ortho-Novum® produced decreases of norethindrone and ethinyl estradiol levels by as much as 56% and 66%, respectively, in individual subjects. Therefore, hormonal contraceptives, including oral, injectable, transdermal, and implantable forms, may not be reliable when TRACLEER® is co-administered. Women should practice additional methods of contraception and 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 3–4-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, 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.

Sildenafil: In healthy subjects, co-administration of multiple doses of 125 mg b.i.d. bosentan and 80 mg t.i.d. sildenafil resulted in a reduction of sildenafil plasma concentrations by 63% and increased bosentan plasma concentrations by 50%. A dose adjustment of neither drug is necessary. This recommendation holds true when sildenafil is used for the treatment of pulmonary arterial hypertension or erectile dysfunction.

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 of 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 (1% 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%). Post-marketing experience: hypersensitivity, rash, angiodema.

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.

OVERDOSAGE: 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 overdosage with bosentan beyond the doses described above. Massive overdosage 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 re-introduction 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 $\geq 2 \times$ 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: See CONTRAINDICATIONS and Drug Interactions. **Dosage Adjustment in Renally Impaired Patients:** The effect of renal impairment on the pharmacokinetics of bosentan is small and does not require dosage 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 to guide 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].

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

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Mississauga, Ontario, CANADA

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South San Francisco, CA

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have. They develop breathing difficulties slowly and presume it is just part of their disease or their age or from deconditioning. They unconsciously limit their activities and do not readily recognize or acknowledge that they are short of breath or that their breathing is getting worse. Rather than just asking them if they are short of breath, specific questions, such as whether they can climb three flights of stairs, carry groceries, or walk up a hill without feeling out of breath should be asked. Patients also have a tendency to describe their breathing difficulties as fatigue or tiredness. It is important, therefore, to listen carefully to their symptoms, because fatigue may actually represent dyspnea with exercise.

It is also important to regularly document their degree of limitation so they can get timely treatment. Careful questioning, the scleroderma Health Assessment Questionnaire (especially the breathing visual analogue scale), a special dyspnea questionnaire (the University of California at San Diego test is easy and reliable), and the 6-minute walk test are useful for accurately quantifying the degree of symptoms that the patient has.¹⁶ The 6-minute walk test is easy to do and measures the greatest distance the patient can walk in 6 minutes. When done per protocol the test is very reproducible. The distance walked, the lowest oxygen saturation achieved during the walk, and the degree of dyspnea and fatigue at the end of the walk are measured on 10-point Likert scales. Although exercise-induced hypoxemia is not specific for pulmonary arterial hypertension, it clearly marks a patient who needs to be evaluated carefully for pulmonary hypertension, pulmonary fibrosis, or heart disease. Patients with exercise-induced hypoxemia need to be monitored to make sure that their routine exercise activity is not causing chronic hypoxia. The 6-minute walk test is also a good way to determine responses to therapy, especially for patients with pulmonary arterial hypertension.

Pulmonary Function Testing

Following serial pulmonary function tests can help identify patients at risk for pulmonary arterial hypertension. A severely decreased DLCO or a FVC%/DLCO% ratio greater than 1.6 are both associated with a high risk. All patients should have a pulmonary function test at the time of diagnosis of scleroderma. Any patient with limited cutaneous disease, more than 5 years of Raynaud's phenomenon and a low DLCO, may also be at risk for pulmonary arterial hypertension. It is important to identify at-risk patients, follow them closely, and clinch the diagnosis as early as possible so intervention can begin long before there is permanent heart damage. This is the wisest approach to turning pulmonary arterial hypertension into a treatable problem.

Resting Echocardiography

Two-dimensional echocardiography is a tool that can estimate the right ventricular systolic pressures (RVSP) as an estimate of PASP. In the case control study described above, the estimated RVSPs on echocardiography in pulmonary arterial hypertension patients and in controls were compared 4 years prior to the diagnosis of PAH.² The RVSP was only slightly higher in the patients, 34 mmHg, compared to controls, 29 mmHg. However, echocardiography is not the best test for diagnosing pulmonary arterial hypertension: right heart catheterization is the gold standard to

Table 2. Predictive Factors for Pulmonary Fibrosis (PF) and Pulmonary Arterial Hypertension (PAH) in SSc

