LETTER TO THE EDITOR

Management Guidelines of CTD-ILD; What is New?

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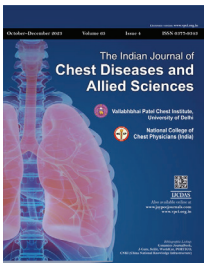

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Dear Editor,

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 summary has been approved by the ACR Board of Directors and These recommendations are pending peer review, which was submitted for publication in Arthritis and Rheumatology and Arthritis Care and Research. The summary is divided into two aspects:

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

A conditional recommendation is made to screen 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] However, one thing that needs to be clarified in the guidelines is the inclusion criteria for patients with SARDs who are at higher risk of developing ILD. 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. For monitoring of a diagnosed ILD among SARD patients, use of PFT, HRCT Chest, and ambulatory desaturation monitoring is conditionally 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]

Of note, the guidelines committee has stressed 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. The guidelines committee has made no comment on prognosis based on the CT chest pattern of ILD or the extent of fibrosis.

Treatment of ILD in People with SARDs

The ACR guidelines provide an insight into the management of various stages of SARD ILD–first-line therapy, progressive ILD, and rapidly progressive (RP) ILD.

First-line Treatment of SARD ILD

Glucocorticoids are the first-line therapy in all SARD ILDs apart from SSc. The guidelines committee has made a strong recommendation 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]

The committee has given a conditional recommendation for the use of mycophenolate, azathioprine, rituximab, and cyclophosphamide 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, but the use of tocilizumab in RA ILD is not yet included in these guidelines.[14] The committee has also given a

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conditional recommendation for the use of Nintedanib as a first-line treatment option in SSc-ILD. Nintedanib has been shown to slow down the decline in FVC in patients with SSc-ILD.[15] However, for SARD ILD apart from SSc-ILD, upfront use of Nintedanib is not recommended.

Janus kinase (JAK) inhibitors 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] The committee has given a conditional recommendation for the use of JAK inhibitors as first-line treatment option in IIM ILDs. Calcineurin inhibitors 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. There are no large-scale studies to support the use of IVIG or plasma exchange for SARD ILD.[18] The committee also advises optical medical management over referral for stem cell transplant or lung transplant as a first-line treatment option.

Management for Progression of ILD Despite First-line Management

For patients with SSc-ILD showing progression despite first-line therapy, long-term use of glucocorticoid is strongly discouraged, while for other SARD ILDs, long-term steroid use is conditionally recommended. For SARD ILDs showing progression despite first-line therapy, the committee has given a conditional recommendation for the use of mycophenolate, rituximab, cyclophosphamide, and Nintedanib. 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, RA, and MCTD ILD, while the use of tocilizumab is not recommended in Sjogren and IIM ILDs. For patients with progressive IIM ILD and MCTD ILD, the use of IVIG is conditionally recommended. However, large-scale trials are not available. The use of plasma exchange is not recommended for SARD ILDs. Stem cell therapy and lung transplants are potential treatment options for patients with progressive ILD. However, CTD disease activity must be in remission before for transplant.[20,21]

Management for RP 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. Methotrexate, leflunomide, azathioprine, tumor necrosis factor (TNF) inhibitors, abatacept, tocilizumab, nintedanib, pirfenidone and plasma exchange are not recommended for first-line therapy in RP ILD. 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 consists of calcineurin inhibitor, cyclophosphamide, and steroids. While lung transplantation can be recommended in RP ILD, stem cell transplant is not recommended.

To conclude, the guidelines for the management of SARD-ILD are exhaustive. However, the finer points need to be discussed. 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.

Availability of Data and Material

The clinical data and the study materials available from the corresponding author on reasonable request.

Author Contributions

YK, RK, PI, and NG: Literature search, planning, conduct, writing the original draft of manuscript, literature search, and editing of the study. All the authors have agreed with the submitted manuscript. PI is corresponding author and guarantor for all.

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