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Short Communication

Updates in Management of Ctd-Ild

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Introduction

Connective tissue diseases (CTDs) can cause a myriad of pulmonary complications, including bronchiolitis and bronchiectasis, pleuritis, and pulmonary hypertension. Interstitial lung disease (ILD) is one of the most serious pulmonary complications associated with CTDs characterized by various patterns of inflammation and fibrosis on high-resolution CT (HRCT) scans and in lung biopsy specimens.

American College of Rheumatology (ACR) recently released a guideline summary for screening, monitoring, and treatment of CTD-associated ILDs [1].

The purpose of this review is to analyse above guidelines and the evidence behind the recommendations.

Screening and Monitoring of ILD in Systemic Autoimmune Rheumatic Disease (SARDs)

Screening for ILD using Pulmonary Functions Tests (PFTs) and HRCT Chest in patients with SARDs who are at increased risk of developing ILD.

Delphi consensus studies in the United States and Europe have concluded that all patients with Systemic sclerosis (SSc) should be screened for ILD, that screening should include HRCT, PFTs, and chest auscultation, and that PFTs should be repeated regularly, whereas the frequency of repeat HRCT scans should be guided by PFTs and the presence of risk factors [2].

Few studies have evaluated some of these risk factors, for e.g., risk factors for the development of ILD in patients with systemic sclerosis include diffuse cutaneous disease, African American ethnicity, older age at onset, shorter disease duration, and positivity for anti-topoisomerase I antibodies [3,4].

Screening for ILD among SARD patients using a 6-minute walk test, Chest X-ray, Bronchoscopy, and Surgical lung biopsy is not recommended. Studies have shown that a relative decline in forced vital capacity (FVC) of 10% or greater or a relative decline in FVC of 5 to 9% with a relative decline in DLCO of greater than 15% at 1 year was predictive of mortality [5].

More frequent monitoring of PFT in cases of SSc and inflammatory myopathies (IIM) associated ILDs as compared to rheumatoid arthritis (RA), Sjogren and mixed connective tissue disorder (MCTD) associated ILDs.

Treatment of ILD in People with SARDs

First-line Treatment of SARD ILD

Glucocorticoids are the first-line therapy in all SARD ILDs apart from SSc. Strong recommendation has been made **against the use of glucocorticoids in SSc-ILD**. This is based on extensive data that suggests that glucocorticoids have limited benefits in SSc-ILD and also precipitate the risk of scleroderma renal crises [6,7].

Mycophenolate, Azathioprine, Rituximab, and Cyclophosphamide are alternatives as the first-line ILD treatment. However, which drug is to be preferred over others is still a matter of debate [8-11].

For SSc-ILD and MCTD ILD, Tocilizumab can be used as the first-line treatment option [12] Studies have shown that tocilizumab slows the decline in FVC in SSc-ILD [13]. Similar results with tocilizumab have been shown in RA ILD as well [14].

Nintedanib has been shown to slow down the decline in FVC in patients with SSc-ILD [15]. Usage of Nintedanib vs Immunosuppression depends on the pace of progression and the amount of fibrotic disease. However, for SARD ILD apart from SSc-ILD, upfront use of Nintedanib is not yet recommended.

Janus kinase (JAK) inhibitors (Tofacitinib) as first-line therapy for IIM associated ILD, especially those with melanoma differentiation associated protein 5 (MDA-5) antibody-positive patients have shown to improve survival [16].They can target multiple aspects of immune and inflammatory diseases by suppressing intracellular signalling. They have been shown to significantly improve or resolve symptoms of ILD in patients of Dermatomyositis (DM) and Juvenile Dermatomyositis (JDM). However, more RCTs are needed to further confirm this.

Calcineurin inhibitors (Tacrolimus) can also be used as first line treatment for IIM ILDs. Studies have shown that combination of tacrolimus with high-dose steroids and cyclophosphamide for patients with IIM ILDs improve muscle testing scores, creatine kinase value, pulmonary function, and survival [17] .

The use of **Intravenous immunoglobulin (IVIG) and Plasma exchange** as first-line therapy for SARD ILDs is not recommended as there are no large-scale studies to support the use of IVIG or plasma exchange for SARD ILD [18]. Optimised medical management should be ensured before referral for Stem Cell Transplant or Lung transplant.

Management for Progression of ILD Despite First-line Management

For SARD ILDs showing progression despite first-line therapy, there is a conditional recommendation for the use of **Mycophenolate, Rituximab, Cyclophosphamide, and Nintedanib** [1]. However, which drug to be given preference is not yet established.

Among SARD ILDs showing progression on first-line therapy, the use of **Pirfenidone** is recommended only in RA ILD. Pirfenidone has been shown to slow the decline of FVC among patients with RA ILD [19].

Tocilizumab has been recommended as a treatment option for SSc [20,21], RA, and MCTD ILD, while its use is not recommended in Sjogren and IIM ILDs [1].

For patients with progressive IIM ILD and MCTD ILD, the use of **IVIG** is conditionally recommended [1]. However, large-scale trials are not available.

The use of **Plasma Exchange** is not recommended for SARD ILDs [1].

Stem cell therapy and lung transplants are potential treatment options for patients with progressive ILD. However, CTD disease activity must be in remission before transplant [22,23].Despite first line ILD treatment ,

people with SSc-ILD progression can be recommended for Stem Cell Transplantation/Early Lung Transplantation.

Management of Rapidly Progressive ILD

Pulse Methylprednisolone has been recommended for patients with rapidly progressive SARD ILD. Other treatment options include Rituximab, Cyclophosphamide, IVIG, Mycophenolate, Calcineurin inhibitors, and JAK inhibitors [1].

Conditional recommendations have also been made for upfront **Combination therapy** (triple therapy for confirmed or suspected MDA5 and double/triple therapy for those without confirmed or suspected MDA5). Triple therapy for confirmed or suspected MDA-5 includes IV Glucocorticoids and 2 additional therapies including Rituximab, Cyclophosphamide, Mycophenolate, Calcineurin inhibitors, JAKi [1].

While Lung transplantation can be recommended in RP ILD, Stem cell transplant is not recommended [1].

For people with SARD and rapidly Progressive ILD, early referral for Lung Transplantation should be preferred after progression on optimal medical management.

To conclude, these are certainly exciting times as there are various upcoming pharmacological as well as non-pharmacological therapies for SARD/CTD associated ILDs. Yet,the risk factors for the development of ILDs, the preference among the immunosuppressants, the role of antifibrotic and immunosuppressants together, the role of Pulmonary rehabilitation, the definition of RP ILD, and failure of first-line therapy are some points that need to be discussed and clarified in coming times.

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