Feature	PAH	PF + PAH	PF
Classification			
Limited	+++	+	+
Diffuse	0 to +	++	+++
Autoantibodies			
ACA	+++	(?)	0
Th/To or U3RNP (nucleolar pattern)	+	++	++
Topo	0	++	+++
U1RNP	+	+	+
RNA Pol III	-	-	-
Pulmonary function tests			
FVC <60	-	++	+++
FVC/DLCO <1.4	-	-	+++
FVC/DLCO >1.6	+++	+++	—
DLCO <60%	+++	+++	+

determine the mean PAP and the PASP. The RVSP on echocardiography correlates poorly with right heart catheterization assessments of PASP, particularly in the range of 35 mmHg to 50 mmHg.¹⁷ In only 50% of patients will the echocardiographic estimation of PAP be within 10 mmHg of the pressures as determined on catheterization. In addition, unless the RVSP is specifically requested on the echocardiography form, many echocardiographers will not report an estimate of RVSP. Echocardiographers primarily focus on evidence of coronary ischemia, aortic and mitral valve problems, and left heart function. Another problem with echocardiograms is that in 10% to 15%, the tricuspid regurgitant jet that is needed to calculate the estimated RVSP cannot technically be determined. Because an elevated RVSP on echocardiography can be caused by left or right ventricular disease as well as intrinsic pulmonary arterial hypertension, patients with elevated RVSP must also be evaluated for evidence of left heart failure, diastolic dysfunction (right or left), pulmonary emboli, or severe hypoxic interstitial fibrosis. The evaluation should include right heart catheterization.

Exercise Echocardiography

There is considerable controversy about the usefulness and reliability of the exercise echo, but several studies have shown that as many as 50% of SSc patients have a marked increase in the RVSP while walking on the treadmill. Grunig found a high frequency of a positive exercise echo in asymptomatic members of a family with the gene for familial pulmonary hypertension.¹⁸ Not all patients with the gene for pulmonary arterial hypertension will get the disease since there is incomplete penetrance, but a positive exercise echo appears to be a risk factor for familial pulmonary arterial hypertension. Perhaps an abnormal exercise echocardiogram in SSc could also be a significant risk factor for pulmonary arterial hypertension. Increases in pulmonary arterial pressures with exercise also occur with left heart failure and diastolic dys-

Table 3. Description of PHAROS

Objectives	<ul style="list-style-type: none">• To determine time to definite pulmonary arterial hypertension (PAH) and risk factors for PAH in patients at high risk• To determine outcome of treatment in patients with PAH
Entry criteria	<ul style="list-style-type: none">• DLCO <55% of predicted• FVC/DLCO >1.6• PASP (echocardiography) >40 mmHg
Study protocol	<p><i>Yearly physician visits with:</i></p> <ul style="list-style-type: none">• Pulmonary function tests• Echocardiography• 6-minute walk test• Laboratory tests <p>Twice yearly patient questionnaires (e-mail or mail) about medication and function</p>
Outcomes	<p><i>For at-risk patients:</i></p> <ul style="list-style-type: none">• Time to definite PAH (mean PAP >25 mmHg with wedge < 16 mmHg on right heart catheterization) <p><i>For definite PAH patients</i></p> <ul style="list-style-type: none">• Time to changes in medication, hospitalization, death, and changes in 6-minute walk distance, oxygen saturation, and patient dyspnea questionnaires

function so the presence of such abnormalities must be confirmed on a right heart catheterization. The diagnosis of PAH includes an increase of the mean pulmonary pressures greater than 30 mmHg with exercise. If the pulmonary pressures are increased with exercise during a right heart catheterization and the wedge pressure does not go above 18 mmHg with exercise, the patient can be defined as having exercise induced pulmonary hypertension. However, unlike in idiopathic pulmonary arterial hypertension, we do not know whether this means that the patient will definitely evolve to resting pulmonary arterial hypertension. If patients have significant dyspnea and exercise-induced pulmonary arterial hypertension without any signs of left heart or diastolic dysfunction, they may potentially be helped with one of the new therapies, but further study is necessary. However, since the use of these medications in patients with other causes of heart disease, particularly congestive heart failure, may cause serious problems, an accurate diagnosis is absolutely necessary prior to beginning therapy.

