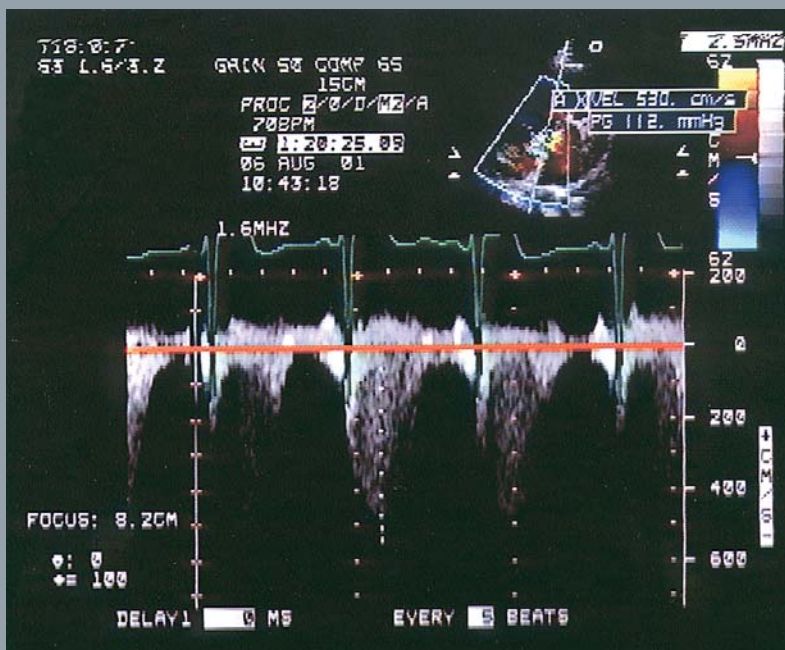


# Scleroderma

## Care and Research

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for Lung Disease in Scleroderma:  
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## Mission Statement

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

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

## About the cover:

Doppler flow measurement of pulmonary artery pressure.

## Editor's Memo

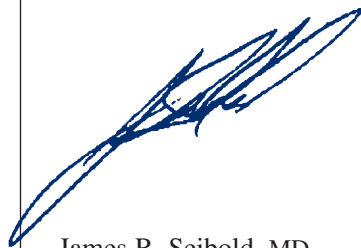
Welcome to the second year of *Scleroderma Care and Research*—the journal of the Scleroderma Clinical Trials Consortium (SCTC).

The initial response to this publication has been quite gratifying. Members of the SCTC had foreseen that *Scleroderma Care and Research* could serve as an effective vehicle to transmit advances in clinical care to the primary care rheumatologist. We also hoped that this journal would serve as a platform for promoting the robust clinical trial repertory of the Consortium.

This issue addresses these goals. Ouimet and Pope review the often neglected area of male sexual function in scleroderma and offer a thoughtful diagnostic and treatment algorithm to assist you in effectively dealing with this important issue of quality of life. Khanna and colleagues take a close look at actual community practice patterns in the critical area of scleroderma lung disease. This field is changing rapidly as experience grows with the approved agents for pulmonary hypertension, as preapproval development continues with at least five additional treatments, and finally, as prospective randomized trials for fibrosing alveolitis are being performed. Perhaps we're overly optimistic, but we feel that strategies for individualized care of the remarkably heterogeneous problem of "scleroderma lung disease" are at hand.

Private sector interest in drug development in scleroderma is at an all-time high. More importantly, the National Institutes of Health have joined the fray as well. The first two NIH-supported trials (cyclophosphamide in fibrosing alveolitis and oral tolerization to type I collagen) are fully recruited and we await reportage of trial results. The most ambitious trial yet, a randomized comparison of immunoablation with stem cell reconstitution compared with monthly bolus cyclophosphamide, begins this year. This study will gain immensely from strong support by the community.

Our primary goal is to provide you with material that is useful in your practice. Protocol participation is the treatment of choice for many patients and we continue to urge that you consider SCTC trials as an approach to patient management. Visit our Web page (<http://www.sctc-online.org>) for updated information about trials and how to contact participating centers.



James R. Seibold, MD  
Editor-in-Chief

# Diagnostic and Management Preferences for Lung Disease in Scleroderma: Results of Survey of Rheumatologists

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## Introduction

Practice patterns regarding diagnosis and treatment of lung disease in systemic sclerosis (SSc) are thought to vary widely. With use of the directory of the American College of Rheumatology, 4600 rheumatologists in the United States and Canada were mailed surveys and 317 (7%) responded. Most of the rheumatologists utilized chest x-ray, pulmonary function testing with diffusion capacity, and high-resolution computed tomography to make the diagnosis of SSc-associated interstitial lung disease (ILD). For the diagnosis of pulmonary arterial hypertension (PAH), there was high utilization of chest x-ray, Doppler echocardiography, and

pulmonary function testing with diffusion capacity. Rheumatologists managing more than 20 patients were more likely to utilize both bronchoalveolar lavage (34%) for the diagnosis of active alveolitis and right heart catheterization for confirming the diagnosis of secondary PAH due to ILD (25%) and of isolated PAH (45%).

For the treatment of ILD, most rheumatologists use prednisone (39%) and cyclophosphamide (30%) in spite of the absence of data from controlled trials. Conversely, use of agents of proven effectiveness for PAH had low utilization—epoprostenol (5%) and bosentan (4%). Calcium channel blockers were widely used for the treatment of PAH, either isolated (22%) or secondary to ILD (27%).

Considerable variation exists regarding key elements of diagnosis and treatment of SSc-associated lung disease.

## Clinical Importance of Lung Involvement

Pulmonary involvement occurs in over 70% of patients with SSc or scleroderma. Scleroderma lung disease is a significant determinant of health outcome, and in the last 10 years has emerged as the leading cause of disease-related death.<sup>1-3</sup> The two main clinical manifestations of lung involvement in SSc are ILD, also called fibrosing alveolitis or pulmonary fibrosis,<sup>1,4</sup> and pulmonary vascular disease,<sup>5-7</sup> which can lead to PAH.

Present evidence suggests that SSc-associated ILD begins as an inflammatory alveolitis that drives, or at least occurs concurrently with, interstitial fibrosis.<sup>8</sup> If patients are to develop clinically significant ILD, they usually develop it within the first 3 to 6 years after SSc onset. Approximately 50% of the patients who develop severe pulmonary restriction, defined as forced vital capacity (FVC) <50% of predicted, do so within 3 years of SSc onset and approximately 70% do so within 6 years of SSc onset.<sup>1,9,10</sup> In a study of a large inception cohort, when the FVC was used as a surrogate for fibrosis, the prevalence of restrictive lung disease was seen in approximately 27% of patients with SSc who had reductions in their FVC to 50% to 75% of predicted (moderate restrictive disease), while 13% had reductions in their FVC to <50% (severe restriction).<sup>1</sup>

PAH may occur in isolation (without ILD) or it may occur within the context of ILD. Isolated PHT tends to occur late (>10 years after SSc onset) and mainly in patients with limited cutaneous SSc (previously termed the CREST syndrome), while PAH in association with ILD tends to occur earlier and predominantly

in the context of diffuse cutaneous SSc.<sup>11</sup> PAH is thought to be the result of an obliterative, proliferative vasculopathy that is characteristic of SSc and/or as the result of fibrotic obliteration of interstitium and interstitial microvasculature that is part of ILD. Although some echocardiographic studies suggest that 30% to 40% of patients with SSc have pulmonary hypertension (right ventricular systolic pressure  $\geq$ 40 mm Hg), PAH of a severity requiring specific second-line therapy is thought to occur in only about 10% to 15% of patients with SSc.<sup>12-14</sup>

New therapies for the treatment of PAH in SSc have recently become available. At the time this survey was conducted, only two therapies had been approved by the Food and Drug Administration for SSc-associated PAH: epoprostenol (Flolan),<sup>15</sup> a prostacyclin and a potent pulmonary vasodilator and inhibitor of platelet aggregation, and bosentan (Tracleer),<sup>16</sup> an endothelin antagonist. Subsequently, treprostinil (Remodulin),<sup>17</sup> a prostacyclin derivative, has also gained FDA approval for PAH secondary to SSc.

Although no therapy has yet been approved by the FDA for treating ILD, hopes remain high that immunosuppressants, if used appropriately, will be associated with arrest of progressive lung injury.<sup>18</sup> Agents thought to be predominantly antifibrotic in mechanism, eg, gamma-interferon have proved disappointing.<sup>19</sup>

The availability of these therapies for treating SSc interstitial and pulmonary vascular disease, and their significant costs and toxicities, makes it important to know the present extent and depth of knowledge about SSc lung disease and its management among physicians who direct these patients' care. Similarly, screening guidelines for lung disease in SSc have been proposed,<sup>18</sup> but the usual practice patterns among physicians is not known.

We conducted a survey among rheumatologists, the principal care providers for most patients with scleroderma, to quantify the screening and treatment practices for lung disease in this patient population.

## Methods

### Survey Instrument

In early 2002 a total of 4600 rheumatologists in the United States and Canada were surveyed by mail regarding their diagnostic and treatment practices of lung disease in their patients with SSc. Mailing was nonselective and derived from the active membership of the American College of Rheumatology. Physicians completed questions regarding the number of patients with SSc in their practices, the estimated frequencies of various pulmonary disease manifestations among these patients, and the physicians' practice regarding diagnostic and treatment patterns for pulmonary disease in SSc. Responses were received by fax or through the Scleroderma Clinical Trial Consortium Web site ([www.sctc-online.org](http://www.sctc-online.org)).

