

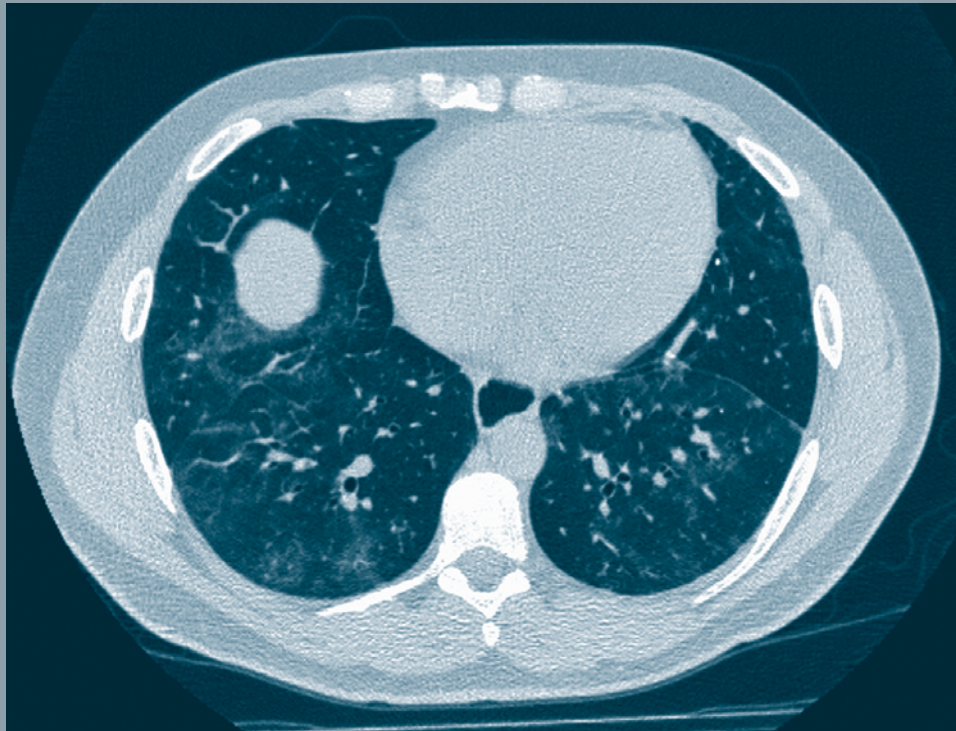
# *Scleroderma*

Care and Research

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Volume 1, Number 1  
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Journal of the  
Scleroderma Clinical  
Trials Consortium



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*Premier Issue:*  
*Lung Involvement in*  
*Scleroderma*

*Contents:*

*Editor's Memo. . . . . 2*

*Interstitial Lung Disease in*  
*Systemic Sclerosis:*  
*Optimizing Evaluation and*  
*Management . . . . . 3*

*Pulmonary Hypertension*  
*Related to Systemic Sclerosis:*  
*A Primer for the*  
*Rheumatologist . . . . . 12*



## 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:

HRCT of scleroderma lung showing focal areas of alveolitis.

## Editor's Memo

# Introducing *Scleroderma Care and Research*

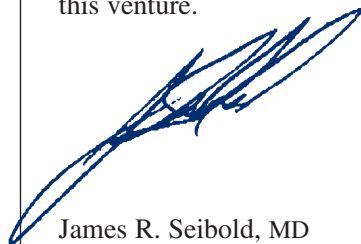
We welcome you to this new publication, *Scleroderma Care and Research*. This is the inaugural issue of a journal developed by the Scleroderma Clinical Trials Consortium (SCTC), and we have lofty goals.

The SCTC was organized in 1994 by a cadre of individuals dedicated to the concept that persons with scleroderma deserved the highest standards in clinical research. The SCTC incorporated as a tax exempt organization in 2001 and has grown to be a dynamic international body. The mission of the SCTC is to develop, conduct, and promote rigorous generalizable interventional research into this most enigmatic and challenging disorder. Activities include trial development, cohesive studies of candidate measures of outcome, and rapid application of bench research to bedside practice. SCTC members are firmly committed to the concept that until therapies for scleroderma are documented to be effective, *protocol participation is the treatment of choice*.

Our underlying motivation is elevation of standards of care in scleroderma. This publication is an important step forward. This issue focuses on the complexities of lung involvement in scleroderma. Lung involvement has emerged to be the leading cause of death. As with any aspect of scleroderma, pathophysiology is complex and multifactorial. In fibrosing alveolitis, rigorous randomized controlled trials are in progress with cyclophosphamide and with bosentan. In pulmonary arterial hypertension, we now have three FDA-approved agents—epoprostenol, bosentan, and treprostinil—and many more are in clinical development.

We hope you find this journal useful in your practice. We hope that you consider SCTC trials as an approach to patient management. We urge you to visit our Web page (<http://www.sctc-online.org>) for updated information about trials and how to contact participating centers.

We thank our partners in this endeavor, including the International Scleroderma Network, the Scleroderma Research Foundation, and the Scleroderma Foundation. Each of these patient-oriented groups stands shoulder to shoulder with the SCTC in the quest to solve scleroderma. Visit their Web pages. Alert your patients to the growing array of resources. Finally, we thank Actelion Pharmaceuticals and United Therapeutics for their initial underwriting of this venture.



James R. Seibold, MD  
Editor-in-Chief

# Interstitial Lung Disease in Systemic Sclerosis: Optimizing Evaluation and Management

**Richard M. Silver, MD, and Philip J. Clements, MD**

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Since angiotensin-converting-enzyme (ACE) inhibitors are saving the lives of the majority of systemic sclerosis (SSc) patients affected by scleroderma renal crisis (SRC), most SSc deaths are now the result of end-stage lung disease (both interstitial and pulmonary vascular). Although ~90% of SSc patients have been found to have pulmonary interstitial fibrotic changes at postmortem examination or on high-resolution computed tomography (HRCT) of the chest, only ~40% develop moderate or severe restrictive pulmonary disease on physiologic pulmonary function testing (forced vital capacity [FVC] of  $\leq 75\%$  of predicted). Not unexpectedly, survival is inversely related to the degree of pulmonary restriction: the 10-year cumulative survival in one study was 87% in patients with minimal or no restriction (%FVC  $>75\%$  of predicted), 75% in patients with moderate restriction (%FVC between 50% and 75% of predicted), and 58% in patients with severe restriction (%FVC  $<50\%$  of predicted).

The earliest interstitial changes in SSc interstitial lung disease (ILD) occur in the subpleural areas in the posterior bases of both lungs. In patients who later go on to develop moderate or severe restriction, the interstitial changes appear in ever-higher levels of the lung (ie, the upper lung fields becoming affected in the most severe instances).

In SSc patients who do go on to develop significant interstitial-restrictive lung disease, the greatest loss of physiologic lung function (especially the %FVC) occurs early. In one study, those patients who went on to develop severe restrictive disease (%FVC  $<50\%$  of predicted) lost 32% of remaining FVC each year for 2 years, then 12% of remaining FVC each year for 2 years and 3% of remaining FVC each year through years 5 and 6. This study suggests that if physicians are going to make a difference in the lives of these SSc patients, we must be able to identify patients who are likely to progress to severe restrictive lung disease, and treat them within the first few years of SSc onset. This goal of early detection in order to initiate rapid and potent treatment is similar to that shared by rheumatologists caring for patients with early rheumatoid arthritis (RA) or for lupus patients at risk for dif-

fuse proliferative glomerulonephritis. Only in recent years have the tools become available to investigate early interstitial and pulmonary vascular disease in SSc patients.

## ETIOPATHOGENESIS

Although it is clear that ILD in SSc is associated with interstitial and alveolar inflammation, pulmonary vascular abnormalities and interstitial fibrosis, it is not clear which, if any, are the primary events. It may well be that there is another as yet unidentified process which, once initiated, leads to all these downstream events. There are strong suggestions, however, that inflammation (seen on lung biopsy or in the bronchoalveolar lavage [BAL] fluid) is an early process and that when present, it predicts progressive decline in physiologic lung function (measured primarily as %FVC). The progressive loss of lung function then predicts increasing morbidity and a progressive decline in survival.

Although long felt to be the result of a bland fibrosing process, the “alveolitis” associated with SSc lung disease is now known to be associated with an active, inflammatory process that culminates in fibrosis and significant alteration of the pulmonary microarchitecture. Numerous studies have confirmed the presence of pro-inflammatory and profibrotic cytokines in the BAL fluid obtained from SSc patients with ILD. For example, levels of the chemokine IL-8 are elevated, perhaps contributing to the neutrophilic alveolitis characteristic of SSc ILD. Tumor necrosis factor-alpha (TNF-alpha) levels are also elevated (in serum and BAL fluid) and have been shown to correlate inversely with FVC. Potent fibroblast mitogens (eg, platelet-derived growth factor [PDGF] and thrombin) and profibrotic factors (eg, transforming growth factor-beta [TGF-beta] and connective tissue growth factor [CTGF]) are elevated in SSc BAL fluid and may play a role in the pathogenesis of ILD in SSc. The presence of such cytokines and growth factors may one day indicate the need for aggressive therapy to neutralize their effects, similar to the use of TNF-alpha inhibitors in patients with RA.

