BEYOND THE BLUE:

What Fellows Are Reading in Other Journals

Novel Therapeutic Approaches for Pulmonary Manifestations of Systemic Sclerosis

Justin K. Lui, Nicholas A. Bosch, Kari R. Gillmeyer, and Christine C. Reardon

Section of Pulmonary, Allergy, Sleep and Critical Care Medicine, Boston University School of Medicine, Boston, Massachusetts

Recommended Reading from Boston University School of Medicine Fellows; Christine C. Reardon, M.D., Director

ORCID IDs: 0000-0002-4745-3766 (J.K.L.); 0000-0001-7161-5254 (N.A.B.); 0000-0002-5333-259X (K.R.G.).

Distler O, et al.; SENSICIS Trial Investigators. Nintedanib for Systemic Sclerosis–associated Interstitial Lung Disease. *N Engl J Med* (1)

Reviewed by Justin K. Lui

Systemic sclerosis (SSc) is frequently complicated by interstitial lung disease (ILD), which can have a profound impact on mortality (2). Treatment of SSc-ILD consists of immunosuppressants (i.e., cyclophosphamide [CYC] [3] and mycophenolate [MMF] [4]). Recently, nintedanib has emerged as a novel agent in treating idiopathic pulmonary fibrosis (5). Acting on a common pathophysiologic pathway shared with SSc, nintedanib can modulate the degree of fibrosis in animal models of disease (6, 7). However, its safety and effectiveness in patients with SSc-ILD is unclear.

In this multicenter, randomized, double-blind, placebo-controlled trial from November 2015 through October 2017, 576 patients with SSc-ILD affecting at least 10% of the lungs on high-resolution computed tomography were randomized to receive nintedanib or placebo. Patients with pulmonary arterial hypertension (PAH) were excluded. The primary outcome was the annual rate of decline in FVC assessed over a 52-week period. Key secondary outcomes included changes from baseline in skin fibrosis (i.e., modified Rodnan skin score) and health-related quality of life (i.e., St. George's Respiratory Questionnaire) at Week 52. Safety and adverse events were assessed until 28 days after the last administered dose of the trial drug or placebo.

Overall, there was a lower adjusted annual rate of decline in FVC in the nintedanib group compared with the placebo group (−52.4 ml/yr vs. −93.3 ml/yr; $P=0.04$). There were no significant changes in the modified Rodnan score or in the total score on the St. George's Respiratory Questionnaire. Though there was no difference in adverse events in either group, the percentage of

patients who discontinued the assigned intervention because of an adverse event was higher in the nintedanib group. Diarrhea was most commonly reported.

In conclusion, although this trial did not find nintedanib effective in treating other manifestations of SSc (i.e., skin fibrosis), nintedanib did show promise in reducing the rate of decline in FVC over a 1-year period. Interestingly, of note, nearly half (48.4%) of all randomized patients were already receiving background MMF therapy at the time of this study. MMF has been shown to temper fibrotic progression in patients with SSc-ILD (2). Though it is not entirely clear where nintedanib fits in the overall therapeutic algorithm for SSc-ILD (i.e., at which point of disease—mild vs. severe fibrotic disease), these results suggest the potential of nintedanib as adjunct therapy in combination with MMF. Studies will need to investigate its long-term effects. ■

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Correspondence and requests for reprints should be addressed to Justin K. Lui, M.D., Section of Pulmonary, Allergy, Sleep and Critical Care Medicine, Boston University School of Medicine, 72 East Concord Street, R-304, Boston, MA 02118. E-mail: justin.lui@bmc.org.

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Hoa S, *et al.*; Canadian Scleroderma Research Group. Association between Immunosuppressive Therapy and Course of Mild Interstitial Lung Disease in Systemic Sclerosis. *Rheumatology (Oxford)* (8)

Reviewed by Nicholas A. Bosch

ILD that complicates SSc is associated with progressive lung function decline (9) and increased mortality (2). Several randomized controlled trials (3, 4, 10) have shown that immunosuppressive drugs (i.e., CYC or MMF) halt the progression of, or even slightly improve, lung function in patients with moderate-to-severe SSc-ILD. However, whether initiating immunosuppressive drugs before the development of potentially irreversible lung fibrosis can improve lung function remains unclear. Thus, the authors of this study (8) sought to determine the association between immunosuppressive drug therapy and changes in lung function at 1 year among patients with mild SSc-ILD and to compare the strength of this association with patients with moderate SSc-ILD.