### Statistical Analysis

Since the survey asked the rheumatologists to "estimate the percentage of patients who receive treatment for scleroderma lung involvement" rather than an actual number, a total of 3339 patients with SSc was assumed for the 317 rheumatologists for the treatment preferences. This estimate was based on averaging the number of patients as 25 patients per doctor seeing more than 20 patients, 15 patients for doctors seeing between 11 and 20, 8 for

those seeing 6 to 10, and 3 for those seeing 1 to 5 patients.

All data counts were analyzed using Stata version 7.0 statistical software (Stata Corporation, College Town, Texas). Group comparisons were tested by chi-square tests or, when appropriate, the 2-tailed Fisher's exact test. A two-tailed significance level of .05 was used.

## Review of Literature and Levels of Evidence

**Search Strategy.**—Medline and the Cochrane Library electronic databases were searched to September 1, 2003. The keywords included *scleroderma*, *systemic sclerosis*, *pulmonary fibrosis*, *lung involvement*, and *pulmonary hypertension*. No language, date, or age restrictions were applied. Proceedings from the American College of Rheumatology and European Congress of Rheumatology meetings were searched for the years 2001 and 2002. American College of Rheumatology 2003 meeting abstracts were also reviewed. The reference lists from the published clinical studies and review articles were reviewed to identify any additional studies.

With regard to the diagnostic patterns of the physicians, the diagnostic tests were divided in to three categories: tests that predict disease progression and mortality; tests that predict disease progression only; and tests that do not predict either disease progression or mortality. The physician treatment practices for scleroderma-related pulmonary disease were annotated as suggested by Shekelle et al<sup>20</sup> and are described in **Appendix** (page 9).

## Results

### Survey Responses

The 317 (7%) rheumatologists who responded were divided into four groups according to the self-reported number of patients with SSc seen in their clinical practice: more than 20 patients, 53 (17%); 11 to 20 patients, 61 (19%); 6 to 10 patients, 98 (31%); and 1 to 5 patients, 105 (33%). The responding rheumatologists reported symptomatic lung involvement in 26 % of their patients with SSc; the percentages were similar across the four groups. Among the patients with either symptomatic or asymptomatic lung disease, 53% were diagnosed with isolated ILD, 17% with pulmonary hypertension secondary to ILD, and 13% with isolated pulmonary hypertension.

### Diagnostic Preferences

**Table 1**, **Figure 1**, and **Figure 2** display the diagnostic tests most frequently utilized by rheumatologists in the evaluation of SSc-associated pulmonary disease. In brief, the majority of rheumatologists utilized chest x-rays, pulmonary function tests, including measurement of the diffusion capacity of carbon monoxide, and high-resolution computed tomography of the chest for the evaluation of ILD. Bronchoalveolar lavage was utilized more frequently by rheumatologists who reported seeing more than 20 patients, although this difference was not significant.

For both isolated PAH and PAH secondary to ILD, there were trends suggesting that rheumatologists taking care of more than 20 patients utilized all of the testing modalities more often than physicians caring for fewer patients. Most notably, right heart catheterization was more frequently utilized for both PAH associ-

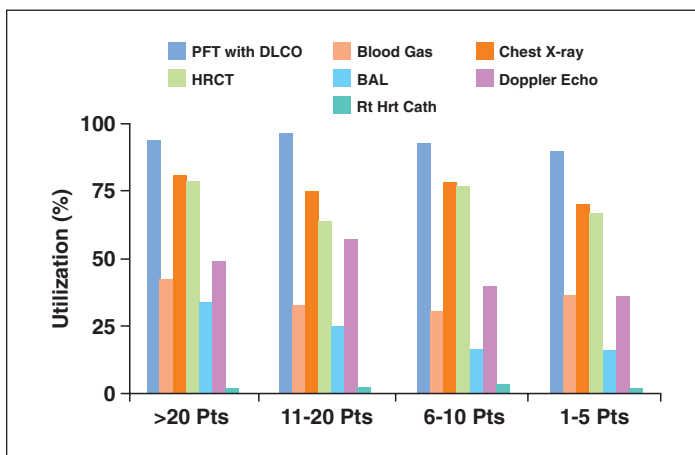
**Table 1. Physician Utilization of Specific Diagnostic Tests for Pulmonary Disease in Scleroderma**

	No. Patients Seen Per Year by Surveyed Physicians				Overall	Review of Literature†
	> 20	11-20	6-10	1-5		
<b>Interstitial Lung Disease</b>						
PFT with DLco	94	97	93	90	<b>93</b>	+++
Chest x-ray	81	75	79	70	<b>76</b>	+
HRCT	79	64	77	67	<b>71</b>	+
Doppler echo	49	57	40	36	<b>44</b>	-
BAL	34*	25	16	16	<b>21</b>	+++
<b>Pulmonary Hypertension Due to Interstitial Lung Disease</b>						
PFT with DLco	92**	87	76	64	<b>77</b>	+++
Chest x-ray	74	66	63	53	<b>62</b>	-
HRCT	68	49	59	48	<b>55</b>	-
Doppler echo	79	70	63	60	<b>66</b>	+++
BAL	28***	15	13	10	<b>15</b>	-
Right heart cath	25	10	11	16	<b>15</b>	+++
<b>Pulmonary Hypertension</b>						
PFT with DLco	74§	62	60	46	<b>57</b>	+++
Chest x-ray	62	40	48	44	<b>48</b>	-
Doppler echo	85£	74	67	55	<b>68</b>	+++
Right heart cath	45 +	25	21	22	<b>26</b>	+++

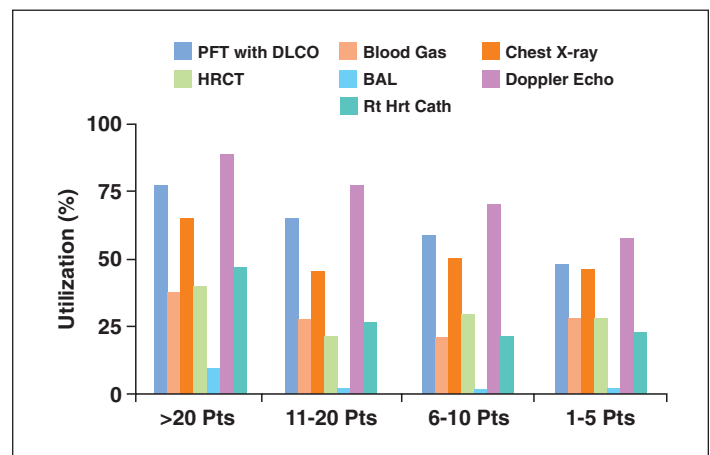
† does not predict; + predicts disease progression; +++ predicts disease progression and mortality.

\* P <.02 for >20 vs 6-10; \*\* P <.04 for >20 vs 6-10, 1-5; \*\*\* P <.01 >20 vs 1-5;

§ P >.003 for >20 vs 1-5; £ P <.04 for >20 vs 6-10, 1-5; + P <.03 for >20 vs others by chi-square and Fisher's exact test.



**Fig. 1—Physician utilization of specific diagnostic tests for interstitial lung disease for patients with scleroderma.**



**Fig.2—Physician utilization of specific diagnostic tests for pulmonary hypertension for patients with scleroderma.**

ated with ILD and isolated PAH, although only the latter comparison was statistically significant.

**Treatment Preferences**

**Table 2, Figure 3, and Figure 4** present potential treatments for SSc pulmonary disease (as of early 2002, the date of the survey) and the percentage of patients who were receiving these treat-

ments, stratified by the number of patients seen by rheumatologists. For isolated ILD, a higher percentage of rheumatologists caring for more than 20 patients used prednisone and cyclophosphamide than did rheumatologists who saw fewer patients. Twenty-two percent of the rheumatologists used calcium channel blockers for the treatment of isolated PAH and 27% used them for secondary PAH, with rheumatologists managing more than 20

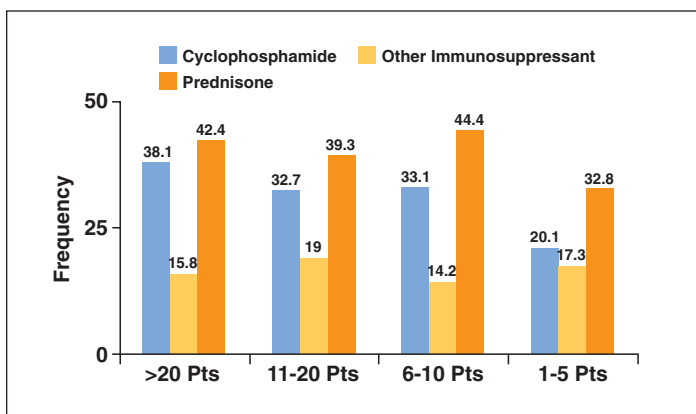
**Table 2. Physician Treatment Practices for Patients with Scleroderma-Related Pulmonary Disease**

TREATMENT	No. Patients Seen Per Year by Surveyed Physicians				Overall	Category Evidence <sup>†</sup>
	> 20	11-20	6-10	1-5		
<b>Interstitial Lung Disease</b>						
Prednisone	42.4 *	39.3	44.4	32.8	<b>39.2</b>	C
Cyclophosphamide	38.1 **	32.7	33.1	20.7	<b>29.8</b>	B
Other immunosuppressants	15.8	19	14.2	17.3	<b>16.4</b>	B
<b>Pulmonary Hypertension Due to Interstitial Lung Disease</b>						
Prednisone	31	24	27	15	<b>23.1</b>	-
Cyclophosphamide	26 +	18	13	10	<b>15</b>	-
Other immunosuppressants	17	15	10	7	<b>11.1</b>	-
Calcium channel blockers	41 <sup>++</sup>	30	26	18	<b>26.5</b>	-
Epoprostenol	5	2	2	1	<b>2.2</b>	-
Bosentan	7	4	3	1	<b>3.3</b>	-
<b>Pulmonary Hypertension</b>						
Calcium channel blockers	35.2 §	27.7	23.7	9.3	<b>21.6</b>	B
Epoprostenol	6.5	5.4	5.5	4.7	<b>5.4</b>	A
Bosentan	9.4	4.1	3.8	3.9	<b>4.2</b>	A

\* P <.03 for >20 vs 1-5; \*\* P <.009 for >20 vs 1-5; + P <.002 for >20 vs 6-10; ++ P <.02 for >20 vs others; § P <.03 for >20 vs 1-5, 6-10.