## CLINICAL EVALUATION OF LUNG FUNCTION AND LUNG INVOLVEMENT

### Symptoms

Dyspnea is the most common complaint of patients with ILD and when severe is a most debilitating symptom. With mild degrees of ILD, the dyspnea usually becomes apparent only with exertion. By the time dyspnea is occurring at rest, it is usually a sign that the lung disease is moderate or severe (either from ILD or from pulmonary vascular disease). In SSc a number of comorbidities (ie,



**Fig. 1—Patient undergoing pulmonary function testing.**

fatigue and musculoskeletal pain/weakness and restricted joint motion) may occur concomitantly and prevent patients from exerting themselves enough to know whether or not they have dyspnea. Because patients may not be able to exert themselves, for reasons other than dyspnea, assessment of the degree of dyspnea in SSc may be difficult or impossible. Thus an alternative approach is being advocated to detect progressive restrictive disease early in its course: SSc patients should be screened with pulmonary function testing (sometimes it is adequate to order only the %FVC [spirometry] and the diffusing capacity [%DL<sub>CO</sub>] every 3 to 6 months in the first 6 years of SSc). This type of screening will document progressive declines in FVC and/or DL<sub>CO</sub>, which should be the signal to evaluate the patient further. Cough is another common symptom of lung fibrosis. Usually, the cough is nonproductive and made worse by exertion. A productive cough, or hemoptysis, requires further evaluation to rule out such conditions as aspiration pneumonia or neoplasm.

### **Pulmonary Function Testing**

Physiologic pulmonary function tests (PFTs) are among the easiest and least invasive ways of measuring lung function and have been used as surrogates for morbidity and survival in most lung diseases, including SSc (**Figure 1**). Rarely, diminished oral aperture precludes adequate PFTs. In such cases, a flexible pediatric mouthpiece might be useful. The most frequently abnormal PFT in SSc is the DL<sub>CO</sub>. Unfortunately this test can reflect damage from a multitude of processes, including obstructive, restrictive, and pulmonary vascular involvement. Fortunately in SSc, obstructive disease is not all that common, and as a result, a reduced DL<sub>CO</sub> usually reflects restrictive and/or pulmonary vascular disease. FVC on the other hand is a better measure of ILD or restrictive lung disease, assuming confounding issues with poor patient effort or weak respiratory muscles can be ruled out.

In SSc we tend to use %FVC and %DL<sub>CO</sub> as measures of evaluating restrictive disease (where %FVC and %DL<sub>CO</sub> tend to decline to the same degree) and pulmonary vascular disease (where there is a disproportionate decline in DL<sub>CO</sub> relative to

decline in FVC). These two measures can be put into a ratio where the %FVC is the numerator and the %DL<sub>CO</sub> is the denominator ( $\%FVC \div \%DL_{CO}$ ). This ratio can help in thinking about whether the patient has predominantly interstitial disease, pulmonary vascular disease, or a mixture of both.

Three examples may help to explain. 1) If the %FVC is less than 75% of predicted and the ratio of the %FVC divided by %DL<sub>CO</sub> is <1.4, it is likely that the patient has a predominantly *restrictive* pulmonary pattern. 2) If the %FVC is >75% and the ratio of %FVC divided by %DL<sub>CO</sub> is >1.4 (ie, a %FVC of 80% and a %DL<sub>CO</sub> of 40% would give a ratio of 2.0), it is more likely that the patient has a primarily *pulmonary vascular* involvement. 3) If the %FVC is <75% and the ratio of %FVC divided by %DL<sub>CO</sub> is >1.4 (ie, a %FVC of 60% and a %DL<sub>CO</sub> of 30% would give a ratio of 2.0), it is very likely that the patient has a mixture of *restrictive and pulmonary vascular* involvement.

It is important for physicians to recognize these three patterns because appropriate recognition can help the physician focus on the appropriate set of evaluations. This should not be taken to mean that a patient who has findings on PFTs that look like a primarily restrictive pattern should not have some attention paid to the possibility of pulmonary vascular involvement (and vice versa) as a cause of dyspnea. What it does mean is that the patient with predominantly restrictive PFTs may need the most intensive attention paid to the causes and treatment of interstitial-restrictive lung disease.

### **Open Lung Biopsy**

The “gold standard” for the evaluation of restrictive lung disease is the open lung biopsy that can show the type and degree of inflammation as well as the degree of fibrosis. It can also show the presence of other processes that may mimic or confound SSc ILD (ie, sarcoidosis, bronchiolitis obliterans with organizing pneumonia [BOOP], aspiration from gastroesophageal reflux). The classifications of the histopathologic patterns in ILD, however, continue to change, perhaps reflecting an incomplete understanding of the pathogenesis of the various ILDs. In addition it is not clear whether the classification really predicts outcome or response to treatment. A recent review from Bouros et al. suggests that the predominant lesion in SSc is nonspecific interstitial pneumonitis (NSIP). Other studies suggest that the lesion found in one area of lung tissue may be different from another found in another area of the same patient with idiopathic pulmonary fibrosis (IPF), a disorder considered by many to be similar to ILD of SSc.

Because the test is invasive, is associated with significant morbidity even if done thoroscopically, can give differing results depending on what area(s) are selected for biopsy, and may not provide accurate prognostic or therapeutic guidance, it is not considered the test of choice.

### **Bronchoalveolar Lavage**

When properly performed, the BAL fluid cell differential reflects inflammatory alveolitis much as synovial fluid analysis reflects inflammatory synovitis. The fact that histopathologic sections from lung biopsies show weak correlations with BAL fluid findings also should not be surprising. Synovial tissue biopsies in

# 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 (> 5cigarettes per day).
- Treatments with immunosuppressive, antifibrotic drugs, high dose corticosteroids (within 4 weeks of randomization).

### **Participating Sites**

Site participation depends on IRB/regulatory approval

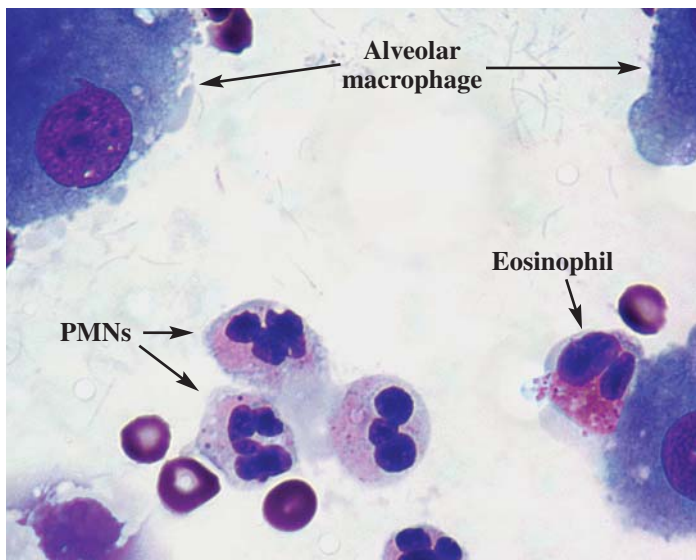
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- Pulmonary institute, Rabin Medical Center, Petach Tikva – Israel – Dr. Kramer

**Steering Committee Chairman:** Dr. Joseph H. Korn.



**Fig. 2**—Bronchoalveolar lavage fluid cells stained with Wright stain.

inflammatory synovitis often show mononuclear cell infiltration, and these findings correlate poorly with the polymorphonuclear cell predominance seen in inflammatory synovial fluids. The cells in the tissue and the cells in the fluid undoubtedly reflect different aspects of disease.

Bronchoscopy itself is widely available in the community, as is the ability to lavage the alveolar airspace. Unfortunately, differences in the BAL technique among practitioners, coupled with the inadequate handling, staining, and interpretation of the differential counting of the BAL fluid cells, often lead to large sources of error and variability and make the procedure less useful than it should be. These problems have made it virtually impossible to use the BAL as a clinical tool unless these sources of error can be reduced. Several studies have suggested that the situation can be improved and that BAL can be made a reliable technique for finding inflammation. Specific training of health professionals in the preparation and interpretation of BAL fluid cells, the need to have BAL fluid cell differentials performed by at least two trained observers (each counting at least 400 cells), the need to come to consensus on cell differentials if the counts between the two observers differ by more than 10%, and the need to culture BAL fluid to identify a potential confounder of SSc alveolitis should improve the validity and the reliability of data derived from BAL. This should improve the ability to trust the BAL results as a guide to diagnosis and therapy of ILD in SSc. It is important for the rheumatologist to work closely with a pulmonologist experienced in the techniques of bronchoscopy with BAL (using American Thoracic Society guidelines) and to assure that the laboratory personnel utilize a standardized methodology for counting cells and preparing cytopsin preps for differential cell counts.

