

Integrating new therapies for systemic sclerosis-associated lung fibrosis in clinical practice.

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Systemic sclerosis-associated interstitial lung disease (SSc-ILD) is a common disease feature and among the most common causes of death in patients with systemic sclerosis [1]. It is the consequence of an autoimmune-mediated inflammatory and fibrotic nexus, leading to lung fibrosis [1].

Our group has classified ILD into subclinical ILD, one with no ILD-specific symptoms, minimal ILD on high resolution computer tomography (HRCT) and normal pulmonary physiology; and clinical ILD, defined as those who are symptomatic and have decrements in their pulmonary physiology and/or moderate-to-extensive disease on the HRCT [2]. The current management of fibrotic ILDs, including SSc-ILD, is largely targeted at patients with clinical ILD. The Scleroderma Lung Study (SLS) I, SLS II, and SENCIS trials included this subgroup as an inclusion criterion.

However, there is lack of consensus on the management of those with early subclinical ILD due to uncertain disease course in this subset. There are known risk factors for progressive ILD in early SSc, including anti-topoisomerase antibody and diffuse cutaneous subset, but there was lack of data that targeting this subset will have a beneficial effect on lung function.

The Phase 2 and 3 trials of tocilizumab have changed this opinion [3,4]. The trials included participants with progressive skin disease, diffuse cutaneous subset, and elevated acute phase reactants, an at-risk population for early ILD with progressive phenotype. In the Phase 3 trial, mean baseline disease duration was less than 2 years, and mean forced vital capacity was 79.6% predicted, and 65% had ILD on HRCT at baseline. No background immunomodulatory therapies were allowed. During the 48-week trial, participants with SSc-ILD on tocilizumab had a least squares mean (LSM) decline of 0.1% vs. 6.4% in the placebo group, a difference of 6.5 (95% CI 3.4, 9.5, nominal p value <0.0001), a clinically meaningful effect which robustly confirmed previous observations from the Phase 2 trial. The beneficial effect on FVC was supported by the HRCT findings. There were trends but no statistically significant differences in improvement in the skin score and quality of life measures.

The tocilizumab data highlight the utilization of HRCT for screening and diagnosis of SSc-ILD. At the trial entry, 30% of participants had a medical history of ILD and an additional 35% were diagnosed as ILD on the baseline HRCT. The participants had early disease but despite that, 36% had > 20% total lung involvement on their HRCT [5]. Tocilizumab was effective in preserving the lung function, irrespective of the degree of lung involvement.

The approval of tocilizumab builds upon the previous experience from the clinical trial data supporting use of targeted biologics for SSc-ILD. Although perhaps less impactful than tocilizumab, other biologics have previously shown preliminary evidence of efficacy on FVC% in early SSc. Published data from abatacept and rituximab showed beneficial trends in FVC when compared to placebo and cyclophosphamide, respectively [6,7].

Although both Phase 2 and 3 trials of tocilizumab included patients with early progressive diffuse skin disease and elevated acute phase reactants, the FDA provided a more inclusive label for slowing the rate of decline in pulmonary function in adult patients with SSc-ILD [8], similar to nintedanib. How should clinicians incorporate these approved therapies in their clinical practice? Our management of SSc patients include an HRCT at baseline (as

pulmonary function test lacks sensitivity for diagnosing early disease) and we further divide patients into subclinical vs. clinical ILD [2]. We believe that initial therapy for an autoimmune ILD should target the dysregulated pathways related to the immune-inflammatory disease leading to lung fibrosis. Therefore, we advocate immunomodulatory therapies as the first line treatment. For those with subclinical ILD with at-risk features for progressive ILD (such as positive topoisomerase antibody, elevated acute phase reactants, progressive skin disease), we currently utilize immunomodulatory therapies such as mycophenolate mofetil. Based on the approval of tocilizumab, we plan to incorporate this as the first line agent for these patients. For those with clinical ILDs, a population that was included in the SLS-1, II, and SENSICIS trials (and also a subset of the Phase 3 trial of tocilizumab), options include mycophenolate mofetil or tocilizumab, among other immunomodulatory therapies. We use nintedanib for those with progressive ILD despite on immunomodulatory therapies, recurrent infections or inability to tolerate immunomodulatory therapies, and for those who may have ILD-predominant disease with dormant skin and musculoskeletal disease (unlikely in early SSc).

This is an exciting time for understanding the natural history and management of fibrotic ILDs. Analysis of the placebo group in the tocilizumab trials provides an opportunity to study secondary prevention in setting of early ILDs. In addition, with large beneficial effects on FVC, skin, and quality of life seen with autologous hematopoietic stem cell transplant (but associated with significant morbidity) [9] in SSc, the scleroderma community has an opportunity to evaluate upfront combination therapy to target early SSc-ILD, such as combining tocilizumab and nintedanib, that target different pathogenetic pathways that may have beneficial impact on overall SSc.

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