All performed using chi-square and Fisher's exact test.

<sup>†</sup> Category of evidence showing benefit in either idiopathic pulmonary fibrosis or ILD due to SSc, primary pulmonary hypertension or PHT due to SSc.<sup>20</sup>

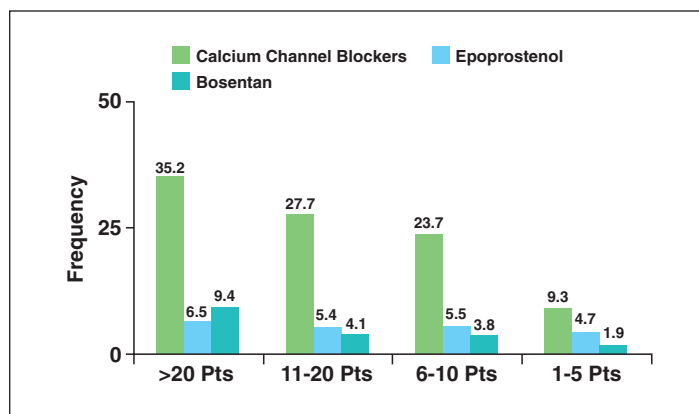


**Fig. 3--Physician treatment practices for interstitial lung disease in scleroderma.**

patients having a higher utilization of calcium channel blockers. Overall, a low percentage of rheumatologists utilized either epoprostenol (5%) or bosentan (4%) for treatment of pulmonary hypertension, either associated with ILD or isolated.

### Discussion

Our results demonstrate the wide range of clinical practices regarding the evaluation and treatment of pulmonary disease in patients with SSc. Increasingly, there are good data to guide physicians in the care of patients with pulmonary disease and sclero-



**Fig. 4--Physician treatment practices for pulmonary hypertension in scleroderma.**

derma as well as new effective medical therapies. We will briefly review the medical literature related to ILD and pulmonary hypertension in SSc and discuss our results as they relate to the current understanding of these problems.

### Diagnostic Tests (Table 1)

**Interstitial Lung Disease.**—Much is understood about ILD and PAH secondary to SSc, including the clinical features, the tools available to help make these diagnoses, and potential treatments. Key features of the natural history of ILD in SSc are known. Steen

et al reported that if patients were to have significant loss of FVC as a result of ILD, the greatest loss occurred within the first 4 to 6 years of SSc onset.<sup>1,9</sup> Significant loss of FVC was slightly more frequent in diffuse cutaneous SSc than in limited cutaneous SSc. Others have shown that early in the course of SSc-ILD, there is an inflammatory phase (active alveolitis), which precedes or occurs concurrently with (and may drive) fibrosis.<sup>21-23</sup> The evidence that inflammation leads to or is at least a marker of interstitial fibrosis derives from multiple sources.<sup>24-28</sup> The degree of alveolar inflammation and the extent of interstitial fibrosis both predict morbidity and mortality in patients with SSc.<sup>21-23</sup>

In the clinical evaluation of alveolitis/ILD, pulmonary function tests are the most direct measure of the level of lung function.<sup>1,9</sup> A chest x-ray is often used for making the diagnosis of ILD; but is an insensitive indicator of active alveolitis.<sup>29</sup> Only later in the disease do chest x-rays show changes, and then the changes are primarily fibrotic.<sup>30</sup> Many patients with SSc with mild symptoms and normal chest radiography results actually have ILD. In these patients, high-resolution computed tomography has been shown to be more sensitive than chest x-ray for showing active alveolitis as well as fibrosis.<sup>26,31-33</sup> In studies where tomography has been compared with lung biopsy, the appearance of ground-glass opacification on tomographic scans has usually been associated with biopsies showing predominantly cellular infiltration.<sup>26,31,33,34</sup> In contrast, a reticular pattern on tomographic scans is associated with a primarily fibrotic disease process on lung biopsy.<sup>32</sup>

Bronchoscopy with lavage can also be used to diagnose active alveolitis as measured by elevated numbers of neutrophils and eosinophils in lavage fluid washings. The concordance between computed tomography and bronchoalveolar lavage in active alveolitis is moderate.<sup>35</sup> The remainder of the correlations among chest x-ray, computed tomography, pulmonary function testing, and lavage are less striking.<sup>21,30,35,36</sup> Current ongoing studies may help determine whether tomography can supplement or supplant bronchoalveolar lavage for making the diagnosis of ILD.

Several markers can predict progressive loss of lung function (ie, declining FVC) and they include 1) declining FVC and diffusion capacity of carbon monoxide,<sup>1,4</sup> particularly in the context of recent SSc onset (less than 4 to 6 years); 2) active alveolitis on bronchoalveolar lavage (with PMNs  $\geq 3\%$  or eosinophil 2 in lavage fluid);<sup>21-23</sup> and 3) ground-glass opacification on computed tomography in patients with less than 4 years of SSc.<sup>26,31-33</sup> If left untreated, patients with any of these findings tend to continue to lose pulmonary function. Plain chest radiography does not seem to help in predicting which patients may need to be treated.

In our survey, most of the rheumatologists utilized chest x-ray, pulmonary function testing with diffusion capacity of carbon monoxide, and computed tomography to make the diagnosis of ILD. A minority of rheumatologists routinely utilized bronchoalveolar lavage for the diagnosis of active alveolitis. Because rheumatologists were not routinely using lavage for the diagnosis of ILD, we assume that they were relying on tomography and pulmonary function tests to make the diagnosis of SSc-ILD.

**Pulmonary Hypertension.**—Assessment of pulmonary vascular injury in SSc relies on alternate specific cardiopulmonary test-

ing. Although chest x-ray may show an enlarged pulmonary artery in PAH, this test is insensitive for detecting early pulmonary vascular disease. A disproportionate decrease in %diffusion capacity of carbon monoxide with respect to %FVC (ratio of %FVC / %DLCO  $>1.4$ ), regardless of the level of FVC, is a predictor of subsequent development of PAH.<sup>5</sup> Doppler echocardiography is often used to evaluate pulmonary artery systolic pressure. Up to 65% of patients with SSc have increased pulmonary artery systolic pressure,<sup>37</sup> but clinically significant PAH probably occurs in only about 10% to 15%.<sup>12,13</sup>

Although echocardiography<sup>12,13</sup> is valuable in diagnosing and predicting PAH, several problems exist in the use of this test. A recent study in patients with advanced idiopathic pulmonary fibrosis (in patients without SSc undergoing lung transplant) showed that Doppler echocardiography usually overdiagnosed pulmonary hypertension compared with the gold standard of right heart catheterization.<sup>38</sup> In addition Doppler estimation of pulmonary artery systolic pressure may not be possible in 20% to 30 % of patients because they lack the tricuspid regurgitant jet required to calculate pulmonary artery pressure.<sup>7</sup> Finally, echocardiography, both resting and stress, cannot measure pulmonary capillary wedge pressure.

Right heart catheterization remains the gold standard for the measurement of pulmonary vascular pressures. Its greatest utility is in the accurate diagnosis of PAH and in the evaluation of the response of PAH to therapy.<sup>21,22</sup> Preferences differ regarding the optimal time to perform a catheterization, but doing so is valuable in confirming PAH in patients where there is a suspicion of clinically important PAH and in monitoring PAH before and during treatment. It is a required procedure for Medicare-subsidized therapies such as epoprostenol and treprostinil.

In our survey there was high utilization of chest x-ray, Doppler echocardiography, and pulmonary function testing with diffusion capacity of carbon monoxide for the diagnosis of PAH. Rheumatologists managing more than 20 patients were more likely to perform right heart catheterization for confirming the diagnosis of PAH secondary to ILD (25%) and of isolated PAH (45%). The infrequent utilization of catheterization suggests that there are several impediments to its performance, which may include reluctance to refer patients for catheterization, difficulty in accessing pulmonologists or cardiologists with the expertise and willingness to do this procedure, and reluctance of third-party payors to reimburse for the procedure. These same factors doubtless influence underutilization of bronchoalveolar lavage, although additional factors include lack of community standardization of lavage procedures and results and most importantly, underappreciation of the value of the test as a guide for effective therapy.