The definitions of alveolitis that best predict declines in FVC and  $DL_{CO}$  in SSc relate primarily to increases in polymorphonuclear (PMN) and eosinophilic (EOS) leukocytes in BAL fluid (**Figure 2**). One common definition of alveolitis includes the presence of  $\geq 3\%$  PMN and/or  $\geq 2\%$  EOS leukocytes in the BAL fluid. Although lymphocytosis ( $\geq 20\%$  of BAL cells) may accompany

increased %PMN and %EOS leukocytes, it is less clear what the presence of an isolated lymphocytosis means with regard to future lung function or therapy in SSc. Using definitions similar to the one listed above, several studies have shown that the presence of increased PMN and/or EOS leukocytes in BAL fluid predicts continued loss of FVC and  $DL_{CO}$ . For example, a recent study by White et al. showed that the presence of alveolitis at entry predicted a 7.1% drop in %FVC and a 9.6% drop in %  $DL_{CO}$  over the next 13 months (median). Consensus of investigators suggests that an increased *percentage* of individual cell types in the BAL fluid are the best predictors of future course, rather than the total numbers of cells obtained from BAL fluids. Although smoking of cigarettes increases the total number of cells from BAL, the percentages of the cell types are not significantly affected by smoking alone. Thus BAL in smokers can still give valuable information about inflammation of alveoli from SSc.

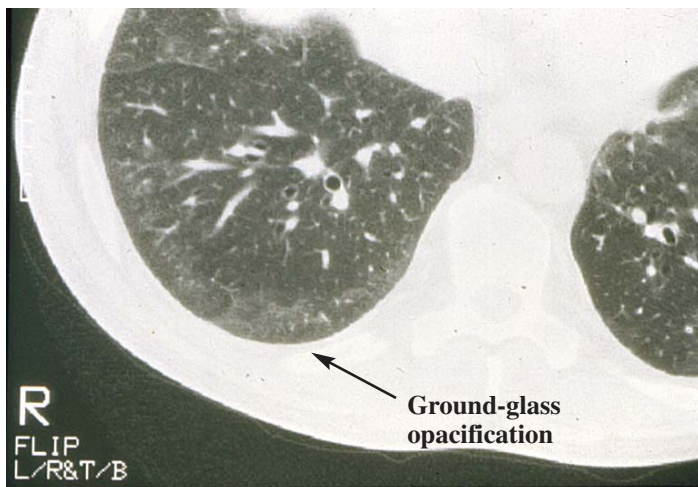
### High-Resolution Computed Tomography (HRCT) of the Chest

Chest HRCT is a tool that is much more sensitive in showing interstitial changes than is standard chest radiography. The hope is that it will also be a tool sensitive enough to find early inflammatory changes that will predict outcome (much as BAL). Ground-glass (GG) opacification (a hazy-appearing opacification through which normal lung architecture can be seen) may be such a sign of inflammation, particularly if there is little or no obvious fibrotic change in the same area (**Figure 3**). This GG opacification unfortunately is not specific for inflammation since the same appearance may be observed in the presence of infection, atelectasis, interstitial or alveolar fluid (ie, pulmonary edema or congestive heart failure), and early fibrosis (changes that have not coalesced enough to be interpreted as obvious fibrosis).

Longitudinal studies suggest that interstitial changes continue to progress over time, but it is not yet clear that GG opacification is a necessary precursor or predictor of future fibrosis. This is somewhat analogous to the situation with alveolitis on BAL: its presence predicts worsening of lung function, but it is not clear that there is a cause and effect relationship between alveolitis and progressive fibrosis. If HRCT studies can be shown to correlate with BAL findings in large-scale studies, it is likely that HRCT scans may replace BAL as a method to evaluate ILD in SSc patients. In the meantime we use both BAL and HRCT to diagnose alveolitis. The advantages of HRCT scans include the noninvasive nature of the study, which facilitates serial studies over time, as well as the fact that with HRCT both lungs can be examined in their entirety.

### Patient Self-Assessment Questionnaires

Although the disability index of the Health Assessment Questionnaire (HAQ-DI) has been validated as a measure of functional ability in early diffuse SSc, it has only recently been shown to correlate with the level of dyspnea and with the levels of physiologic pulmonary function testing in patients with early alveolitis (diagnosed by BAL and HRCT). Several patient-assessed measures of dyspnea (eg, the Mahler Baseline Dyspnea Index and the pulmonary visual analogue scale [VAS] of the scleroderma modi-



**Fig. 3—High-resolution computed tomographic scan showing ground-glass opacification.**

fied HAQ) are being studied in the context of randomized controlled trials (RCTs). Early experience suggests that the level of dyspnea correlates with function (assessed by HAQ-DI) and with health-related quality of life (HRQoL) as assessed by the SF-36 (Medical Outcomes Study Short Form-36). Several experiences have also shown a correlation of the physical component score (PCS), a subscale of the SF-36, with early diffuse SSc and with early alveolitis (again diagnosed by BAL and HRCT).

How the patient assesses disease is clearly very important in clinical management, but the role of these questionnaires in the evaluation and management of ILD is still unclear. Since dyspnea is the most important clinical symptom in SSc-ILD, ways to measure this most important symptom will be important. Ongoing studies will help to clarify the role of these patient self-assessments in the clinical management of patients with ILD in SSc.

### DIFFERENTIAL DIAGNOSIS

Although dyspnea and cough are the prime symptoms of ILD in SSc, they can also be symptoms of other SSc-related processes. Among these are pulmonary vascular involvement with pulmonary hypertension and cardiomyopathy with diastolic dysfunction, processes that can occur in isolation or concurrently with ILD.

Esophageal dysmotility occurs in ~90% of SSc patients, even though symptoms that typically suggest GERD (ie, heartburn, dysphagia, regurgitation) are reported by only 60% to 70% of patients with SSc. Occult GERD may present with atypical symptoms, such as cough, asthma-like respiratory complaints, wheezing, pneumonia, or hoarseness (symptoms not usually associated with GERD). Because occult GERD is so common, it must always be considered to be part of the problem in patients with respiratory complaints and should be treated aggressively with antireflux measures.

Pulmonary infection (often the result of occult or overt reflux with mini-aspirations) may also confound the evaluation and management of ILD and should be considered in all SSc patients who report increased dyspnea and cough, especially if the cough is productive.

## TREATMENT

### Immunosuppressives

No treatment yet has been proven to alter the course of ILD in SSc, although a number of treatments have been studied and reported in case series to be possibly effective. Although a cause and effect relationship between early lung inflammation and progressive lung fibrosis has not been proven, the hypothesis underlies a number of treatment strategies. Case series and a small number of RCTs have lent support (although considered lukewarm by most authorities) for the use of cyclophosphamide and azathioprine in treating idiopathic pulmonary fibrosis (IPF), a condition with many similarities to the ILD of SSc. In SSc, several case series and one open controlled study (using nonrandomized control subjects as the comparator group) have suggested that cyclophosphamide (given orally or intravenously) might alter the course of ILD for the better. The question of efficacy of immunosuppressive therapy remains open, however. Two RCTs (one of intravenous cyclophosphamide in the United Kingdom and one of oral cyclophosphamide in the United States) comparing cyclophosphamide to placebo are currently under way. The results of these trials will not be known for ~2 years, and until then the use of immunosuppressive therapy must be considered empirical for patients with ILD in SSc.

### Antifibrotic Therapy

ILD in SSc is characterized by low levels of interferon-gamma (IFN- $\gamma$ ), both in serum and in the BAL fluid. Because IFN- $\gamma$  has antifibrotic properties, there has been, and continues to be, interest in using it as a pharmacologic agent. One group reported the results of a randomized (but open) trial in which 9 subjects with IPF were randomized to receive IFN- $\gamma$  plus small doses of corticosteroids and 9 subjects with IPF were randomized to higher doses of corticosteroids but no IFN- $\gamma$ . After one year, the group treated with IFN- $\gamma$  showed significant improvements in total lung capacity and in arterial oxygen pressures at rest and with exercise. In addition there was normalization of BAL levels of mRNA for a profibrotic cytokine, transforming growth factor- $\beta$  (TGF- $\beta$ ), and for an antifibrotic cytokine, IFN- $\gamma$ . A recent company-sponsored trial of IFN- $\gamma$  in IPF reportedly failed to demonstrate clinical or physiologic benefit. Additional study of IFN- $\gamma$  is needed.

