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EDITORIAL

Diagnostic and Therapeutic Conundrums in Systemic Sclerosis Interstitial Lung Disease

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Introduction

Systemic Sclerosis (SSc) is a disease characterized by a complex interplay between inflammation, vascular and fibrotic mechanisms with no single unifying pathogenic mechanism. The clinical phenotype is a result of vascular endothelial dysfunction (digital scars, Reynaud's', isolated pulmonary artery hypertension, digital gangrene), ongoing inflammation and autoimmunity (dermal oedema, early interstitial lung disease, myositis, and antibodies- anti centromere, SCL-70, RNA polymerase III and Topoisomerase -1) or fibroblastic dysfunction (dermal sclerosis, oesophageal dysmotility, fibrotic interstitial lung disease). [1] Interstitial lung disease (ILD) and pulmonary artery hypertension (PAH) are the two predominant cardiopulmonary manifestations. Though these manifestations occur in isolation, progression of each this is however interdependent and it is therapeutically challenging to uncouple them. With more cautious use of glucocorticoids based on the phenotypic expression of SSc, the mortality has shifted from renal crisis (6%) to cardiopulmonary diseases (ILD -33% & PAH 28%). [2] Cumulative survival of patients at 10 yrs in SSc-ILD is much lower than patient with SSc without ILD. [3] Though the immunosuppressives such as Cyclophosphamide, Mycophenolate, Rituximab & Tocilizumab have proven to be beneficial in SSc-ILD, there is a paucity of evidence regarding maintenance treatment, switching of therapies and how to manage that subset of patients with disease progression despite treatment.

Issues in Diagnosis

Prevalence of ILD ranges from 40% to 70 % of patients with SSC[4] and it often occurs early in the course of the disease irrespective of whether SSc is limited or diffuse. Risk factors for ILD include age, reflux/dysphagia symptoms, SSc subtype, antibody status (anti-topoisomerase antibody (ATA) anti-centromere antibody (ACA), anti-RNA polymerase III antibody (ARA)), baseline FVC, baseline diffusion capacity of Carbon Monoxide (DLCO), disease duration, skin involvement measured by modified Rodnan skin score (mRSS), erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels, dyspnoea class, treatment, synovitis and muscle weakness . [5] High resolution Computerized tomography (HRCT) and pulmonary function tests (PFT) together with DLCO form the baseline tests in assessment of ILD. Quantitative CT densitometry and the extent of lung involvement along with PFT is more sensitive in monitoring progression of lung disease rather than the pattern of non-specific interstitial pneumonitis (NSIP) or usual interstitial pneumonitis (UIP) on HRCT. [5]Use of 9 HRCT cuts along with lung ultrasound which quantifies and detects thickened interlobular septa (lung comet tail sign - B lines) and pleural irregularities have somewhat

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mitigated the effect of radiation exposure compared to the standard HRCT. [6] Other modalities such as MRI, SPECT and PET for evaluation of ILD have not been standardized.

Elevated serum levels of the glycoprotein Krebs von den Lungen-6 (KL-6), chemokine (C-C motif) ligand 2 and 18, surfactant protein D (SP-D), interleukin-6 and CXC chemokine ligand 4 have been linked to the degree of inflammation and fibrosis and may predict lung involvement and disease progression in patients with SSc-ILD. Serum biomarkers levels may prompt further assessment for ILD but as yet, there use in routine clinical practice has not been established. [7]

In clinical practice, diagnosis of SSc-ILD is based on evolution of respiratory symptoms, limitations of activities of daily living, reduced exercise tolerance and imaging modalities together with serial PFTs. Predictive models by Ryerson et al. showed that the modified du Bois index (which includes parameters of age, respiratory-related hospitalization in the past 6 months, and predicted baseline and 24-week change in FVC) is superior to the earlier deployed indices namely composite physiologic index, ILD-gender, age, physiology index, and the du Bois index in predicting 1-year mortality in SSc-ILD. [8] Forced vital capacity (FVC) and 6 min walk test distance (6MWT) which are independent predictors of mortality in ILD are limited by concomitant organ involvement such as Raynaud's, pulmonary artery hypertension, arthritis and myositis.

Formal guidelines in serial monitoring of structural and functional progression of SSc-ILD are lacking. Imaging together with PFT and 6-minute walk tests are often monitored every 3-6 months in different clinical scenarios. [5, 9] In real world scenario, accessibility to repeated assessments is challenging. Comprehensive evaluation of cardiopulmonary involvement in SSc mandates independent assessment of PAH in the form of right heart catheterization using the DECTECT algorithm [10] or Australian scleroderma interest group (ASIG) algorithm which involve additional tests such as NTpro BNP, serum urate levels and the presence of telangiectasias.

Issues in the management

In the treatment of SSc-ILD, prevention of progression is an important therapeutic goal as no currently available immunosuppressive agent reverses the lung damage. The treatment aspect of SSc-ILD is divided into immunosuppressive medications, antifibrotics (such as nintadanib) and lung transplant. Cyclophosphamide & mycophenolate [12], rituximab [13] and tocilizumab [14] have been shown to prevent the deterioration of FVC and DLCO. The SENSCIS trial which evaluated the efficacy of nintedanib with placebo, showed a tendency to retard progression of FVC in the nintedanib treated arm. [15] Approaches such as hematopoietic stem cell transplantation and lung transplantation require careful selection of patients and are not universally available.

Identifying patients with subclinical ILD, optimal doses of glucocorticoids at initiation of immunosuppression and timing of switching of immunosuppressive agents based on rate of FVC decline, duration of treatment and drug related adverse effects pose challenges in the management of SSc-ILD.

The treatment of SSc is targeted on the phenotypic expression of the disease with aggressive treatment directed towards those with ILD than those without ILD. Existing immunosuppressive drugs may not be effective in patients with predominant vasculopathic manifestations or those with widespread dermal or gastrointestinal manifestations. Combination therapy for different pathogenic mechanisms seems to be the most viable option at present.

Conclusion

In SSc too, as in any rheumatic disease, the focus is on early identification of different manifestations of SSc and preventing their progression. With advances in the therapeutic options in ILD, it remains to be seen whether

Janus kinase inhibitors and the use of combination immunosuppressives prove to be more effective in the management of SSc -ILD.

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Conflicts of Interest

There are no conflicts of interest.

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