### **Treatment Preferences (Table 2)**

**Interstitial Lung Disease.**—Despite the high frequency, morbidity, and mortality of SSc-associated ILD, few studies have been performed to evaluate the effectiveness of medical therapy. Glucocorticoids have been reported to be both effective<sup>39</sup> and ineffective<sup>24</sup> in uncontrolled case studies. Cyclophosphamide, with or without concomitant glucocorticoids and given by either oral or intravenous routes, has been reported as effective in treat-

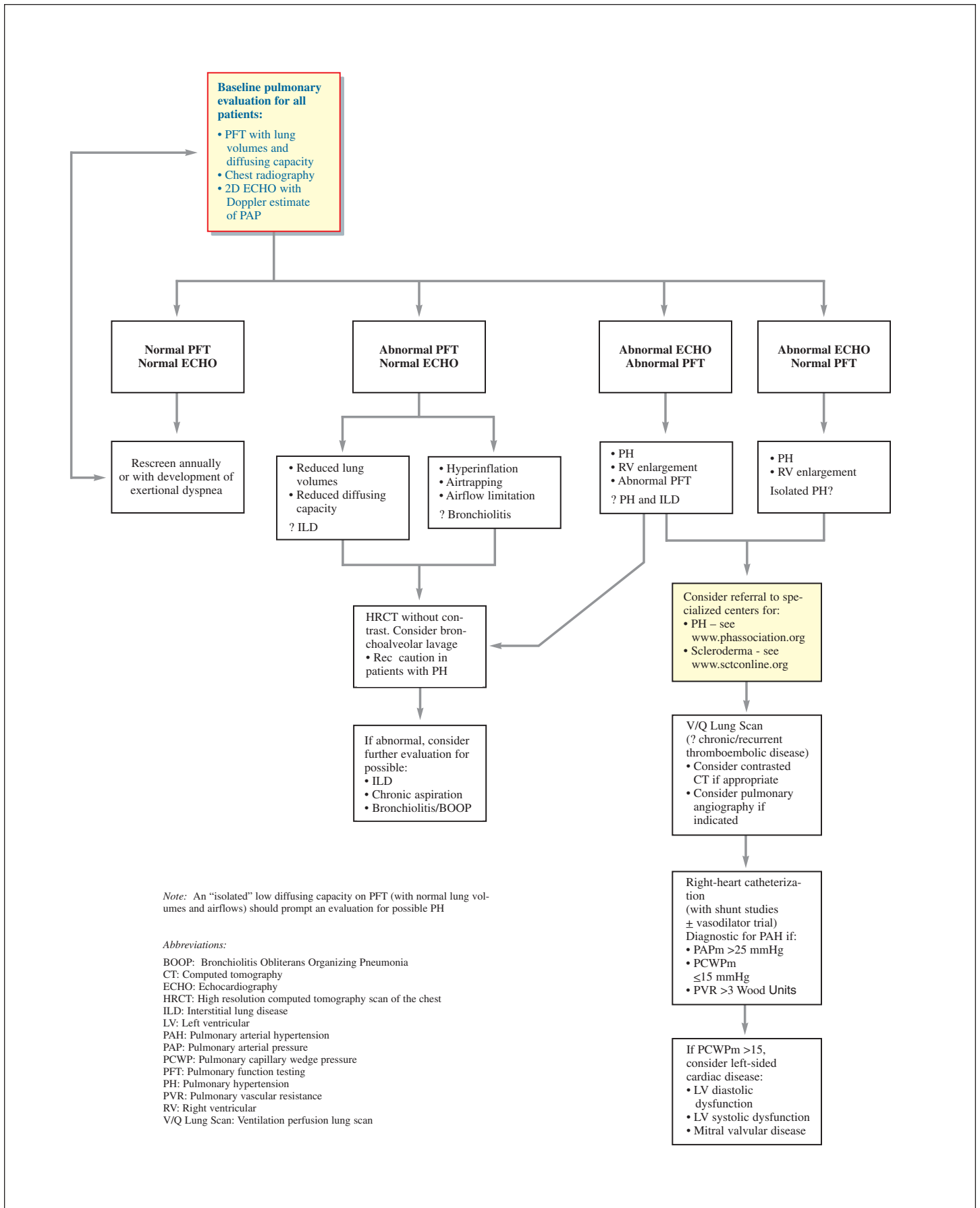


Fig. 5—Pulmonary Diagnostic Algorithm for Patients With Scleroderma. Courtesy of Badesh DB, Seibold JR. *Adv Pulm Hypertension*. 2002;1:13-14.

## APPENDIX

### Category A evidence

Based on evidence from at least one randomized controlled trial or on the meta-analyses of randomized controlled trials.

### Category B evidence

Based on evidence from at least one controlled trial without randomization or at least one other type of experimental study or on extrapolated recommendations from randomized controlled trials or meta-analyses.

### Category C evidence

Based on nonexperimental descriptive studies, such as comparative studies, correlational studies, and case-control studies, which are extrapolated from randomized controlled trials, nonrandomized controlled studies, or other experimental studies.

### Category D evidence

Based on expert committee reports or opinions or clinical experience of respected authorities, or both, or on extrapolated recommendations from randomized controlled trials, meta-analyses, nonrandomized controlled trials, experimental studies, or nonexperimental descriptive studies.

ing alveolitis in SSc, based on open retrospective studies.<sup>22,40</sup> Although these data are encouraging, open uncontrolled studies and case series do not reach the level of evidence needed for adoption of cyclophosphamide as the standard of care for this syndrome. It is anticipated that the ongoing NIH-sponsored placebo-controlled study evaluating oral cyclophosphamide (2 mg/kg/day) in the treatment of active alveolitis associated with SSc will provide a more definitive answer.

Despite the lack of clear supportive data on treatment efficacy for SSc-associated ILD, in our survey, rheumatologists routinely prescribe prednisone (39%), cyclophosphamide (30%), or other immunosuppressants (16%) for the treatment of ILD. This relatively high, but not universal, use of toxic medications highlights the need for both standardization of care and better clinical trial data on which to base therapeutic decisions.

**Pulmonary Hypertension.**—There are more therapeutic options with proven benefit available for treating PAH in SSc. PAH secondary to SSc has important differences from idiopathic or primary PAH. In primary disease, calcium channel blockers are effective in patients whose condition responds (defined as near normalization in pulmonary artery pressure and peripheral vascular resistance) to a vasodilator challenge during hemodynamic monitoring.<sup>41</sup> Patients with SSc-associated PAH, however, rarely show a response in acute vasodilator challenges. The routine use of the calcium channel blockers without initial right heart catheterization is not recommended in SSc<sup>42</sup> and their role, safe-

ty, and long-term benefit in the treatment of PAH of SSc is unclear.

The prostacyclin analogs, epoprostenol and treprostinil, have been tested in randomized, placebo-controlled trials in patients with scleroderma-associated PAH. Evidence of efficacy includes significant decreases in pulmonary arterial pressure and improved exercise tolerance in those randomized to receive epoprostenol.<sup>43</sup> Other prostacyclin analogs and delivery systems, including inhaled and oral formulations, remain investigational.

Bosentan is a nonselective endothelin receptor antagonist that has been demonstrated safe and effective in treating PAH in randomized, controlled trials including patients with PAH secondary to SSc. Benefits include improvement in 6-minute walking distance in bosentan-treated patients compared with placebo-treated patients<sup>16</sup> and a favorable effect on the hemodynamic parameters and exercise capacity of the patients.<sup>44</sup> Other applications of bosentan, including as a treatment of peripheral vascular features of SSc and ILD secondary to scleroderma remain investigational (see the Current Studies Section of this journal). Other endothelin antagonists of selective specificity for endothelin-A receptors are in early stages of investigational study.

In our survey, the majority of rheumatologists utilize calcium channel blockers for the treatment of SSc-associated pulmonary hypertension: 22% for isolated disease and 27% for that due to ILD. Use of epoprostenol and bosentan, which were FDA approved for use in SSc-associated PAH at the time this survey was conducted, is sparse. In the case of epoprostenol, this may reflect the complexity of initiation and management of the drug, which requires training of the patient and caregivers and placement and maintenance of central venous access. In the case of bosentan, it may well be that the timing of the survey (early 2002) was too soon after FDA approval for use to seep down to the primary care community. The high cost of both agents and limitations of the use and coverage by insurance and other third-party payors may also be an obstacle to providing these treatments.

## Conclusion

Our survey is the first of its kind inquiring about the diagnostic and management patterns of rheumatologists treating SSc-associated lung disease. This is important, since scleroderma lung disease has emerged as the leading cause of disease-related death. The limitations of our survey included a low response rate (7%), challenging its applicability to all practicing rheumatologists. Second, we did not ask questions regarding screening procedures undertaken by the rheumatologists in the diagnosis of scleroderma lung disease. This may explain the low use of bronchoalveolar lavage and right heart catheterization for the diagnosis of ILD and pulmonary hypertension, respectively, since rheumatologists may be relying on high-resolution computed tomography and echocardiography to make these diagnoses. Both lavage and catheterization require partnership with experienced and skilled pulmonologists and cardiologists. Nonetheless, these tests have evolved to represent the standard of care in the community of experts. The goal is to achieve comparable levels of care in the community at large. This survey does provide a snapshot of practice patterns in

an estimated 3300 patients with SSc. This survey revealed a striking need to get the word out about screening and treatment of pulmonary disease in SSc. Aggressive efforts at diagnosis, including right heart catheterization, were undertaken by only 26% of respondents. In general, physicians caring for higher numbers of patients with SSc tend to make more frequent use of gold standard testing, including lavage and catheterization.

Finally, caregivers of scleroderma patients have access to three FDA-licensed therapies for PAH secondary to SSc, and the future holds great promise of additional treatment options. Since pulmonary hypertension predicts an increase in mortality and better treatment options are available, more aggressive diagnostic efforts are justified and should be used. **Figure 5** provides a pulmonary diagnostic algorithm for patients with scleroderma.