### Antiendothelin Therapy

Bosentan, a dual inhibitor of the A and B receptors for endothelin-1 (ET-1), has shown antifibrotic activity in the laboratory, presumably through blockade of the B receptor. Bosentan (Tracleer) already has been approved for oral use in the management of SSc-related pulmonary hypertension. An international RCT of bosentan versus placebo in early pulmonary fibrosis in SSc is under way.

### Anticytokine Therapy

TGF- $\beta$  and connective tissue growth factor (CTGF) are both thought to play pivotal roles in fibrosis (in the skin and lung in particular). Several proprietary compounds that trap TGF- $\beta$ , block its interaction with TGF- $\beta$  receptors on cells, or block the

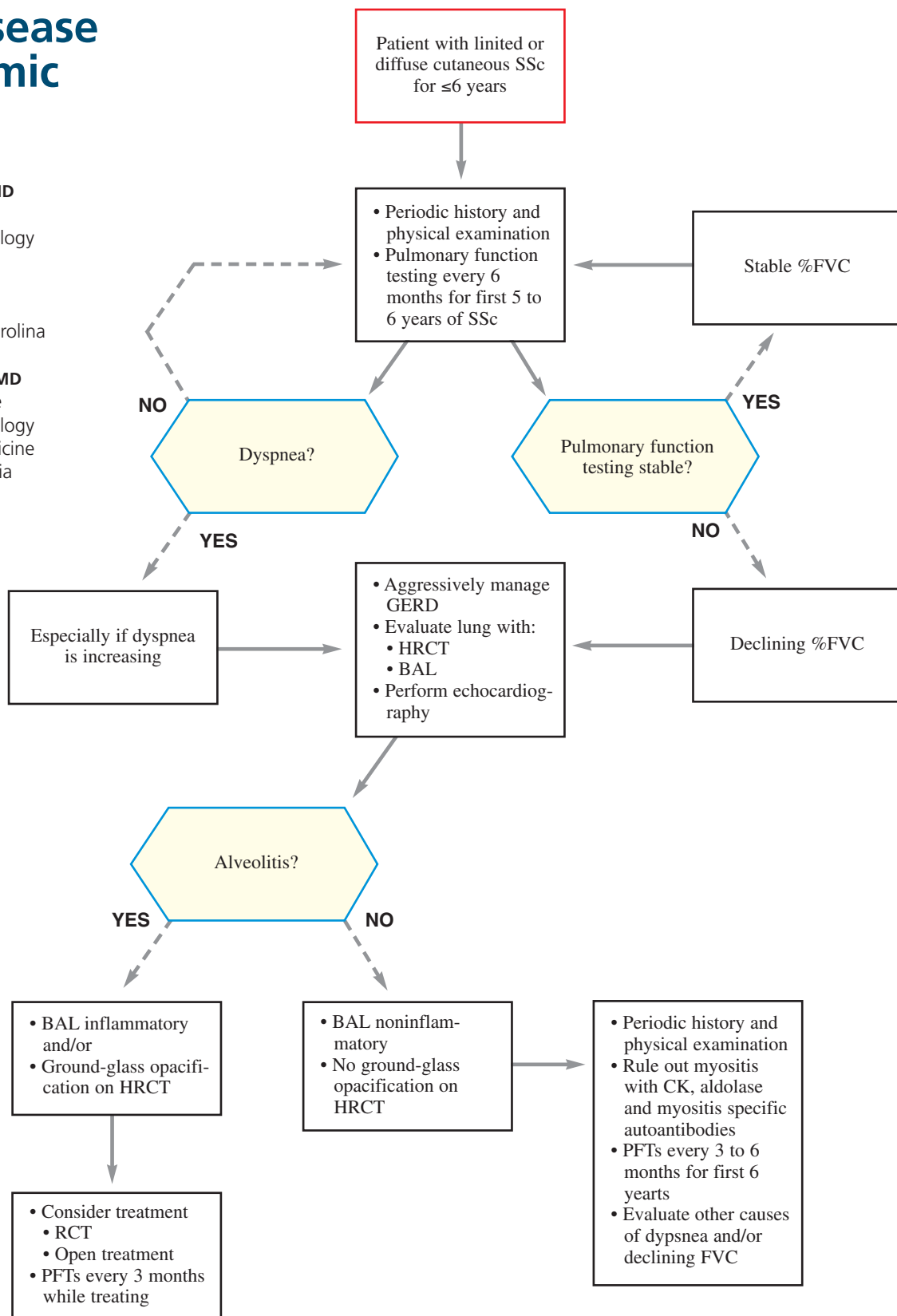
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## Clinical Algorithm

# Evaluation of Interstitial Lung Disease in Systemic Sclerosis

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(continued from page 9)

intracellular signal generated by the TGF- $\beta$  receptor after it has interacted with TGF- $\beta$  are in various stages of development. Because the treatments were derived from good molecular science, they are particularly intriguing. Whatever we learn during the investigation of these compounds will help us learn more about ILD in SSc and possibly how to treat it.

### PLAN FOR EVALUATING AND MANAGING ILD IN SSc

The time in the course of SSc when the greatest loss of lung function occurs from ILD is the first 4 to 6 years after SSc onset (dated from the onset of the first sign or symptom characteristic of SSc other than the Raynaud phenomenon). Moderate to severe ILD occurs only slightly more commonly in diffuse cutaneous SSc (SSc with widespread skin thickening, often involving the torso) than in limited cutaneous SSc. Thus, all SSc patients (whether they have limited or diffuse distribution of skin thickening) are at risk of ILD.

These at-risk patients should be seen every 3 to 6 months for a history and physical examination as well as PFTs (especially FVC and DLCO, as percent of predicted) every 6 months for the first 5 to 6 years of SSc. The examinations should look specifically for signs/symptoms and PFT abnormalities that suggest ongoing, progressive loss of lung function (especially declining %FVC). As long as patients deny dyspnea and have stable, normal PFTs, they can continue to be followed by periodic history and physical examinations and PFTs every 6 months.

Overt and occult GERD are very frequent in SSc, even if patients do not complain of signs/symptoms considered typical of GERD. Patients with GERD should be aggressively managed even if they do not have respiratory symptoms. In patients with symptomatic dyspnea, cough, and/or declining PFTs, it is especially important to treat GERD aggressively: elevate the torso during the night, avoid eating late (after 6 PM), and take proton pump inhibitors and promotility agents.

If patients report dyspnea (and particularly if the dyspnea is worsening) or their %FVC is falling, they should be promptly evaluated. Although a number of tests can be performed, the ones we feel are most likely to uncover inflammation (which we think is a precursor to fibrosis) are the HRCT and BAL. If the BAL is inflammatory and/or ground glass is seen on the HRCT, we consider the patient to have alveolitis. Since alveolitis-positive patients are at risk for progressive loss of FVC, we suggest discussing the various treatment options outlined earlier. Because we

feel that there is no therapy proven to be effective, we encourage our alveolitis-positive patients to consider an RCT, either at our institution or at another institution, if the circumstances are better. If this is not an option, then consideration of one of the available but unproven interventions would be appropriate.

If the HRCT and BAL are negative for alveolitis, a major component of alveolitis is unlikely. We would then entertain alternative reasons for increasing dyspnea and/or declining lung function, including GERD-related respiratory problems, infection, pulmonary vascular disease (especially pulmonary hypertension), occult heart disease (especially diastolic dysfunction secondary to SSc cardiomyopathy), myositis/myopathy with weak muscles (especially the respiratory muscles) and deconditioning. Echocardiography should be performed annually 1) in all diffuse cutaneous SSc patients for the first 5 to 6 years and 2) in all dyspneic patients, to monitor for cardiac and pulmonary vascular involvement. Patients should continue to be monitored by periodic history and physical examination and by PFTs every 6 months for the first 5 to 6 years after SSc onset. If PFTs show decline or patients develop increasing dyspnea, further evaluation is necessary.

If patients make it through the first 5 to 6 years of SSc without significant ILD, it is unlikely that significant ILD will appear in the future. Patients who have already developed significant ILD in the first years of their SSc are likely to continue to have dyspnea and may have slowly progressive loss of %FVC. This continued loss may not be related to active alveolitis, and the management of such patients can be frustrating. ■

### Recommended Reading

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# Pulmonary Arterial Hypertension Related to Systemic Sclerosis: A Primer for the Rheumatologist

Robyn J. Barst, MD, and James R. Seibold, MD

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Pulmonary arterial hypertension (PAH) is the leading cause of death in patients with systemic sclerosis (SSc) with limited scleroderma and increasingly recognized as a cause of pulmonary morbidity in diffuse scleroderma as well. PAH can occur in the absence of interstitial lung disease, most typically in patients with SSc with limited scleroderma, or as a reflection of both vascular and microvascular injury in the setting of diffuse scleroderma. Overall, regardless of its etiology, PAH is now an important cause of significant morbidity and mortality in SSc.