Right Heart Catheterization

Once other causes of pulmonary arterial hypertension have been ruled out, a right heart catheterization must be done to determine the actual mean pulmonary arterial pressure. The diagnosis of pulmonary arterial hypertension is a mean PAP of greater than 25 mmHg at rest, with a wedge pressure less than 16 mmHg (or a mean PAP of 30 mmHg with exercise, with a wedge pressure of

less than 18 mmHg). It is important that we remember that the most common cause of increased pulmonary pressures is left heart disease. The heart can also be involved in scleroderma and may be the cause of these elevated pressures. Subtle myocardial fibrosis or diastolic dysfunction is often not obvious and can mimic findings of pulmonary arterial hypertension but can usually be picked up on right heart catheterization, especially with exercise.

Predictive Factors for Lung Disease in SSc

Using what we've reviewed above, we have developed a table (Table 2) that summarizes several of the predictive factors, including disease subset (limited or diffuse), autoantibodies, and pulmonary function tests, which enrich for interstitial lung disease, for pulmonary arterial hypertension, and for mixed ILD-PAH.

Treatment of Pulmonary Arterial Hypertension

Until recently, the diagnosis of pulmonary arterial hypertension in a patient with scleroderma was the most sure death sentence in all of rheumatology. Since epoprostenol was shown to improve function and survival, we have seen the approval by the Food and Drug Administration of additional therapies, including other prostacyclins (treprostinil and inhaled iloprost), endothelin antagonists (bosentan, and possibly ambrisentan and sitaxsentan in the near future) and phosphodiesterase inhibitors (sildenafil, and possibly the longer acting ones as well).¹⁹ A recent *Scleroderma Care and Research* report summarized these exciting new advances.²⁰

PHAROS (Pulmonary Hypertension Assessment Registry of Scleroderma)

PHAROS is a multicenter study being conducted by members of the Scleroderma Clinical Trials Consortium to evaluate patients with and at risk for pulmonary arterial hypertension. Its primary objectives are to determine the time to definite pulmonary arterial hypertension (mean PAP greater than 25 mmHg on right heart catheterization) in patients at high risk for the disease and which of the different potential risk factors that have been discussed best predicts future disease (Table 3). Eligible high-risk patients include those with a DLCO less than 55% of predicted, an FVC%/DLCO% ratio greater than 1.6, or an estimated RVSP greater than 35 mmHg on echocardiography. Patients will be seen once yearly for pulmonary function tests, echocardiography, 6-minute walk tests, and laboratory tests, which are the standards of care of management of these patients and should be covered by insurance. Patients will complete questionnaires twice yearly via Internet or mail.

The second major objective of PHAROS is to determine the long-term outcomes of therapy in SSc patients with definite pulmonary arterial hypertension. Patients diagnosed with pulmonary arterial hypertension on right heart catheterization within the past 6 months are eligible for entry into this part of the study. The end points for this part of the study focus on the changes in medications, hospitalization, and death. Patients will get biannual evaluations, 6-minute walk tests, echocardiography, and questionnaires. Members of the Scleroderma Clinical Trials Consortium are excellent sources for consultation in management of complicated lung patients and will be pleased to discuss or evaluate patients.

NATIONAL REGISTRY FOR CHILDHOOD ONSET SCLERODERMA

**LOCALIZED AND SYSTEMIC
FORMS OF SCLERODERMA**

**CHILDREN AND ADULTS
(WITH ONSET BEFORE AGE 16)**

**University of Pittsburgh
Thomas A. Medsger, Jr., MD
Principal Investigator**

**Children's Hospital of Pittsburgh
Thaschawee Arkachaisri, MD, FACR
Co-Investigator**

one blood sample required (sent via mail kit)

no visits to Pittsburgh necessary

yearly questionnaire (HAQ or CHAQ) to be completed by patient

**IRB approved, HIPAA compliant yearly one page data collection
form to be completed by patient's attending physician**

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**

Please ask your interested patients to call the Registry at 1-800-603-8960.