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PULMONARY ARTERIAL  
HYPERTENSION  
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- From <10%<sup>1</sup> to 50%<sup>2</sup> of scleroderma patients develop PAH
- Dyspnea in scleroderma can indicate PAH<sup>3</sup>
- WHO recommends annual screening with echocardiogram<sup>4</sup>
- Only a right heart catheterization can confirm PAH diagnosis and assess precise hemodynamics<sup>3,5</sup>



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

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- Prescriptions can be filled only through TAP
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\*Clinical worsening defined as combined endpoint of death, hospitalization or discontinuation due to worsening PAH, or initiation of epoprostenol therapy<sup>6</sup>

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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). To date, in a setting of close monitoring, elevations have been reversible, within a few days to 9 weeks, either spontaneously or after dose reduction or discontinuation, and without sequelae. Elevations in aminotransferases require close attention (see DOSAGE AND ADMINISTRATION). TRACLEER® should generally be avoided in patients with elevated aminotransferases (> 3 x ULN) at baseline because monitoring liver injury may be more difficult. If liver aminotransferase elevations are accompanied by clinical symptoms of liver injury (such as nausea, vomiting, fever, abdominal pain, jaundice, or unusual lethargy or fatigue) or increases in bilirubin  $\geq$  2 x ULN, treatment should be stopped. There is no experience with the re-introduction of TRACLEER® in these circumstances.

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

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

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

**CONTRAINDICATIONS:** TRACLEER® is contraindicated in pregnancy, with concomitant use of cyclosporine A, with co-administration of glyburide, and in patients who are hypersensitive to bosentan or any component of the medication. Pregnancy Category X. TRACLEER® is expected to cause fetal harm if administered to pregnant women. The similarity of malformations induced by bosentan and those observed in endothelin-1 knockout mice and in animals treated with other endothelin receptor antagonists indicates that teratogenicity is a class effect of these drugs. There are no data on the use of TRACLEER® in pregnant women. TRACLEER® should be started only in patients known not to be pregnant. For female patients of childbearing potential, a prescription for TRACLEER® should not be issued by the prescriber unless the patient assures the prescriber that she is not sexually active or provides negative results from a urine or serum pregnancy test performed during the first 5 days of a normal menstrual period and at least 11 days after the last unprotected act of sexual intercourse. Follow-up urine or serum pregnancy tests should be obtained monthly in women of childbearing potential taking TRACLEER®. The patient must be advised that if there is any delay in onset of menses or any other reason to suspect pregnancy, she must notify the physician immediately for pregnancy testing. If the pregnancy test is positive, the physician and patient must discuss the risk to the pregnancy and to the fetus.

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

**PRECAUTIONS: Hematologic Changes:** Treatment with TRACLEER® caused a dose-related decrease in hemoglobin and hematocrit. The overall mean decrease in hemoglobin concentration for bosentan-treated patients was 0.9 g/dl (change to end of treatment). Most of this decrease of hemoglobin concentration was detected during the first few weeks of bosentan treatment and hemoglobin levels stabilized by 4–12 weeks of bosentan treatment. 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:** CYP Isoenzymes: Bosentan is metabolized by CYP2C9 and CYP3A4. Inhibition of these isoenzymes may increase the plasma concentration of bosentan. Bosentan is an inducer of CYP3A4 and CYP2C9. Consequently, plasma concentrations of drugs metabolized by these two isoenzymes will be decreased when TRACLEER® is co-administered. Contraceptives: Specific interaction studies have not been performed to evaluate the effect of co-administration of bosentan and hormonal contraceptives, including oral, injectable or implantable contraceptives. Since many of these drugs are metabolized by CYP3A4, there is a possibility of failure of contraception when TRACLEER® is co-administered. Women should not rely on hormonal contraception alone when taking TRACLEER®. Cyclosporine A: During the first day of concomitant administration, trough concentrations of bosentan were increased by about 30-fold. Steady-state bosentan plasma concentrations were 3- to 4-fold higher than in the absence of cyclosporine A. The concomitant administration of bosentan and cyclosporine A is contraindicated. 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. Therefore, the concomitant administration of TRACLEER® and glyburide is contraindicated, and 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  $\beta$ -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, such as lovastatin and atorvastatin. The possibility of reduced statin efficacy should be considered. Patients using CYP3A4 metabolized statins should have cholesterol levels monitored after TRACLEER® is initiated to see whether the statin dose needs adjustment. Warfarin: Co-administration of bosentan 500 mg b.i.d. for 6 days decreased the plasma concentrations of both S-warfarin (a CYP2C9 substrate) and R-warfarin (a CYP3A4 substrate) by 29 and 38%, respectively. Clinical experience with concomitant administration of bosentan and warfarin in patients with pulmonary arterial hypertension did not show clinically relevant changes in INR or warfarin dose (baseline vs. end of the clinical studies), and the need to change the warfarin dose during the trials due to changes in INR or due to adverse events was similar among bosentan- and placebo-treated patients. Digoxin, Nimodipine and Losartan: Bosentan has been shown to have no pharmacokinetic interactions with digoxin and nimodipine, and losartan has no effect on plasma levels of bosentan.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** Two years of dietary administration of bosentan to mice produced an increased incidence of hepatocellular adenomas and carcinomas in males at doses about 8 times the maximum

recommended human dose [MRHD] of 125 mg b.i.d., on a mg/m<sup>2</sup> 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/m<sup>2</sup> 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 10 days 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 8 months. For the adverse drug reactions that occurred in  $\geq$  3% of bosentan-treated patients, the only ones that occurred more frequently on bosentan than on placebo ( $\geq$  2% difference) were headache (16% vs. 13%), flushing (7% vs. 2%), abnormal hepatic function (6% vs. 2%), leg edema (5% vs. 1%), and anemia (3% vs. 1%).

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

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

**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 overdose with bosentan beyond the doses described above. Massive overdose may result in pronounced hypotension requiring active cardiovascular support.

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

### Dosage Adjustment and Monitoring in Patients Developing Aminotransferase Abnormalities

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

If TRACLEER® is re-introduced it should be at the starting dose, aminotransferase levels should be checked within 3 days and thereafter according to the recommendations above. If liver aminotransferase elevations are accompanied by clinical symptoms of liver injury (such as nausea, vomiting, fever, abdominal pain, jaundice, or unusual lethargy or fatigue) or increases in bilirubin  $\geq$  2 x ULN, treatment should be stopped. There is no experience with the re-introduction of TRACLEER® in these circumstances. Use in Women of Child-bearing Potential: TRACLEER® treatment should only be initiated in women of child-bearing potential following a negative pregnancy test and only in those who practice adequate contraception that does not rely solely upon hormonal contraceptives, including oral, injectable or implantable contraceptives. Input from a gynecologist or similar expert on adequate contraception should be sought as needed. Urine or serum pregnancy tests should be obtained monthly in women of childbearing potential taking TRACLEER®. Dosage Adjustment in Renally Impaired Patients: The effect of renal impairment on the pharmacokinetics of bosentan is small and does not require dosing adjustment. Dosage Adjustment in Geriatric Patients: Clinical studies of TRACLEER® did not include sufficient numbers of subjects aged 65 and older to determine whether they respond differently from younger subjects. In general, caution should be exercised in dose selection for elderly patients given the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy in this age group. Dosage Adjustment in Hepatically Impaired Patients: The influence of liver impairment on the pharmacokinetics of TRACLEER® has not been evaluated. Because there is *in vivo* and *in vitro* evidence that the main route of excretion of TRACLEER® is biliary, liver impairment would be expected to increase exposure to bosentan. There are no specific data 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.

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# Erectile Dysfunction in Men with Scleroderma

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Erectile dysfunction (ED) may occur more frequently among men with scleroderma than among men with other chronic diseases. The pathophysiological characteristics of systemic sclerosis (SSc), such as microvasculopathy and fibrosis of the skin and organs, are potential organic causes of ED. However, it is difficult to rule out other comorbid factors that could contribute to ED, as well as psychosocial factors that may increase ED in men who are suffering from chronic disease. The objective of this paper is to review the evidence for increased prevalence of ED in men with scleroderma and the available information about pathogenesis and treatment.

## Prevalence of Erectile Dysfunction in Systemic Sclerosis

Several case reports of erectile dysfunction occurring with scleroderma have been published.<sup>1-7</sup> Three case series<sup>8-10</sup> and only two case-control studies have specifically addressed the association between ED and SSc.<sup>11,12</sup> The prevalence of ED in scleroderma has been reported as ranging from 12% to 81%.<sup>8-12</sup> Several methodological differences may have contributed to the heterogeneity of the prevalence point estimates. Differences included the definition of ED or impotence and which of these terms was used (where impotence may have been considered as a complete inability to achieve an erection sufficient for penetration, and ED was considered as varying degrees of erectile problems); small sample sizes (the largest case-control study had an SSc sample comprising 43 men and a control sample of 23 men with rheumatoid arthritis; the largest case series comprised 91 men, but only ED at presentation to the clinic was reported in this group); temporal considerations (ED/impotence ever, current ED/impotence at time of study, or ED/impotence at time of presentation to a tertiary referral center were all used as outcomes); and the study samples may have contained heterogeneous cases (diffuse vs limited, early vs longstanding, different comorbidities) that could have affected

ED, and thus, the prevalence estimates. In addition, because of the personal nature of sexual dysfunction, the validity of the prevalence estimates may vary depending on the comfort level of the subjects and willingness to address the issue with investigators. Study characteristics are summarized in **Table 1**.