While any consideration of scleroderma lung involvement forces a consideration of the relative contributions of alveolitis, fibrosis, aspiration, and vascular injury, recent advances in therapy have been accompanied by a recognition that the vascular component is both under-recognized and undertreated.

PAH is a progressive disease characterized by increased pulmonary artery pressure (PAP) and pulmonary vascular resistance (PVR), ultimately producing right heart failure and death. Treatments aim to improve PAH symptoms and increase survival. Although current treatments for PAH are efficacious, the diagnosis is often made late in the course of the disease. Diagnosis of PAH related to SSc requires a thorough and specific evaluation. The objectives of this review are to increase the awareness of PAH related to SSc and to suggest a diagnostic algorithm as well as treatment guidelines. In addition to idiopathic pulmonary hypertension (IPAH), previously designated as primary pulmonary hypertension, PAH is related to a variety of conditions, including connective tissue disorders (CTDs), congenital heart disease, HIV infection, portal hypertension, and exposure to appetite suppressants.

Of all CTDs, PAH is most often seen in SSc. Although it occurs in both limited cutaneous SSc (lcSSc) and diffuse cutaneous SSc (dcSSc), the etiology and progression of the PAH dif-

fers between these two variants. In lcSSc, isolated PAH develops slowly, typically presenting 10 years after the initial diagnosis of SSc and in the absence of lung complications. In one series describing this patient subset, survival rarely extends beyond 12 months after diagnosis. In contrast, PAH appears early in the natural history of dcSSc in the context of interstitial lung disease (ILD). Furthermore, although the severity of ILD is an indicator of survival, the development of fibrotic parenchymal lesions may stabilize over time, whereas PAH pulmonary vascular abnormalities are thought to progressively worsen.

Early recognition of PAH is paramount as recent years have witnessed the development of several highly effective therapies. Epoprostenol, administered via continuous intravenous infusion, improves exercise capacity and hemodynamics in patients with PAH related to SSc. Epoprostenol is a synthetic prostacyclin and potent vasodilator. Treprostinil is a prostacyclin analogue amenable to delivery by continuous subcutaneous infusion. These prostacyclin analogues have been shown to slow disease progression, with some data speculating that reverse remodeling may occur. Endothelin receptor antagonists (ERAs) may be efficacious in blocking pathogenic abnormalities in PAH, eg, vasoproliferation, vasoconstriction, and vascular fibrosis. Bosentan, an oral, nonpeptide dual ERA, also improves symptoms and functional status in PAH related to SSc (Rubin 2002). Selective endothelin A receptor antagonists (sitaxsentan, ambrisentan) are in later stages of drug development.

## Definition and Functional Assessment of PAH

PAH is defined as a mean pulmonary artery pressure (PAP) of >25 mm Hg at rest, or >30 mm Hg during exercise, the absence of an elevated pulmonary capillary wedge pressure or left ventricular end diastolic pressure (ie, <15 mm Hg) and a pulmonary vascular resistance >3 U • M<sup>2</sup>. To assess functional class, a modification of the NYHA functional classification (**Table**) is useful with PAH patients. Both functional classification and hemodynamics correlate with survival.

## EPIDEMIOLOGY

Most cases of PAH are not IPAH. IPAH occurs in 1 to 2 persons per million each year, whereas 24 to 30 persons per million pres-

*(continued on page 15)*

**SEE  
SCLERODERMA**



**SUSPECT PAH  
PULMONARY ARTERIAL  
HYPERTENSION  
WHO CLASS III OR IV**

- 1 in 3 scleroderma patients develops PAH<sup>1</sup>
- Dyspnea in scleroderma can indicate PAH<sup>2</sup>
- WHO recommends annual screening with echocardiogram<sup>3</sup>



**TREAT  
PAH WHO CLASS III OR IV  
WITH TRACLEER**

### The Oral Endothelin Receptor Antagonist

Endothelin (ET) concentrations are elevated in the plasma and lung tissue of patients with pulmonary arterial hypertension (PAH), suggesting a pathogenic role for ET in PAH.<sup>4</sup> The effects of ET are mediated by binding to ET<sub>A</sub> and ET<sub>B</sub> receptors. Only Tracleer is a specific and competitive antagonist for both ET receptors.<sup>4</sup>

Tracleer improves exercise ability and reduces the rate of clinical worsening,\* while also improving hemodynamics (CI, PAP, PVR, RAP).<sup>4</sup>

#### Important safety information

- 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
  - Potential damage to a fetus: Pregnancy must be excluded and prevented; monthly pregnancy tests should be obtained
- Contraindicated for use with cyclosporine A and glyburide

#### Tracleer Access Program (TAP)

- Prescriptions can be filled only through TAP
- Call 1-866-228-3546 for a Patient Enrollment Form

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

\*Clinical worsening defined as combined endpoint of death, hospitalization or discontinuation due to worsening PAH, or initiation of epoprostenol therapy<sup>4</sup>

**Tracleer**<sup>®</sup>  
BOSENTAN TABLETS

**A REVOLUTIONARY ADVANCE**

[www.TRACLEER.com](http://www.TRACLEER.com)



## 62.5 mg and 125 mg film-coated tablets

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

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

**WARNING: Potential liver injury.** TRACLEER® causes at least 3-fold (upper limit of normal; ULN) elevation of liver aminotransferases (ALT and AST) in about 11% of patients, accompanied by elevated bilirubin in a small number of cases. Because these changes are a marker for potential serious liver injury, serum aminotransferase levels must be measured prior to initiation of treatment and then monthly (see WARNINGS: Potential Liver Injury and DOSAGE AND ADMINISTRATION). To date, in a setting of close monitoring, elevations have been reversible, within a few days to 9 weeks, either spontaneously or after dose reduction or discontinuation, and without sequelae. Elevations in aminotransferases require close attention (see DOSAGE AND ADMINISTRATION). TRACLEER® should generally be avoided in patients with elevated aminotransferases ( $> 3 \times$  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 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, 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  $3 \times$  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  $> 3 \times$  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 ( $> 3 \times$  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.

**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. 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 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  $\geq 3\%$  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%).

**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 $\leq 5 \times$ 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 $\leq 8 \times$ 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).
$> 8 \times$ 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  $\geq 2 \times$  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: 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.

**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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<b>Manufactured by:</b> Pathon Inc. Mississauga, Ontario, CANADA	<b>Marketed by:</b> Actelion Pharmaceuticals US, Inc. South San Francisco, CA
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**Table—WHO Functional Assessment of Pulmonary Arterial Hypertension\***

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**A. Class I**

Patients with pulmonary hypertension but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or near syncope.

**B. Class II**

Patients with pulmonary hypertension resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnea or fatigue, chest pain or near syncope.

**C. Class III**

Patients with pulmonary hypertension resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnea or fatigue, chest pain, or near syncope.

**D. Class IV**

Patients with pulmonary hypertension with inability to carry out any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnea and/or fatigue may be present even at rest. Discomfort is increased by any physical activity.

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\*Modified after New York Heart Association Functional Classification

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(continued from page 12)

ent with PAH related to CTDs, HIV infection, congenital heart disease, portal hypertension, and anorexigens. PAH occurs in 23% to 53% of patients with mixed connective tissue diseases, 0.5% to 14% of patients with systemic lupus erythematosus and much more rarely in patients with rheumatoid arthritis, Sjögren syndrome and dermatomyositis. The incidence of PAH related to SSc ranges from 4% to 35%, with slightly more PAH cases associated with lcSSc than with dcSSc. In some series, 50% to 90% of SSc patients with PAH had lcSSc, whereas 8% to 50% had dcSSc. Others have reported 13% to 50% of lcSSc patients develop PAH. The prevalence of PAH related to SSc correlates with the underlying systemic disease, ie, more often in women 35 to 55 years of age.

**PATHOPHYSIOLOGY AND NATURAL HISTORY**

Regardless of etiology, PAH is characterized by pulmonary vascular smooth muscle hypertrophy, intimal fibrosis, and in situ thrombosis. Recent evidence suggests endothelial dysfunction is important in its pathobiology. A schematic representation of the pathobiology of PAH is shown in **Figure 1**. A genetic predisposition combined with vascular injury may lead to an imbalance of mediators favoring vasoconstriction, vascular proliferation and platelet aggregation. These pathways ultimately result in plexogenic and thrombotic pulmonary arteriopathy.