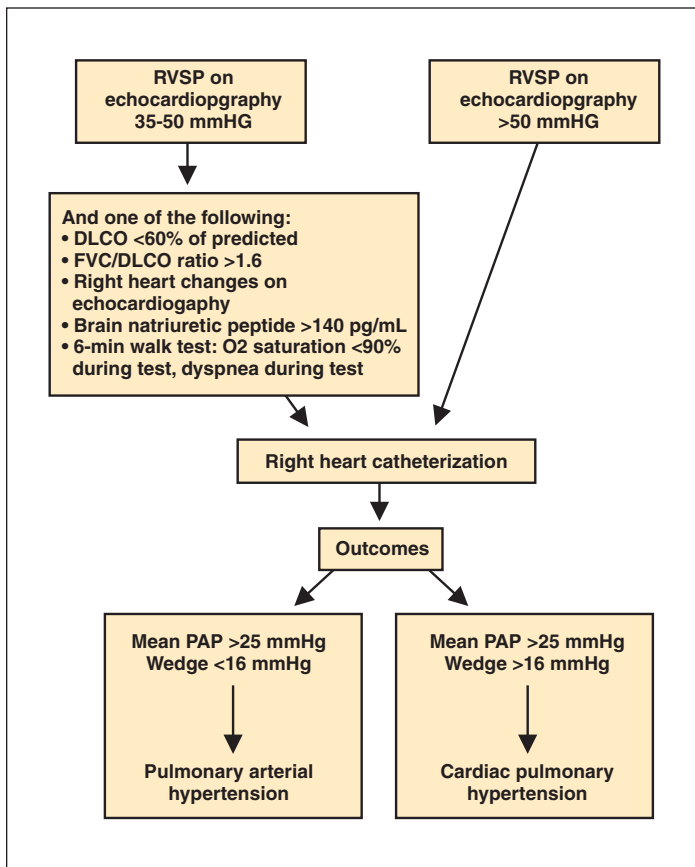


Figure 5. Diagnosing pulmonary arterial hypertension.

The Consortium's Web site (www.sctc-online.org) lists the sites and contact information for participation in PHAROS. It is extremely important that we take this opportunity to make a major difference in the long-term outcome of pulmonary hypertension. PHAROS participation will give physicians and patients the best way to contribute to really making a difference in scleroderma.

Conclusions

In summary, identifying, appropriately evaluating, and following patients at high risk for pulmonary arterial hypertension is extremely important and challenging. **Figure 5** summarizes our recommendations for diagnosing patients at high risk for pulmonary arterial hypertension and for distinguishing those with primary vasculopathy as the cause from those with left ventricular disease that raises pulmonary artery pressure secondary to left ventricular failure. Scleroderma-associated lung disease can occur primarily as interstitial fibrosis or as pulmonary vascular disease, or as a combination of both. Understanding the ways to diagnose and treat both is vitally important. Consultation with rheumatologists with expertise in scleroderma lung disease is the best way to be sure that these complicated conditions can be properly evaluated to determine the primary type of lung disease and the most appropriate treatment. It is indeed an exciting and important time to improve and make a difference for scleroderma patients with lung disease.

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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

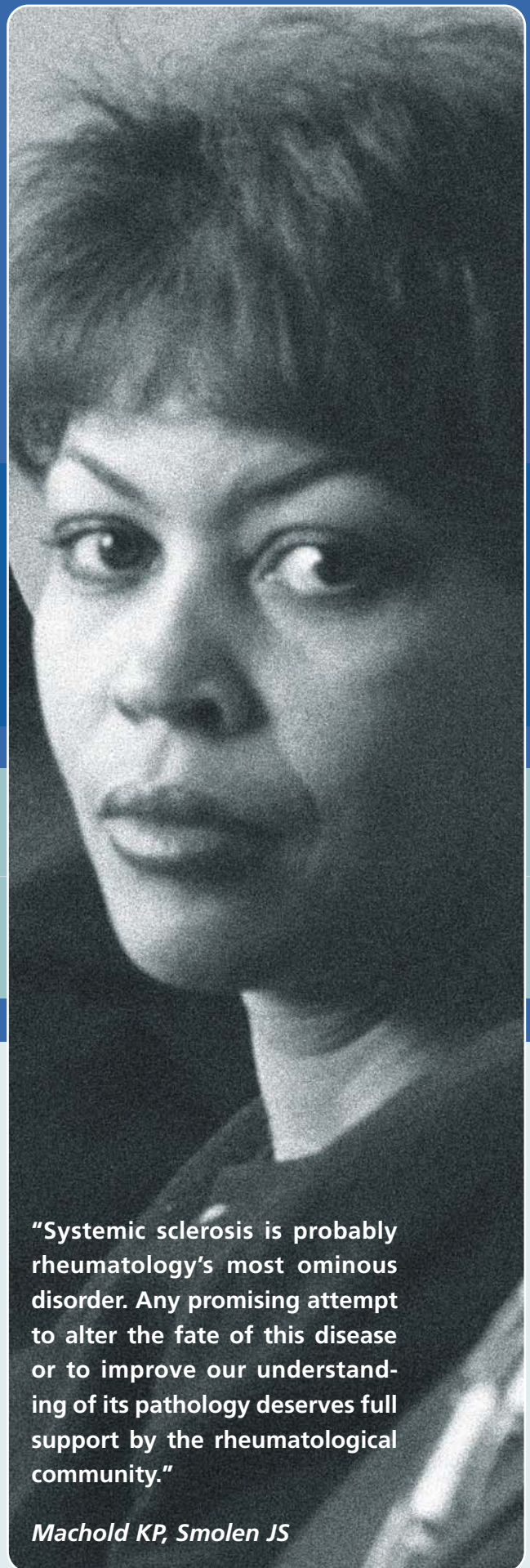
- Families are eligible when an adult or child member meets criteria for:
 - Systemic sclerosis (SSc, scleroderma)
 - Rheumatoid arthritis (RA) or
 - Juvenile Rheumatoid Arthritis (JRA) or
 - Systemic lupus erythematosus (SLE) or
 - idiopathic inflammatory myopathy (IIM, meaning any form of adult or 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.