## Erectile Dysfunction in Systemic Sclerosis Compared With Prevalence in Normal Population, in Older Adults, and in Other Chronic Diseases

The two case-control studies conducted to date, although 20 years apart, reported a similar prevalence of ED “ever” during the course of the disease (80%) in men with scleroderma. This figure is well above that estimated for the US male population in 1992 by the National Institutes of Health, which was reported as 5% at age 40, increasing to 15% to 25% at age 65 and older. The mean ages for the scleroderma subjects in the studies were 52 and 55 years.<sup>13</sup> Although the mean age was not specifically reported for two of the case series, the prevalence estimates for impotence were above 21%.<sup>9,10</sup> In the remaining case series the mean age was 48 and the impotence prevalence estimate was 12%, which is approximately double that expected in the US male population.<sup>8,13</sup> However, a community-based epidemiologic study of ED in a rural population (Central New York State) reported the prevalence of ED was between 21.3% and 46.3% in men aged 50 to 76 years. Hence, ED appears to be increased among men with SSc compared with men in the general population. However, as estimates vary widely, it is difficult to determine the magnitude of this effect.<sup>14</sup>

A literature search revealed only one Swedish study that addressed sexual dysfunction in men with chronic diseases, including glaucoma, diabetes, and angina pectoris, in comparison with a random sample from the general population.<sup>15</sup> Authors reported significantly increased prevalence estimates of ED for men with diabetes (30%) and angina pectoris (29%) compared with controls.<sup>14</sup> Thus, it appears that ED is increased more so in men who have SSc compared with those who have other chronic diseases. However, the estimates provided appear to be based on current ED at the time of the study, and so may not be directly comparable to the case-control studies of SSc (in which ED “ever” was reported).<sup>11,12,15</sup>

## Temporal Relationship

The temporal occurrence of ED in relation to the natural disease course of scleroderma has been considered in several studies. In

**Table. Summary of Literature Studying Risk of Erectile Dysfunction in Scleroderma.**

Study	Design	No. with SSc (total)	Assessment of ED	% SSc with ED (OR)	Assessment for Organic Basis	Temporal Relationship to Diagnosis
Hong 2004. <sup>11</sup>	CC; controls with rheumatoid arthritis	43 (66)	SR with standardized, validated questionnaire	81% (4.8) ED (ever)	Questioned on N and D factors; H assessment in subset	ED occurred at mean of 2.7 years after diagnosis
Nowlin 1986. <sup>12</sup>	CC; controls with rheumatoid arthritis (not taking steroids)	10 (20)	SR of ED and impotence (when questioned on ability for penetration)	80% (9.3) 60% (vs 0% rheumatoid arthritis) impotent	H, N, D, vascular factors (penile, arm and ankle blood pressures taken)	Current impotence not associated with Raynaud's phenomenon duration
Lally 1981. <sup>8</sup>	Case series	43	Presented as clinical complaint	12% had impotence	N, P (n = 4), H	All 5 presented with impotence as early symptom of SSc
Lally 1988. <sup>9</sup>	Case series	91	Not described	29% had ED, 21% presented with impotence	Not described	Not described
Simeon 1994. <sup>10</sup>	Case series	8	SR of impotence	50% (impotence)	Peyronie's disease in one fourth of men; other factors not described	Not described

CC = case control; D = drug related/pharmacological; ED = erectile dysfunction; H = hormonal/endocrinologic; N = neurological; P = psychological; SR = self-report; SSc = systemic sclerosis.

1981 Lally and Jimenez suggested that ED (impotence) may often be an early manifestation of SSc, and subsequent case reports have confirmed that ED may occur as a presenting symptom or very early in the disease.<sup>1-10</sup> Nowlin et al did not provide details of temporal relationship except to comment that disease duration (assessed by duration of Raynaud's phenomenon) was not associated with ED, while Hong et al found that ED occurs relatively early in the disease course but typically after diagnosis (mean, 2.7 ± 1.2 years).<sup>11,12</sup>

Studies are limited by the difficulty of determining disease onset of scleroderma, as symptom onset and diagnosis may be separated by a substantial time period dependent on many factors. The temporal occurrence of ED onset in SSc compared with ED onset in other chronic diseases has not been studied in a large sample of patients, but future research in this area may be beneficial for clarifying this important question.

### Etiology of Erectile Dysfunction in Systemic Sclerosis

Previous literature tends to support that the etiology of ED associated with scleroderma is organic rather than psychogenic.<sup>2,3,7,8,16,17</sup> Several recognized causal factors for ED that have been ruled out in various studies of individual SSc cases

include psychological, hormonal, and neurological conditions, as well as pharmacological exposures (**Table 1**). Although the pathophysiological mechanisms remain unclear, several vascular, fibrotic, and neurogenic factors have been suggested as being instrumental in the etiology of ED in scleroderma.<sup>3,6,7,8,12,16</sup> In particular, Nowlin et al have speculated that small artery lesions may be responsible for ED secondary to scleroderma,<sup>12</sup> while Hong et al have suggested that ED is associated with Raynaud's phenomenon independent of other vascular disease.<sup>11</sup>

### Vasculogenic Basis

In the first study to identify ED associated with early SSc, Lally and Jimenez ruled out certain known causes of ED (hormonal, psychogenic, and neurogenic) and postulated that vascular or autonomic nervous system alterations were possible underlying causes for ED, based on the concomitant occurrence of Raynaud's phenomenon and failure to achieve erections but maintenance of libido.<sup>8</sup> Assessments of penile vasculature were not part of this study but were conducted by several other groups. The strongest support comes from Nowlin et al, who measured arm, leg, and penile blood pressures and found that penile blood pressures were significantly lower in men with SSc and impotence compared to



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controls with rheumatoid arthritis and nonimpotent men with SSc. Four of the six impotent men with SSc met the definition of vasculogenic impotence (penile blood pressure index <0.6).<sup>12</sup> Evidence also comes from case reports. Barnadas et al described a patient with silicosis-induced SSc who was observed to have defective repletion of the corpora cavernosa while other arteriographic studies were normal<sup>2</sup> and Rossman and Zornigotti reported altered corporeal architecture and vascular abnormalities secondary to fibrosis in three men with SSc and ED.<sup>5</sup> Hence, in 1990, Lally and Jimenez summarized that the accumulated evidence supported vascular and neurogenic factors (in response to a report by Sukenik et al described below<sup>3,16</sup>) as likely causal factors in ED secondary to SSc.<sup>18</sup>

Subsequent reports provided additional support for penile arterial insufficiency and collagenization of corporeal smooth muscle.<sup>6,7</sup> In a case-control study, Hong et al reported that SSc subjects were more likely to have noticed a changed appearance of the penis or testes, thus suggesting ED was due to fibrosis secondary to SSc,<sup>11</sup> and in a case series of four men with SSc and ED, Simeon et al discussed a possible causal association with Peyronie's disease, a condition characterized by fibrosis of the corpora cavernosa.<sup>10</sup> Thus, most of the literature supports that ED associated with SSc is due to underlying vasculopathic and fibrotic alterations.

### Neurological Basis

ED in SSc could result from an autonomic neuropathic process. Although compression neuropathies (eg. carpal tunnel syndrome) are common in SSc, peripheral neuropathies from other causes may not be. Several studies reported no association of neurological causes with ED in SSc.<sup>5,8,12</sup> Sukenik et al described a man with SSc and impotence, peripheral neuropathy, and carpal tunnel syndrome, and they suggested that in addition to vascular alterations, abnormalities in the autonomic nervous system may be pathogenic in ED associated with SSc.<sup>3,16</sup>

### Association with Raynaud's Phenomenon

Raynaud's phenomenon is present in the majority of patients with SSc. Interestingly, it may be a risk factor for ED. Hong et al reported that men with Raynaud's phenomenon had more ED compared with those who did not have it ( $P < .01$ ) in both SSc and rheumatoid arthritis. However, in a subset of men with only SSc, Raynaud's phenomenon was not found to be an independent risk factor for ED.<sup>11</sup> Other groups have reported cases of ED occurring concomitantly with severe Raynaud's phenomenon secondary to SSc.<sup>17,19,20</sup> Another group reported that men with chemotherapy-induced Raynaud's had significantly more ED compared with those who did not have Raynaud's, while in men with acral (saddle) paresthesia from tumor resection ED was not

increased.<sup>21</sup> These data suggest that ED may be a vasculopathy associated with Raynaud's phenomenon. Future studies of ED in men with primary Raynaud's disease may be informative in defining the association between vasospastic disorders and ED in the absence of chronic disease.

### Psychogenic Basis

Several case reports and one case-control study did not state whether psychogenic factors were assessed,<sup>2-4,7,12</sup> and three reported no clear association of psychological factors and ED.<sup>1,5,6</sup> In addition, virtually all case reports noted that libido had remained constant both before and after ED onset. Psychiatric evaluations were conducted on all five men in the study by Lally and Jimenez; none were remarkable as potential causes of their ED.<sup>8</sup> Hong et al did not specifically address in their questionnaire whether subjects had a psychogenic basis for ED, but did determine that SSc subjects with ED were less likely to have had night or morning erections. This evidence supports that ED in SSc is not usually due to psychological causes.<sup>11</sup>

### Hormonal Basis

ED secondary to SSc does not appear to be associated with low testosterone or elevated prolactin levels in the majority of cases. Two studies reported a correlation between testosterone and/or other hormone levels and ED in at least one of the study subjects with SSc. In one case report the subject had mild hypogonadism that did not respond to hormone replacement therapy;<sup>4</sup> and Lally and Jimenez reported that two of five men with ED and SSc were treated with hormones (one of whom had some response) and that testosterone levels were higher in subjects with some residual degree of sexual functioning.<sup>8</sup> An endocrinologic basis for ED was not confirmed by the majority of case reports.<sup>3,5-7,9,12,16</sup> Hong et al reported that ED had not improved in any of the small proportion of men who had been taking testosterone treatment.<sup>11</sup> Nowlin et al have described a case in which a man who presented with ED was diagnosed simultaneously with scleroderma and Klinefelter's syndrome, and in whom ED improved in response to testosterone replacement therapy.<sup>22</sup> Thus, hormonal complications can be assessed prior to work-up for other underlying causes of ED in patients with SSc, as some men may respond to testosterone replacement, although this appears not to be the causal factor in the majority of SSc patients.