Endothelin-1 (ET-1), a peptide produced primarily by vascular

endothelial cells, increases vascular tone through receptor-mediated signaling mechanisms that induce profibrotic, proinflammatory, proliferative, and vasoconstrictive pathways. In PAH, ET-1 signaling activity is enhanced as a result of increased circulating ET-1 and increased expression of ET<sub>A</sub> receptors that mediate pulmonary vasoconstriction. In addition to sustained vasoconstrictive signaling, vasodilator mediators such as prostacyclin and nitric oxide are decreased. Hence, vasoconstrictive signaling is increased due to increased activity in the absence of vasodilator mediators. In addition to vasoconstriction, vascular remodeling occurs, which until recently has been considered irreversible. ET-1 and its receptors have been implicated in the proliferation of pulmonary artery smooth muscle cells, consistent with the medial hypertrophy and intimal hyperplasia observed in PAH. Additionally, ET-1 induces platelet aggregation, which may contribute to the PAH.

Survival times in SSc patients with organ involvement are decreased compared to patients without organ involvement. Renal complications were previously the leading cause of death; deaths from renal impairment have been reduced with hemodialysis and angiotensin-converting enzyme inhibitors. Mortality rates are now the highest in patients with pulmonary involvement. PAH is a very significant pulmonary complication in SSc. One series reported that 33% to 63% of pulmonary-related deaths in patients with SSc were due to PAH. Others have observed that patients with isolated PAH had a 2-year survival rate of 40% compared with 88% of SSc patients without PAH. Patients with lcSSc and PAH have a median survival of 12 months. Although survival for patients with PAH related to SSc is very poor if untreated, recent therapeutic advances can significantly improve a patient's overall quality of life.

**DIAGNOSIS**

Recognition of PAH and initiation of treatment as early as possible may improve its overall prognosis (**Figure 2**). The key to the diagnosis, however, is to maintain a high index of suspicion because the first manifestations of PAH are often subtle and nonspecific. Slowly progressive exertional dyspnea is the most common symptom of PAH. Recognizing exertional dyspnea is a challenge in patients with CTDs such as SSc because these individuals often already have restricted their physical activity as a result of pain or fatigue. Such patients should be carefully questioned about the presence of dyspnea. The Baseline (BDI) and Transition Dyspnea Index (TDI) are two questionnaires that may be useful in determining the tasks and efforts that produce dyspnea. The diagnosis of PAH is a process of exclusion. In the absence of other causes, dyspnea should prompt evaluation for PAH in SSc patients, particularly those with lcSSc. It is currently recommended that all patients with SSc be screened annually, and that patients with other CTDs be screened if they develop symptoms suggestive of PAH.

Diagnostic testing of patients suspected of having PAH should begin with noninvasive tests to identify potential underlying diseases and rule out alternative diagnoses. These tests include electrocardiography, echocardiography, pulmonary function tests, chest radiography, ventilation-perfusion lung scan, and high resolution CT. In patients in whom noninvasive tests suggest PAH, right heart catheterization is necessary to confirm the diagnosis.

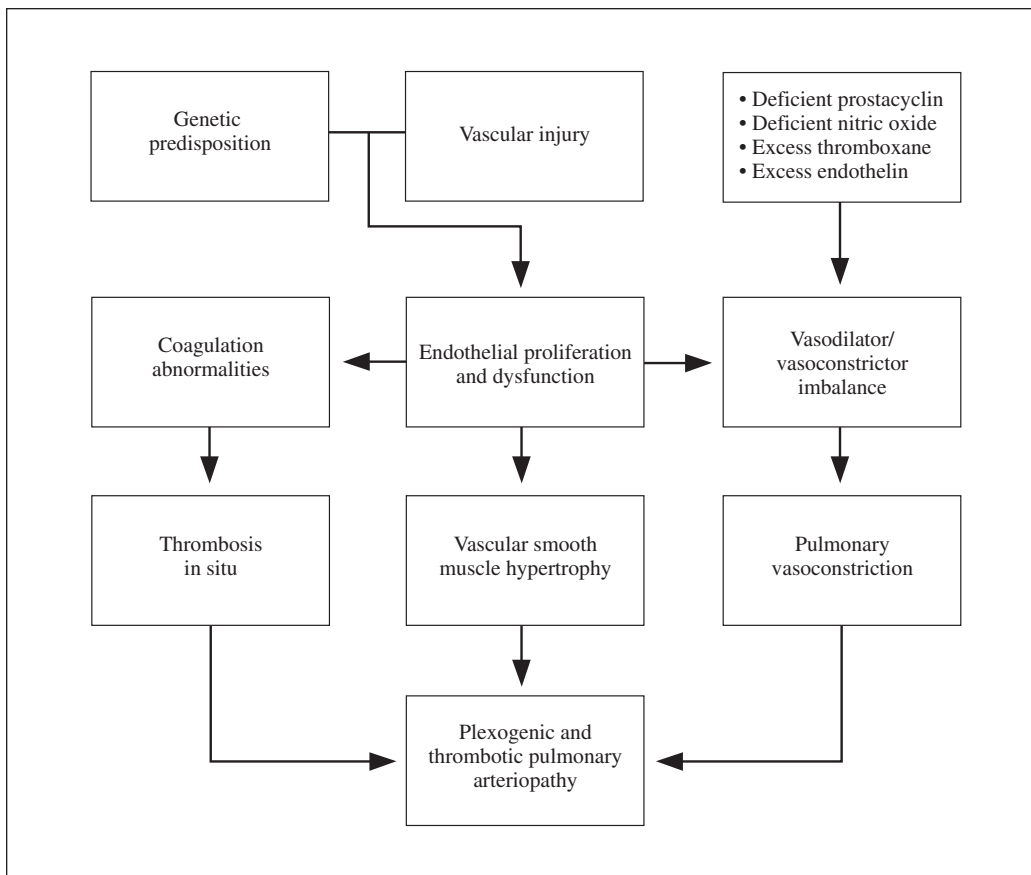


Fig. 1—Pathobiology of pulmonary arterial hypertension.

### Pulmonary Function Testing

As noted, dyspnea is commonly the first sign of PAH. Dyspnea occurs in many conditions, but if PAH is suspected, pulmonary function tests (PFTs) should be performed. Spirometry defines respiratory function by variables including forced expiratory volume in 1 second ( $FEV_1$ ), forced vital capacity (FVC), and diffusing capacity ( $DL_{CO}$ ). Values are expressed as a percentage of the predicted normal values. Abnormal values not only indicate the existence of pulmonary dysfunction, but may also suggest specific abnormalities. In general,  $FEV_1$  values are low, ie,  $FEV_1 < 1L$ , in obstructive lung disease, whereas patients with pulmonary hypertension secondary to restrictive lung disease typically have a FVC and/or  $DL_{CO} < 50\%$  of predicted. A retrospective analysis of 106 patients with SSc identified reduced  $DL_{CO}$  an average of 4.5 years prior to their diagnosis of PAH. Serial evaluations are recommended for dcSSc patients presenting with signs of lung disease, as manifestations of PAH often appear within 3 years after detecting lung disease.

An isolated drop in  $DL_{CO}$  suggests PAH and decreases in  $DL_{CO}$  antedate PAH. Several groups reported reduced  $DL_{CO}$  for all patients with PAH/SSc. One study showed that 11% of SSc patients with isolated decreases in  $DL_{CO}$  developed isolated PAH. PAH is strongly associated with a  $DL_{CO} < 55\%$  of predicted, and a  $FVC (\% \text{ of predicted}) / DL_{CO} (\% \text{ of predicted}) > 1.4$ . This value holds true for PAH due to PPH and PAH-associated SSc, including dcSSc and lcSSc. Normal PFT values do not, however, rule out PAH. The importance of conducting both PFTs and echocar-

diography (see below) as part of the initial evaluation for PAH has been clearly demonstrated.

### Chest Radiography

Chest radiographs are useful to obtain an overview. In PAH, chest radiographs often show enlarged central pulmonary arteries and an enlarged right ventricle.

### 2-D Echocardiography with Doppler Interrogation

Echocardiography is a noninvasive test that can estimate pulmonary arterial pressure and rule out most heart diseases, eg, valvular heart disease. The test is also useful to examine right and left heart systolic function although echocardiography cannot definitively rule out left ventricular diastolic dysfunction, ie, heart failure with normal systolic function. This is especially important in patients with SSc, many of whom are older or have a history of systemic hypertension, since age and systemic hypertension are both risk factors for left ventricular diastolic dysfunction. Cardiac catheterization is needed to rule this out. Echocardiography can reveal typical features observed in patients with PAH: enlarged right heart chambers, right ventricular hypertrophy, abnormal interventricular septal position, and a normal to small left ventricle. With Doppler interrogation, the right ventricular systolic pressure, which is equal to the pulmonary arterial systolic pressure in the absence of pulmonary stenosis, can be estimated by the velocity of the tricuspid regurgitation jet. Although PAP estimated by Doppler echocardiogram is often accurate, ie, the same as measured during right heart catheterization, false positives and false negatives do occur.