Have You Seen this Patient?

- **Rapidly progressing systemic sclerosis (SSc)**
- **Extensive skin involvement (modified Rodnan skin score ≥ 16)**
- **Early internal-organ involvement**

Severe cases of SSc are characterized by early, rapid advancement of visceral and skin involvement. Current data suggest that SSc patients who develop severe organ involvement during the first 5 years of illness have a survival rate of 50% at 5 years and 38% at 10 years.

SCOT (**S**cleroderma: **C**yclophosphamide **o**r **T**ransplantation) is a pivotal, clinical research study comparing autologous stem cell transplantation versus high-dose cyclophosphamide in patients with severe forms of systemic sclerosis (SSc).



“Systemic sclerosis is probably rheumatology’s most ominous disorder. Any promising attempt to alter the fate of this disease or to improve our understanding of its pathology deserves full support by the rheumatological community.”

Machold KP, Smolen JS

A total of 226 subjects will be enrolled across North America over a 3-year period and randomly assigned in a 1:1 ratio to one of the following:

Monthly IV Pulse Cyclophosphamide for 12 Months

Cyclophosphamide has been used widely by clinicians to treat scleroderma; however, it has never been compared scientifically to other therapies for scleroderma. The rationale for monthly cyclophosphamide is based upon a significant amount of anecdotal data.

The dose of 750 mg/m² for 12 monthly infusions is approximately twice the dose of cyclophosphamide given as part of the stem cell transplant arm and was chosen to strengthen equipoise between the two regimens. In addition, the cyclophosphamide schedule in SCOT is similar to the schedule in the ASTIS study (an international "sister" study), which will allow eventual comparison of the 2 studies.

OR

High-dose Immunosuppressive Therapy (HDIT) with Autologous Stem Cell Transplantation

Evidence from pilot studies* suggests that patients with rapid advancing disease may benefit from high-dose immunosuppressive therapy followed by autologous stem cell transplantation. Altering the patient's immune system may stop progression of the disease.

Although early pilot experiences with stem cell transplantation in SSc showed a slightly higher than expected transplant-related mortality, the stringent eligibility requirements and modified regimens for SCOT are expected to reduce the mortality risk.

**FHCRC Protocol 1019 and preliminary ASTIS trial data*

Event-free survival at 44 months after randomization is the primary endpoint.

To learn more about SCOT or to refer a potential subject, please call or visit our Web site.

**1.866.909.SCOT (7268)
www.sclerodermatrial.org**

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 Diseases, National Institutes of Health, under Contracts No. N01-AI-25481 and N01-AI-05419.

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Scleroderma: Cyclophosphamide Or Transplant



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The Scleroderma Medical Resource

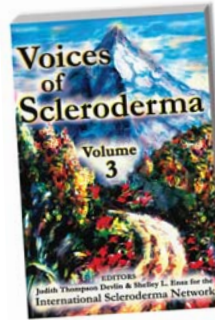
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