### Pharmacological Basis

Consideration of the possible relationship with pharmacological agents was reported in a subset of studies.<sup>3,6,8,11,12</sup> Hong et al reported that oral steroid use was similar between SSc cases and controls but did not report any drug associations with ED.<sup>11</sup> Nowlin et al reported a possible protective effect of D-penicillamine for ED in SSc, but no association with nifedipine,<sup>12</sup> while other groups described cases that did not respond to D-penicillamine or nifedipine,<sup>3,17</sup> or androgens.<sup>3</sup>

### Fertility in Men With Systemic Sclerosis

Nowlin et al reported that all of the men in their study except one (who had both SSc and ED) had fathered children.<sup>12</sup> In their case-

control study Hong et al found that the number of biological children of subjects with SSc was significantly less than that of the controls, and men with Raynaud's phenomenon also had significantly fewer children compared with men who did not have Raynaud's.<sup>11</sup> Conclusions about infertility in men with SSc cannot be drawn from the data examined in this review, as the studies were not powered to detect differences and/or this was not the hypothesis of the studies.

### Potential for Therapy: Suggestions and Comments

The studies included in this review did not focus on treatment options but instead the study objectives were often to describe the association and characterize the pathophysiology involved. Investigators commented on therapeutic interventions that had been attempted; however, no clinical trials that specifically focused on treatment options in this group were found in the literature. Available therapies for primary ED include phosphodiesterase-5 (PDE-5) inhibitors, intraurethral (suppository) and intracavernosal (injection therapy) prostacyclins, penile implants, testosterone replacement therapy, vacuum erection devices, and treatment of underlying psychological conditions (eg, psychotherapy for depression).<sup>23</sup>

There is limited anecdotal evidence that conventional therapy for ED may successfully treat ED secondary to SSc in some cases (at least one man regained sexual function following implantation of a penile prosthesis<sup>6</sup>), although investigators either did not report outcomes of therapy or reported that improvement was minimal. No reports of treatment of ED in SSc with sildenafil (Viagra) or other PDE-5 inhibitors were found in a search of the literature.

Several groups have reported that penile prostheses were implanted.<sup>1,2,3,5,6</sup> Some have commented that implantation was difficult because of fibrosis of the corpora cavernosa,<sup>2,3,5,6</sup> and in at least one case the prosthesis was subsequently removed because of pain and necrosis of the glans penis.<sup>2</sup> Other treatments, including penile revascularization (one case reported in whom there was minimal improvement<sup>5</sup>), intracorporeal papaverine,<sup>5</sup> hormone therapy,<sup>8</sup> and pharmacological agents,<sup>3,12,17</sup> have yielded limited success in this group of patients.<sup>5,8,12,17</sup> Anecdotal treatment with application of a nitroglycerin patch to the penis resulted in temporary improvement of sexual functioning in one study.<sup>20</sup> As discussed in the literature, penile revascularization may be inappropriate in SSc patients considering the pathophysiological fibrotic and vasculogenic changes characteristic of this disease.<sup>5,7</sup> In addition, side effects of conventional ED treatments may affect this group of men differentially. An adverse effect of oral yohimbine treatment for ED in a man with CREST was reported, in which both severity and frequency of attacks of Raynaud's phenomenon were increased with the drug, and improved with drug withdrawal.<sup>24</sup>

Treating ED associated with SSc may present a challenge for physicians. The optimal course of action may be to assess whether there is a hormonal, psychological, or other commonly recognized basis for ED (eg, alcoholism, diabetes, side effects of drug therapies), and if so, to treat accordingly. Beyond this, referral to a urologist who specializes in ED may be necessary. Penile blood pres-

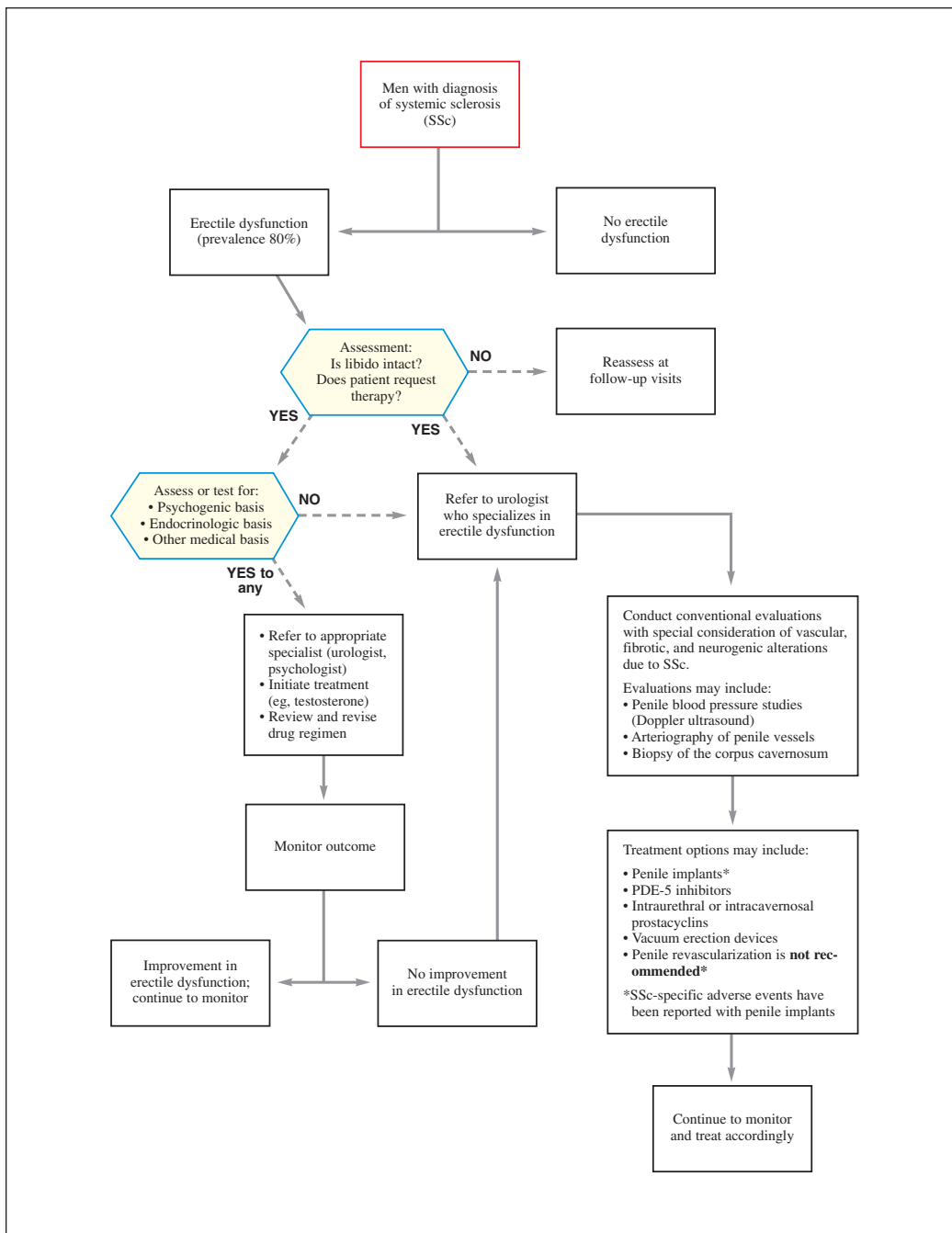


Fig.—Evaluation and treatment options for men with systemic sclerosis and erectile dysfunction.

tures and investigations of vascular alterations (penile blood pressure assessments using Doppler ultrasound, arteriographic studies, corpus cavernosum biopsy), as well as abnormalities in the autonomic nervous system could be conducted in order to clarify the degree of pathophysiological changes and allow physicians to determine the most appropriate choice of therapeutic intervention (Figure 1). Clinical trials to determine the effectiveness of available treatments for ED in this population could be informative and improve the quality of life for men with SSc.

### Limitations

We recognize that there are substantial shortcomings in the quality of the literature assessing the association of ED and SSc. No prospective cohort studies have been conducted, and thus the best

evidence is from two case-control studies and several case series and reports. Sample size is a considerable problem; case series and reports have no control group and supply limited information, and questionnaire studies may be prone to subject bias, misinterpretation of the questions (especially considering the personal nature of the subject matter), and low response rates. This association warrants further study, which may be best undertaken in the context of a large multicenter prospective registry in which data on ED could be collected on an ongoing basis.

### Conclusions

ED occurs more frequently in men with scleroderma compared to the overall North American male population, and it may occur relatively early in the disease course. Treating physicians should be aware of this association and address the issue as part of their clinical assessment. The underlying pathophysiology is organic, likely multifactorial, and may respond to therapy in some cases. Further research in this area is feasible and may result in substantial benefit to affected patients.

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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"](mailto:jablonj@msx.dept-med.pitt.edu)  
[jablonj@msx.dept-med.pitt.edu](mailto:jablonj@msx.dept-med.pitt.edu)**

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

# BUILD 2

## Bosentan Use in Interstitial Lung Disease

**A double-blind, randomized, placebo-controlled, multicenter study to assess the efficacy, safety, and tolerability of bosentan in patients with active interstitial lung disease associated with systemic sclerosis**

Oral bosentan 125 mg / placebo b.i.d.