### Thin-Section, High-Resolution CT

High-resolution computed tomography (HRCT) is often helpful in patients with suspected PAH. In patients with abnormal PFTs indicating interstitial lung disease (ILD), thin-section HRCT without contrast is recommended to help identify whether pulmonary hypertension is secondary to the underlying pulmonary disorder. HRCT images correlate with the macroscopic appearances of pathological specimens and thus HRCT is often more sensitive than chest radiography. Several features are suggestive of PAH in patients with ILD, eg, enlarged central pulmonary arteries and a mosaic pattern of dark and light patches; typically, sections of the lung with small vessels are seen as dark patches and conversely, the lighter patches show vessels with larger diameters. Whether due to airway or vascular disease, differences in perfusion result



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in dark areas of decreased alveolar blood flow and lighter areas of normal or increased alveolar blood flow. At end expiration, if both the dark and light patches become lighter, pulmonary vascular disease is suspected; if the dark patches stay dark at the end of the expiration, then airway disease is suspect. In patients with PAH, vessels in ground-glass attenuation areas are often enlarged whereas changes in vessel size in patients with infiltrative lung disease are nonexistent.

### Ventilation-Perfusion Lung Scan

For patients suspected of having isolated PAH, chronic thromboembolic disease must be ruled out. If a ventilation-perfusion (V/Q) lung scan is read as high probability or indeterminate probability, pulmonary angiography is needed to rule out chronic thromboembolic disease. In patients with PAH, ventilation-perfusion lung scans are most often normal or show small diffuse patchy defects. In patients with suspected chronic thromboembolic disease, multiple larger perfusion defects occur.

### Right Heart Catheterization

Right heart catheterization is necessary to confirm the diagnosis of PAH. The importance of right heart catheterization, when echocardiography suggests PAH, is that pulmonary artery pressure measurements obtained by right heart catheterization are not estimations as they are with echocardiography. Furthermore, left sided heart disease, a frequent cause of elevated pulmonary artery pres-

sure ie, PCWP or LVED<sub>p</sub> > 15 mm Hg, can be ruled out only by right heart catheterization. In addition, during the right heart catheterization, acute vasodilator testing (with inhaled nitric oxide, IV epoprostenol or IV adenosine) can be performed to determine the most appropriate treatment for a given patient.

### Exercise Capacity

Cardiopulmonary exercise testing (CPET) is often useful in evaluating the etiology of decreased exercise capacity as well as in assessing the response to treatment. In addition, the 6-minute walk test has been shown to correlate with outcome, particularly during long-term therapy.

## MANAGEMENT

### Goals of Therapy

The goals of treatment are to improve overall quality of life and outcome. Guidelines for a treatment algorithm are shown in **Figure 3**. The primary efficacy endpoint of most clinical trials for the treatment of PAH has been exercise capacity assessed by the 6-minute walk test. The 6-minute walk test, a brief, easily conducted measurement of exercise capacity, has been shown to be a reliable predictor of outcome in PPH patients. Additional efficacy measures have included the Borg dyspnea index, which reflects the severity of dyspnea during the 6-minute walk test, clinical worsening, hemodynamic parameters, and functional class.

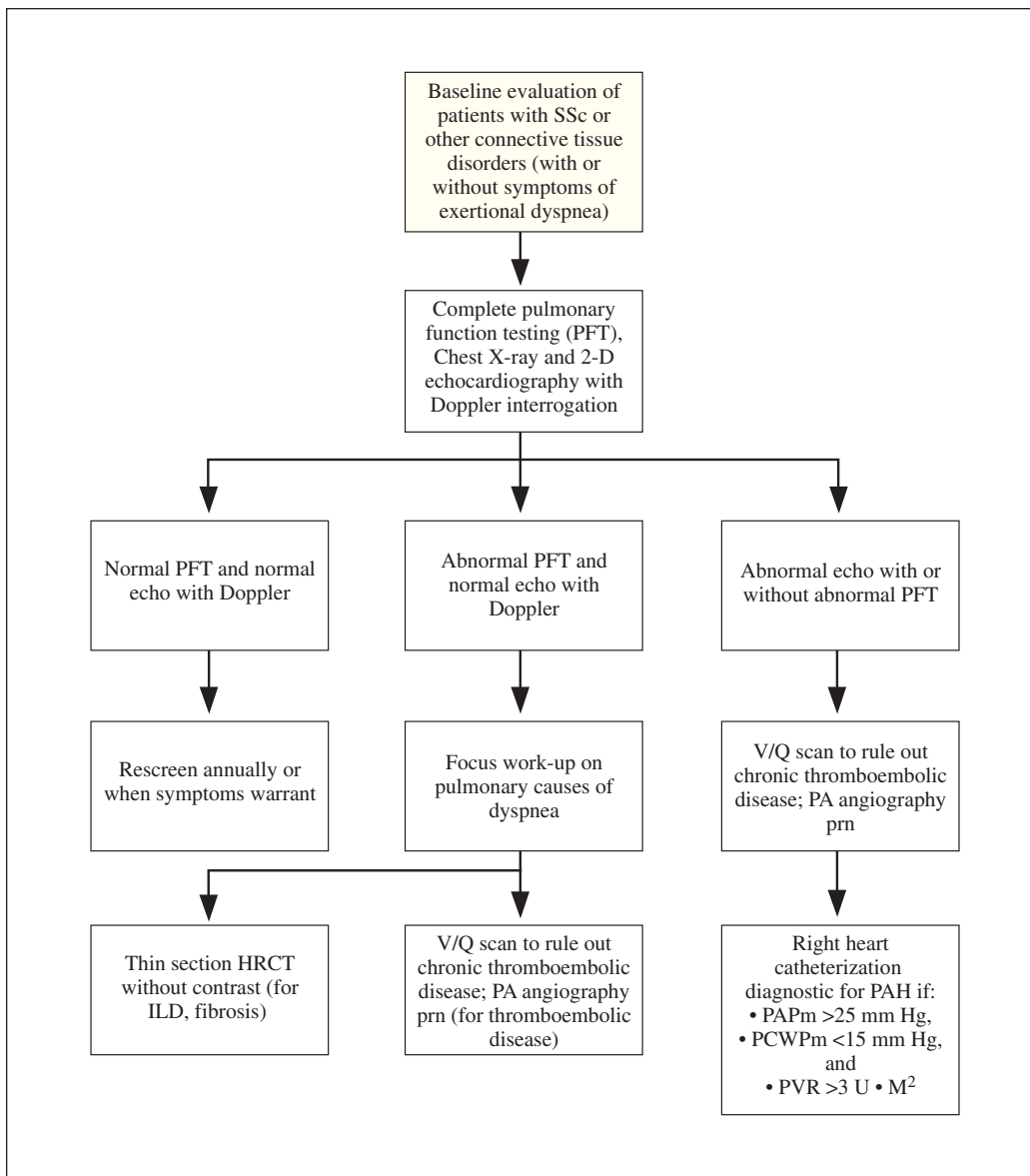


Fig. 2—Algorithm for evaluating patients with suspected pulmonary arterial hypertension.

## Treatment

Despite similarities in the pathobiology of IPAH and PAH related to CTDs, treatment is not always identical. Previous studies have demonstrated that anticoagulant therapy increases survival in IPAH patients. Although this approach has not been evaluated in patients with PAH-associated SSc, most patients with PAH related to SSc are currently treated with anticoagulants. However, risk-benefit considerations may preclude anticoagulation therapy for certain patients, eg, patients with significant esophagitis who have an increased risk for gastrointestinal bleeding; or on the other hand, if patients are hypercoagulable (eg, positive lupus anticoagulant or positive anticardiolipin antibodies), they may require a higher level of anticoagulation.

Calcium channel blockers at relatively high doses have also been demonstrated to be effective in patients who respond with acute vasodilator drug testing; this occurs in approximately 10% to 20% of IPAH patients. The definition of a positive acute vasodilator response in a PAH patient is a fall in PAPm of at least

10 mm Hg to  $\leq$  40 mm Hg with an increased or unchanged cardiac output (European Society of Cardiology IPAH Guidelines, Venice Symposium 2003, American College of Chest Physicians Consensus Statement, 2003). Although the efficacy of calcium channel blockers in patients with PAH related to SSc is much lower than for IPAH patients, long-term oral calcium channel blockers have been effective in some patients. Nevertheless, it must be emphasized that empiric treatment with calcium channel blockade is contraindicated, and can result in fatalities.

Currently, cyclophosphamide is used to treat declining lung function in patients with SSc, although reliable data to support this are lacking. At present, there is little rationale for the use of immunosuppressive therapy in the management of PAH without ILD.

