

## Is systemic sclerosis interstitial lung disease slowly progressive?

A doença pulmonar intersticial na esclerose sistêmica é lentamente progressiva?

Chitra Lal, Charlie Strange

“Success is the ability to go from one failure to another with no loss of enthusiasm”

– Sir Winston Churchill

In most patients, systemic sclerosis (SSc), also known as scleroderma, is a slowly progressive disease. However, in a subset of patients, there is a rapid decline in lung function and quality of life. Such patients often do not enter clinical trials because of the imperative to try a given form of therapy, even if the therapeutic options are limited. In this issue of the *Brazilian Journal of Pulmonology*, Lopes et al.<sup>(1)</sup> present a compelling case that an accelerated decline in lung function is the norm and not the exception in patients with SSc-related interstitial lung disease (ILD).

Why do these SSc patients in Brazil have such rapid decline in lung function? The first point to be made is that an abnormal CT scan was required for inclusion in the Lopes et al. study. From our experience in the United States and from the results of a study conducted at the Royal Brompton Hospital in London,<sup>(2)</sup> we know that fibrosis observed on CT scans of the chest is a strong predictor of lung disease progression and death. The Brompton staging system has consistent prognostic value regardless of whether patients are started or continued on treatment. Another difference is that Lopes et al. excluded smokers. In idiopathic pulmonary fibrosis (IPF), the consensus is that the lead-time bias imposed by the added burden of smoking slows IPF progression.<sup>(3)</sup> However, the impact that smoking has on nonspecific interstitial pneumonitis (NSIP), the most common pathology in SSc patients, has never been quite as clear. This study could force us to re-examine the effects of smoking on the presentation and progression of SSc-related ILD. Last, we cannot discount the role of pharmacotherapy in the differences observed. Two studies, one conducted in the United States and the other conducted in the United Kingdom, produced nearly identical results using cyclophosphamide, administered by oral and intravenous routes, respectively.<sup>(4,5)</sup> Although the magnitude of the

changes in lung function were small in favor of cyclophosphamide use, this drug is often used in other parts of the world when lung function is declining. When cyclophosphamide is used in the setting of acutely declining lung function, the benefits can be much more robust.<sup>(6)</sup>

Another interesting aspect of the Lopes et al. study is the prognostic value of honeycombing. Honeycombing is most commonly seen in usual interstitial pneumonitis (UIP) which can be found in diffuse SSc.<sup>(7)</sup> Because we do not have pathology to further inform this observation in the Lopes et al. study, it is possible that a higher prevalence of UIP in the SSc population evaluated accounted for the fact that the decline in FVC was more rapid than that observed in other studies. It is not surprising that patients with fibrosis that is more severe, possibly with UIP on the baseline HRCT, had the greatest declines in FVC over the five-year treatment period.

The results of the Lopes et al. study underscore the idea that the extent of disease on chest CT can indicate the rate of physiological and functional decline in SSc-related ILD. The strength of this five-year longitudinal natural history study of SSc demands that we now put forth some effort toward finding a cure. By using honeycombing as a “biomarker” of accelerated disease, we might select a population in which the effects of treatment will be more apparent. However, we might also find a population, similar to that of IPF patients, in which treatment-resistant fibrosis further frustrates our efforts to find a cure. Therefore, the pessimist in all of us would suggest that conducting trials in this population with honeycombing and rapidly progressive disease will lead us down a path toward treatment failure in SSc. The optimists will insist that we keep trying to find all of the clues that can help stratify risk in this problematic disease.

**Chitra Lal**  
Physician. Division of Pulmonary and  
Critical Care,  
Allergy and Sleep Medicine  
Medical University of South Carolina,  
Charleston, SC, USA

**Charlie Strange**  
Physician. Division of Pulmonary and  
Critical Care,  
Allergy and Sleep Medicine  
Medical University of South Carolina,  
Charleston, SC, USA

## References

1. Lopes AJ, Capone D, Mogami R, de Menezes SL, Guimarães FS, Levy RA. Systemic sclerosis-associated interstitial pneumonia: evaluation of pulmonary function over a five-year period. *J Bras Pneumol.* 2011;37(2):144-51.
2. Goh NS, Desai SR, Veeraraghavan S, Hansell DM, Copley SJ, Maher TM, et al. Interstitial lung disease in systemic sclerosis: a simple staging system. *Am J Respir Crit Care Med.* 2008;177(11):1248-54.
3. King TE Jr, Tooze JA, Schwarz MI, Brown KR, Chermiack RM. Predicting survival in idiopathic pulmonary fibrosis: scoring system and survival model. *Am J Respir Crit Care Med.* 2001;164(7):1171-81.
4. Hoyles RK, Ellis RW, Wellsbury J, Lees B, Newlands P, Goh NS, et al. A multicenter, prospective, randomized, double-blind, placebo-controlled trial of corticosteroids and intravenous cyclophosphamide followed by oral azathioprine for the treatment of pulmonary fibrosis in scleroderma. *Arthritis Rheum.* 2006;54(12):3962-70.
5. Tashkin DP, Elashoff R, Clements PJ, Goldin J, Roth MD, Furst DE, et al. Cyclophosphamide versus placebo in scleroderma lung disease. *N Engl J Med.* 2006;354(25):2655-66.
6. Silver RM, Warrick JH, Kinsella MB, Staudt LS, Baumann MH, Strange C. Cyclophosphamide and low-dose prednisone therapy in patients with systemic sclerosis (scleroderma) with interstitial lung disease. *J Rheumatol.* 1993;20(5):838-44.
7. Harrison NK, Myers AR, Corrin B, Soosay G, Dewar A, Black CM, et al. Structural features of interstitial lung disease in systemic sclerosis. *Am Rev Respir Dis.* 1991;144(3 Pt 1):706-13.