In this registry-based, multicenter, retrospective cohort study, the authors stratified patients with SSc-ILD into mild ($n = 116$) or moderate ($n = 130$) severity using baseline FVC% predicted measurements. The association between exposure to immunosuppressive drugs (CYC or MMF) at baseline visit and the primary outcome of FVC% predicted at 1-year follow-up was then determined using multivariable linear regression separately for patients with mild and moderate SSc-ILD. The authors also examined several secondary outcomes, including FVC% predicted at 2-year follow-up and the DL_{CO}% predicted at 1- and 2-year follow-up. Among patients with mild SSc-ILD, exposure to immunosuppressive drugs compared with no exposure was associated with improved FVC, and the difference was greater compared with those with moderate disease. Exposure to immunosuppressive drugs was not associated with DL_{CO}% predicted at 1- or 2-year follow-up in either mild or moderate SSc-ILD.

The results of this study provide compelling observational data that patients with mild SSc-ILD may benefit from early initiation of immunosuppressive drugs to potentially improve lung function based on FVC. The lack of an association between immunosuppression and DL_{CO}% predicted may be due to high intertest variability of the DL_{CO} test or to comorbid diseases (i.e., PAH) that decrease DL_{CO} but that may not respond to immunosuppression. Of note, the study did not control for exposure to corticosteroid, which can contribute to immunosuppression, although its usefulness in SSc appears limited because of increased risk of scleroderma renal crisis. Lastly, given the observational nature of the study and risks of selection bias and residual confounding, causal inferences should be limited. Clinical trials are likely needed to

clarify the role of early immunosuppressive drugs in patients with SSc-ILD. ■

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Pan Z, *et al.* Early Treatment with Ambrisentan of Mildly Elevated Mean Pulmonary Arterial Pressure Associated with Systemic Sclerosis: A Randomized, Controlled, Double-Blind, Parallel Group Study (EDITA Study). *Arthritis Res Ther* (11)

Reviewed by Kari R. Gillmeyer

PAH is a complication of SSc that portends a poor prognosis with a median survival of 1 year after diagnosis if left untreated (12). Clinical trials of pulmonary vasodilators in PAH associated with SSc (SSc-PAH) have shown improvement in symptoms, exercise capacity, hemodynamics, and time to clinical worsening (13). Given the new definition of PAH recently proposed during the sixth World Symposium on Pulmonary Hypertension (14), which lowered the threshold for mean pulmonary arterial pressure (mPAP) from ≥ 25 mm Hg to > 20 mm Hg, the authors of the EDITA study (11) sought to establish whether patients with SSc-PAH with mildly elevated mPAP may benefit from earlier initiation of PAH-specific therapy.

In this single center, double-blinded, placebo-controlled trial from December 2014 to April 2017, 38 patients with SSc with a resting mPAP of 21–24 mm Hg or exercise-induced mPAP > 30 mm Hg without significant left heart or severe lung disease were randomized to receive ambrisentan or placebo. The primary outcome was change in resting mPAP from baseline to 6 months, with secondary outcomes including other hemodynamic parameters (i.e., pulmonary vascular resistance, pulmonary arterial wedge pressure, cardiac output, and cardiac index), World Health Organization functional class, 6-minute-walk distance, and quality of life assessment. Though there was no difference in the primary outcome between the treatment and the placebo group, individuals in the ambrisentan group exhibited a decreased pulmonary vascular resistance as well as increased $\dot{Q}$ and cardiac index at rest and at peak exercise on follow-up, reflecting improved right ventricular function when compared with the placebo group. There were no significant improvements in World Health Organization functional class, 6-minute-walk distance, or quality of life at the end of the study.

Although this study was limited by a small sample size and single-center design, these results show that early initiation of

pulmonary vasodilators may be beneficial in SSc patients with mildly elevated mPAP or exercise-induced PAH. Larger multicenter trials are needed to confirm these findings and to further evaluate for unintended consequences of pulmonary vasodilator therapy given the high prevalence of ILD in this population, in whom vasodilators may worsen hypoxemia. Future studies are also needed to evaluate mild SSc-PAH and exercise-induced SSc-PAH independently given that few studies have addressed the prognostic relevance of exercise-induced SSc-PAH (15). Lastly, studies will also need to follow composite endpoints reflecting time to clinical worsening as recently recommended (16). ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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