Primary endpoint: Change from baseline to month 12 in 6-minute walk distance.

Main secondary endpoint: Time to death or worsening pulmonary function tests.

### **Main Inclusion Criteria**

- Systemic sclerosis diffuse or limited.
- Significant interstitial lung disease on HRCT scan.
- DLco <80% of predicted.
- Dyspnea on exertion.
- Walk not limited for musculoskeletal reasons.

### **Main Exclusion Criteria**

- Interstitial lung disease due to conditions other than systemic sclerosis.
- End-stage restrictive or obstructive lung disease.
- Severe cardiac or renal diseases.
- Significant pulmonary arterial hypertension.
- Smoker (>5 cigarettes per day).
- Treatments with immunosuppressive, antifibrotic drugs, high dose corticosteroids (within 4 weeks of randomization).

### **Participating Sites**

Site participation depends on IRB/regulatory approval

#### **USA**

Boston Univ School of Medicine, Boston – Dr. Korn  
Cleveland Clinic, Cleveland – Dr. Chatterjee  
Denver Health Medical Center, Denver – Dr. Collier  
Georgetown University, Washington, DC – Dr. Steen  
Jefferson Medical College, Philadelphia – Dr. Jimenez  
Mayo Clinic, Rochester – Dr. Kalra  
Medical Univ South Carolina, Charleston – Dr. Silver  
St. Peters Hospital, Albany – Dr. Shapiro  
UCLA Med School, Los Angeles – Dr. Furst  
UMDNJ, New Brunswick – Dr. Hsu  
Univ Texas Houston Medical School, Houston - Dr. Mayes  
University of Illinois, Chicago – Dr. Varga  
University of Miami, Miami – Dr. Glassberg  
University of Michigan, Ann Arbor – Dr. Kaplan  
University of Pittsburgh, Pittsburgh – Dr. Medsger  
University of Washington, Seattle – Dr. Raghu  
Virginia Mason Medical Center, Seattle – Dr. Molitor

#### **EUROPE/ISRAEL**

Centre Hospitalier Universitaire, Grenoble, France – Dr. Carpentier  
Charité Universitätsklinikum, Berlin, Germany – Dr. Riemekasten  
CHRU Claude Huriez, Lille, France – Dr. Hachulla  
Hôpital Avicenne, Bobigny, France – Dr. Guillevin  
Hôpital Notre-Dame, Montreal – Dr. Rich  
Hôpital Saint Antoine, Paris, France – Dr. Cabane  
Istituto di Clinica, Firenze, Italy – Dr. Matucci Cerinic  
Leeds General Infirmary, Leeds, UK – Dr. Emery  
Lund University Hospital, Lund, Sweden – Dr. Akesson  
Ospedale Maggiore, Milano, Italy – Dr. Scorza  
Policlinico Universitario, Padova, Italy – Dr. Todesco  
Pulmonary institute, Rabin Medical Center, Petach Tikva, Israel - Dr. Kramer  
Royal Free Hospital, London, UK – Dr. Black  
Sint Maartenskliniek, Nijmegen, Netherlands – Dr. van Den Hoogen  
University Hospital, Zürich, Switzerland – Dr. Brühlmann  
**Steering Committee Chairman:** Dr. Joseph H. Korn

# RAPIDS-2

A **RA**ndomized, double-blind, **P**lacebo-controlled, multicenter study to assess the effect of bosentan on healing and prevention of **I**schemic **D**igital ulcers in patients with systemic **S**clerosis.

*There is no evidence that bosentan is safe and effective in digital ulcers.*

**Study drug:** Bosentan 125 mg b.i.d.

**Design:** Multicenter, randomized, double-blind, placebo-controlled, phase III study.

**Sponsor:** Actelion Pharmaceuticals Ltd.

**Principal Investigators:** (J. Korn, Boston University, and J. Seibold, University of Medicine and Dentistry of NJ)

## Patient Selection Criteria

### *Inclusion Criteria (main):*

- Systemic Sclerosis, diffuse or limited.
- SSc patients with at least one digital ulcer at baseline qualifying as a cardinal ulcer
- Male or female patients > 18 years of age.
  - Women of childbearing potential must have a negative pre-treatment pregnancy test and use a reliable method of contraception during study treatment and for at least 3 months after study treatment termination.
  - Women not of childbearing potential are defined as postmenopausal (i.e., amenorrhea for at least 1 year), or surgically or naturally sterile.

### *Exclusion Criteria (main):*

- Digital ulcers due to conditions other than SSc.
- Severe PAH (WHO class III and IV).
- Malabsorption or any severe organ failure (e.g., lung, kidney, liver) or any life-threatening condition.
- Treatment with parenteral prostanoids (prostaglandin E, epoprostenol, treprostinil sodium or other prostacyclin analogs) 3 months prior to randomization.

- Treatment with inhaled or oral prostanoids one month prior to randomisation
- Previous treatment with bosentan

### **Outcome Measures**

#### *Primary:*

- Time to healing of the cardinal ulcer.
- Number of new digital ulcers during the treatment period.

#### *Secondary:*

- Hand functionality indices.
- Hand pain

### **Time Line**

- Recruitment period: October 2003 – February 2004.
- Completion: 1st quarter 2005.
- Date of expected analysis: 2nd quarter 2005.

To date, one clinical trial, RAPIDS-1, has been performed in the same indication including scleroderma patients with or without digital ulcers at baseline. The RAPIDS-1 study showed that bosentan reduces significantly the number of new digital ulcers versus placebo. The safety profile of bosentan observed in the RAPIDS-1 study was similar to that observed in pulmonary hypertension, an indication currently approved in the countries where the RAPIDS-2 study is performed.

If you have a patient that you think might be suitable, or if you would like more information about the study please visit our web site on [www.sctc-online.org](http://www.sctc-online.org).

## Centers involved (site participation depends on IRB/regulatory approval):

### USA

University of Colorado Hospital, Denver, CO, Dr. Collier  
Froedtert / Medical College, Milwaukee, WI, Dr. Csuka  
Tulane University Health Sciences Center, New Orleans, LA, Dr. Doyle  
University of Chicago Hospitals, Chicago, IL, Dr. Ellman  
University of Alabama at Birmingham, Birmingham, AL, Dr. Fessler  
UCLA School of Medicine, Los Angeles, CA, Dr. Furst  
North Shore University Hospital, Manhasset, NY, Dr. Goldberg  
University of Medicine and Dentistry of New Jersey, New Brunswick, NJ, Dr. Hsu  
Thomas Jefferson University, Philadelphia, PA, Dr. Jimenez  
Ruppert Health Center, Toledo, OH, Dr. Kahaleh  
Spokane Rheumatology Group, Spokane, WA, Dr. Kenney  
Boston University Medical Center, Boston, MA, Dr. Korn  
University of Texas, Houston, TX, Dr. Mayes  
University of Pittsburgh, Pittsburgh, PA, Dr. Medsger  
Virginia Mason Research Center, Seattle, WA, Dr. Molitor  
Mayo Clinic, Rochester, MN, Dr. Osborn  
University of Connecticut Health Center, Farmington, CT, Dr. Rothfield  
The Center for Rheumatology, Albany, NY, Dr. Shapiro  
Medical University of South Carolina, Charleston, SC, Dr. Smith  
Johns Hopkins University School of Medicine, Baltimore, MD, Dr. Wigley

### Canada

SMBD-Jewish General Hospital, Montreal, Quebec, Dr. Baron  
St. Joseph's Health Care London, London, Ontario, Dr. Pope  
Hôpital Notre-Dame, Montreal, Quebec, Dr. Rich

### Europe

Centre Hospitalier Universitaire, Grenoble, FR, Dr. Carpentier  
Hôpital Cochin, Paris, FR, Dr. Guillevin  
Hôpital Pitie Salpetriere, Paris, FR, Dr. Frances  
Centre Regional Hospitalier Universitaire, Lille, FR, Dr. Hachulla  
Inselspital, Universitätsspital Bern, Bern, CH, Dr. Oertle  
Universitätsklinikum, Köln, GER, Dr. Krieg  
Universitätsklinikum, Erlangen, GER, Dr. Manger  
Universitätsklinikum, Dresden, GER, Dr. Meurer  
Universitätsklinik, Freiburg, GER, Dr. Peter  
Rheumaklinik, Bad Bramstedt, GER, Dr. Hellmich  
Azienda Ospedaliera Carreggi, Firenze, IT, Dr. Matucci Cerinic  
Ospedale Maggiore, Milano, IT, Dr. Scorza  
Azienda Ospedaliera Luigi Ssacco, Milano, IT, Dr. Carrabba  
Azienda Policlinico di Modena, Modena, IT, Dr. Ferri  
Policlinico Umberto 1, Roma, IT, Dr. Salsano  
Sint Maartenskliniek, Nijmegen, NL, Dr. Vvan den Hoogen  
AKH, Universitätsk. Klinik für Innere Medizin III, Wien, AUS, Dr. Aringer  
Universitäts. klinik für Dermatologie und Venerologie, Innsbruck, AUS, Dr. Fritsch Dr. Aringer  
Royal Free Hospital, London, UK, Dr. Black  
St. George's Hospital, London, UK, Dr. Bourke Dr. Fritsch  
Freeman Hospital, Newcastle, UK, Dr. Griffiths  
Selly Oak Hospital, Birmingham, UK, Dr. Bowman  
Hospital Vall d'Hebron, Barcelona, SP, Dr. Fonollosa  
Hospital Dr. Peset, Valencia, SP, Dr. Roman

# **Scleroderma**

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