Clinical Approach to Scleroderma Lung Disease

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Introduction

Cardiopulmonary disease is the major cause of death in scleroderma (systemic sclerosis). Both restrictive lung disease and pulmonary hypertension cause significant morbidity and mortality in scleroderma patients. Restrictive lung disease and pulmonary hypertension occur in both either diffuse and limited cutaneous scleroderma and can occur alone or together. For example, at our scleroderma center, 23% of patients have isolated restrictive lung disease, 19% have isolated pulmonary artery hypertension, and 18% have both problems.

Clinical Approach to Restrictive Lung Disease

It remains unclear what set of clinical parameters is optimal to identify scleroderma patients at greatest risk for progressive lung fibrosis. Currently, practicing rheumatologists will consider a number of parameters in estimating risk. These factors include, but are not limited to; disease duration; race of the patient; presence of anti-DNA topoisomerase I antibodies; pulmonary symptoms, presence and severity of restrictive lung disease on PFTs, changes in forced vital capacity (FVC) or diffusing capacity for carbon monoxide (DLco) over time; presence of and changes in radiographic evidence of lung fibrosis; radiographic suggestion of lung inflammation; and bronchoalveolar lavage (BAL) cell differential; and concomitant pulmonary hypertension. Higher risk for decline in FVC or DLco seems to be associated with early disease, black race, presence of anti-DNA topoisomerase I antibodies, presence of pulmonary symptoms, recent decline in FVC or DLco, ground glass appearance on high resolution CT scan of the lungs, increased percentages of neutrophils and eosinophils on BAL cell differential, and pulmonary hypertension. The extent of testing that is done in an individual patient to assess this risk will be determined by clinical judgment. At a minimum, in addition to history and physical examination at the time of initial evaluation, nearly all scleroderma patients will need PFTs done, including spirometry, lung volumes and DLco, as well as a Doppler echocardiogram to estimate pulmonary artery pressures.

The presence of lung inflammation, often assessed by BAL, does allow the clinician to identify patients at greater risk for decline in DLco and FVC, but these parameters do not identify all vulnerable patients. Among a cohort of patients who underwent BAL for diagnosis of lung inflammation, about 25% of patients without lung inflammation had a greater than 10% decline in FVC and about 40% of patients without lung inflammation had a decline in DLco. Conversely, about one quarter of patient with lung inflammation had stable lung function during follow-up. Several groups have found inconsistency between the finding of lung inflammation on BAL cell differential and ground glass appearance on high resolution CT scan of the lungs. There are no studies correlating ground glass appearance on CT scans with long-term pulmonary function outcome.

Drug Treatment of Restrictive Lung Disease in Scleroderma

In retrospective cohort studies, patients with lung inflammation who received oral cyclophosphamide are more likely to have stabilization in FVC and DLco than untreated patients with lung inflammation. Improved survival

has also been reported. Clearly, there is a need for a randomized, prospective trial of cyclophosphamide in scleroderma lung disease, to determine whether these findings hold true in a larger group of patients in which potential bias has been minimized by study design. Available data suggests that intravenous cyclophosphamide may also be helpful in scleroderma patients with lung inflammation.

In addition, patients with restrictive lung disease should be assessed for need for supplemental O_2, especially during exercise. They may benefit from pulmonary rehabilitation programs.

Clinical Approach to Pulmonary Hypertension in Scleroderma

The two-year survival of scleroderma patients with pulmonary hypertension is 40-55%. The risk of developing severe pulmonary hypertension is higher in elderly onset scleroderma patients, patients with limited scleroderma, and patients with initial DLco < 50% predicted. All scleroderma patients need some periodic assessment for pulmonary hypertension, even if it is just a history and physical examination and periodic doppler echocardiograms. Testing for pulmonary hypertension is especially warranted in scleroderma patients with worsening pulmonary symptoms, but no evidence of worsening interstitial lung disease, and in patients with disproportionately low DLco, compared to FVC. Initial screening with Doppler echocardiogram to estimate pulmonary artery pressures is appropriate. If clinical suspicion of pulmonary hypertension remains high in the face of a negative doppler echocardiogram, an exercise echocardiogram may uncover pulmonary hypertension. Right-sided cardiac catherization can confirm the diagnosis, and, at this time, probably should be done in all patients before institution of therapy with epoprostenol, bosentan, or treprostinil.

Usual clinical care for pulmonary hypertension may benefit scleroderma patients with this problem. This includes management of any right-sided heart failure, with special attention to volume status, O_2 therapy, and anti-coagulation. Calcium-channel blockers are beneficial in only 10-20% of scleroderma patients, but have the advantage of oral administration and lower cost. For patients who are WHO class III or IV, treatment with epoprostenol, bosentan, or treprostinil should be considered. Epoprostenol is a synthetic prostacyclin analogue that is administered by constant intravenous infusion. It has been shown to improve exercise capacity, pulmonary arterial pressure, WHO classification and dyspnea indices. Treprostinil is another potent vasodilator that is administered constantly by the subcutaneous route. It improves exercise capacity, dyspnea indices and pulmonary artery pressures. It is approved for use in patients who are WHO class II. Bosentan is an endothelin A and endothelin B receptor antagonist that is given orally, which is a preferred route of administration by patients. Bosentan effects include improved six minute walking distance, slowing of time to clinical worsening, and improved cardiopulmonary hemodynamics. Phosphodiesterase type 5 inhibitors such as sildenafil (Viagra) are under study for use in combination with other agents in the treatment of pulmonary hypertension.

Lung Transplantation in Scleroderma

Recent results of lung transplantation for pulmonary hypertension, pulmonary fibrosis, or the combination in scleroderma show post-transplant results comparable to those in patients with idiopathic pulmonary fibrosis. Success in transplantation requires careful screening of patients prior to referral, excluding patients with concomitant renal insufficiency, aspiration, and skin breakdown.