Interventional/surgical options for the treatment of PAH include atrial septostomy, which can provide palliative therapy, and lung or heart-lung transplantation. Aside from the limited supply of donor organs and the general problems associated with transplantation, additional concerns in patients with PAH related to CTD include the risk of aspiration from chronic gastroesophageal reflux, as well as the

increased risk overall in patients with renal impairment.

## Advances in Pharmacologic Treatment Options

Recent advances in the understanding of the pathobiology of PAH have shifted the focus of management from agents that are non-specific vasodilators, eg, calcium channel blockers, to agents that may also reverse the vasoproliferative changes. Currently, three drugs are approved in the United States for the treatment of PAH: continuous intravenous epoprostenol infusion; the prostacyclin analogue treprostinil administered via continuous subcutaneous infusion; and the orally active, nonpeptide dual ERA bosentan.

**Prostacyclin Analogues.** Epoprostenol, a synthetic prostacyclin, is a potent vasodilator with antiproliferative and antiplatelet effects, as well as possibly positive inotropic effects. Continuous intravenous infusion of epoprostenol, using a portable infusion pump, improves exercise capacity, functional class, hemodynamics and survival in IPAH patients. It also improves exercise capacity in patients with PAH related to SSc. Epoprostenol is widely

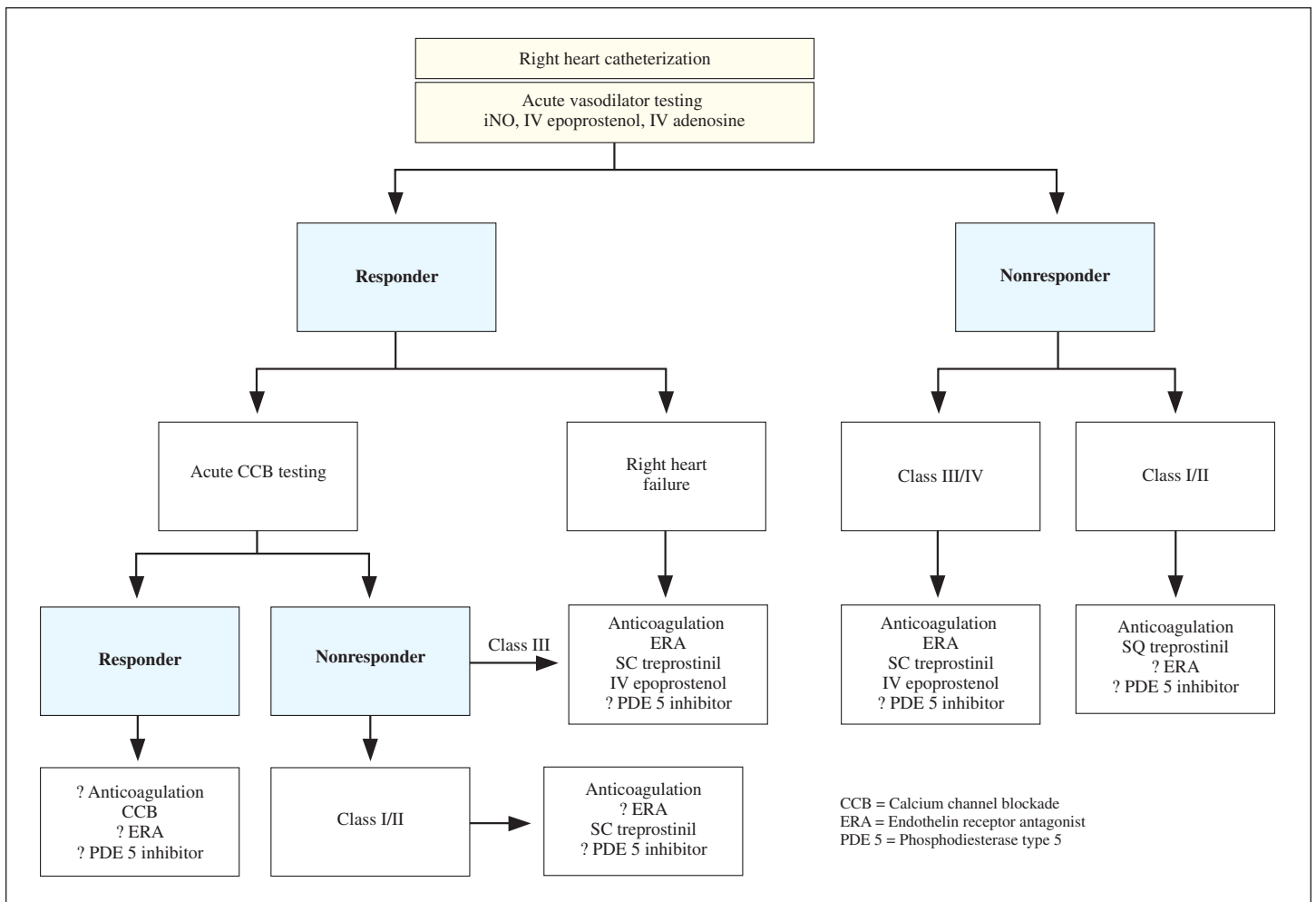


Fig. 3—Pulmonary arterial hypertension—treatment algorithm guidelines.

used for patients who do not respond to calcium channel blockers. Epoprostenol is FDA approved for class III/IV IPAH and PAH associated with SSc.

Despite its efficacy, epoprostenol's delivery system—ie, continuous intravenous infusion through a permanent central venous catheter, can result in serious adverse effects, including sepsis and thromboembolic events. In addition, because of its short half-life in the circulation (2 to 3 minutes), temporary infusion interruptions can lead to life-threatening pulmonary hypertensive crises. In an effort to overcome these limitations, alternative delivery routes have been investigated. Treprostinil, a prostacyclin analogue administered by continuous subcutaneous infusion, is FDA approved for Class II-IV PAH including PAH associated with SSc. Pain and local inflammation at the site of infusion may limit its use. Beraprost, an oral prostacyclin analogue, is available in Japan and iloprost, an aerosolized prostacyclin analogue, is available in Europe.

**Endothelin Receptor Antagonists.** Both dual  $ET_A/ET_B$  receptor antagonists and selective  $ET_A$  receptor antagonists have been, and continue to be, investigated. Bosentan, an orally active dual ERA, improves exercise capacity, functional class, and quality of life in IPAH as well as in PAH related to SSc. Bosentan is FDA approved for Class III/IV PAH, including PAH associated with

SSc. Having an oral agent available for the treatment of PAH (as opposed to a drug that requires continuous intravenous infusion, ie, epoprostenol, or continuous subcutaneous infusion, ie, treprostinil), may significantly improve the overall risk-benefit profile for treating PAH patients. The safety concern with bosentan is liver toxicity. However, with close monitoring, ie, at least once a month, to date, hepatotoxicity with bosentan has been completely reversible in all patients. In addition to hepatotoxicity, ERAs are teratogenic and may cause irreversible male infertility. Furthermore, oral contraceptives cannot be considered adequate birth control in the presence of ERA treatment. The use of selective  $ET_A$  receptor antagonists, eg, sitaxsentan and ambrisentan, may benefit patients with PAH by blocking the vasoconstrictor effects of  $ET_A$  while maintaining the vasodilator and clearance functions of  $ET_B$  receptors. Sitaxsentan has recently been shown to improve exercise capacity and functional class in PAH patients, including PAH related to SSc. Additional clinical trials are in progress with both sitaxsentan and ambrisentan. Finally, short-term studies suggest vasodilatory benefit with sildenafil, an oral phosphodiesterase type 5 inhibitor, and a possible synergistic effect in the setting of prostacyclin therapy; clinical investigation is ongoing with sildenafil. Combination therapies will doubtless be studied in the future.

## SUMMARY

PAH is a life-threatening condition that can occur in patients with various CTDs including SSc, and in particular patients with limited SSc. Because of their role in the management of SSc and other CTDs, rheumatologists are uniquely positioned to identify CTD patients with PAH who may benefit from PAH therapy.

Of the currently available approaches for treating PAH, the synthetic prostacyclin epoprostenol, the prostacyclin analogue treprostinil, and bosentan, an oral endothelin receptor antagonist, have all shown improvement in functional class, exercise capacity and overall quality of life. Despite epoprostenol's known efficacy, it has serious limitations due to the need for continuous intravenous delivery. Some of these limitations may be overcome by using the subcutaneously delivered prostacyclin analogue treprostinil. Bosentan, an oral agent, offers another approach to the treatment of PAH. In addition, whether combining an ERA with epoprostenol or a prostacyclin analogue will improve the overall risk-benefit profile for PAH patients will require further investigation.

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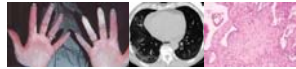
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