

Review Article

Management of Interstitial Lung Disease Associated with Rheumatoid Arthritis

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Interstitial Lung Disease (ILD) is a common extra-articular manifestation of Rheumatoid Arthritis (RA) and that causes mortality in RA patients. Usual Interstitial Pneumonia (UIP) and Non Specific Interstitial Pneumonia (NSIP) are the most common forms of ILD in RA. While the response to treatment for NSIP is good, UIP responses poorly to treatment and prognosis is similar to idiopathic pulmonary fibrosis. Smoking, structure of genetic, HLA haplotip, male gender, high titrated RF or/and presence of anti-CCP are thought to be risk factors for ILD in RA patients. One the other hand some drugs are used in treatment of RA like methotrexate, leflunomide, TNF inhibitors or non-TNF biologic drugs may contribute emerging or progression of ILD. By developing of the new treatment options, RA is considered to be a treatable disease and a notable number of the patients go in remission. Despite successful results have been reported with various therapeutic agents in the treatment of RA-associated ILD, no ideal specific treatment has yet been established, supported by a large randomized controlled trial.

Keywords: Lung disease; Rheumatoid arthritis; Pulmonary; Rituximab

Introduction

Rheumatoid Arthritis (RA) is a chronic inflammatory disease that primarily affects joints and leads to reduced survival [1]. RA may be complicated by many extra-articular manifestations beyond joints [2]. Lungs are one of the most frequently affected organs of extra-articular involvement in RA patients. Pulmonary involvement in RA includes pleural disease, rheumatoid nodules, Caplan's syndrome, bronchiectasis, vasculitis, and interstitial lung disease [3,4].

Although considered to be related to various genetic, humoral and environmental factors, the pathogenesis of RA-ILD is not fully understood [5-7]. Conventional synthetic DMARDs (such as methotrexate and leflunomide) and biological agents (such as anti-TNF alpha, non-TNF biologics) used in RA treatment may cause ILD-like appearance or exacerbation of an existing ILD which may make the RA-associated ILD more complicated [8-10]. In this review, the current treatment approach and difficulties in management were evaluated in RA-ILD.

Epidemiology and Prognosis

The prevalence of ILD in patients with rheumatoid arthritis ranges from 1% to 58% [11-17] and varies depending on the screening method and the criteria for selecting patients for the study. Since High-Resolution Computed Tomography (HRCT) is a sensitive method for detecting asymptomatic or subclinical ILD cases, studies using computerized tomography for diagnosis showed higher frequency of ILD [14].

It has also been reported that there is a positive correlation between clinical disease activity Index and HRCT findings of patients [18]. In 2002, the American Thoracic Society and the European Respiratory Society (ATS/ERS) defined a classification for acute and

chronic parenchymal lung diseases [19]. It has also been adopted for the identification of the ILD (Table 1). According to the ATS / ERS classification, the ILD associated with RA can be seen as any of seven forms of idiopathic interstitial pneumonia. Usual Interstitial Pneumonia (UIP) is the most common form and frequently follows Non Specific Interstitial Pneumonia (NSIP). Lymphocytic Interstitial Pneumonia (LIP), organised pneumonia, diffuse alveolar damage, respiratory bronchiolitis, and desquamative interstitial pneumonia are other ILD patterns that may be seen in RA [20,21]. In RA patients with extra-articular findings mortality was higher than patients without these findings. Cardiovascular disease, infections and pulmonary involvement are the leading causes of mortality in RA patients. Mortality is higher in the first five-seven years of the diagnosis, and this rate is higher in male patients than in female patients [22,23]. Cause of mortality in 10-20% of RA patients is lung involvement [24].

Etiology and Pathogenesis

The etiology and pathogenesis of ILD associated with rheumatoid arthritis still remains unclear. It is well known that some genetically susceptible patients develop ILD due to some environmental factors. Several genetic polymorphisms and HLA-DRB common epitomes have been reported to contribute to the development of ILD [25].

In patients with RA, there are some risk factors that facilitate the development of ILD. Some of these risk factors are related to the patient itself and some to the disease. Although RA is a more common disease in female, ILD develops more common in male with RA [26]. Smoking is a risk factor for development of RA [27]. As the package/year increases, the risk of developing RA also increases at that rate [28]. Smoking also increases the risk of developing ILD. Smoking has been shown to be associated with both radiographic ILD findings and

Table 1: ATS/ERS Classification of Idiopathic Interstitial Pneumonia.

Histologic Pattern	Clinical/Radiologic/Pathologic Diagnosis
Usual interstitial pneumonia	Idiopathic pulmonary fibrosis/cryptogenic fibrosing alveolitis
Nonspecific interstitial pneumonia	Nonspecific interstitial pneumonia
Organizing pneumonia	Cryptogenic organizing pneumonia
Diffuse alveolar damage	Acute interstitial pneumonia
Respiratory bronchiolitis	Respiratory bronchiolitis interstitial lung disease
Desquamative interstitial pneumonia	Desquamative interstitial pneumonia
Lymphoid interstitial pneumonia	Lymphoid interstitial pneumonia

deterioration in lung function tests [7]. The presence of advanced age, male sex, severe arthritis, excessively high RF and/or anti-CCP titers, presence of subcutaneous nodules, or other extra-articular findings increase the risk of ILD development in patients with RA. In clinical practice, one of the most controversial issues is the mediating effects of ILD on drugs used in RA treatment. Indeed, agents such as methotrexate, leflunomide, anti-TNF alpha agents and rituximab may be associated with ILD occurrence or progression [29]. There are reports that almost all medicines used in RA treatment lead to an ILD exacerbation or ILD-like appearance. However, it should be kept in mind that the risk of developing ILD will decrease if RA is controlled by any of these drugs.

Diagnosis of Interstitial Lung Disease Associated with Rheumatoid Arthritis

Patients with rheumatoid arthritis-associated interstitial lung disease (RA-ILD) may be asymptomatic, while the majority of patients are presenting with effort dyspnea and dry cough. Pleuritic chest pain, fever, hemoptysis and tachypnea are other symptoms of the disease. The most frequent finding on physical examination was crepitant rales in bilateral baselines in pulmonary auscultation [30]. Sensitivity of X-ray to ILD diagnosis is very low and may be normal in early stages [30]. Reticular and small nodular opacities can be in the lower lung zones seen on plain chest X-ray.

In the majority of patients, respiratory function tests have low Force Vital Capacity (FVC), Low Total Lung Capacity (TLC), low/normal carbon monoxide diffusion capacity (DLCO), and restrictive respiratory pattern with exercise or resting hypoxemia [30]. Since the earliest functional disorder in patients with ILD is decreasing in DLCO; DLCO is one of the important tests for the early diagnosis of ILD. FVC may not be affected until advanced disease. The pulmonary function tests also reveal a normal or high FEV1/FVC (restrictive type lung disease finding) ratio. DLCO and FVC are also usefully to assess treatment response. Changes in the follow-up must be 10% in the FVC or 15% in the DLCO in order to be considered "statistically significant" [31].

HRCT has been accepted as the gold standard noninvasive imaging method in the diagnosis of ILD in RA patients [32]. HRCT results were consistent with the results of open lung biopsy [33]. The most common HRCT findings in patients with RA-ILD are UIP, NSIP, LIP, organizing pneumonia, diffuse alveolar damage, respiratory bronchiolitis, and desquamative interstitial pneumonia [30].

Since there may be some alterations in Bronchoalveolar Lavage (BAL) fluid in the absence of ILD, BAL is not routinely used as a diagnostic tool to demonstrate the presence of RA-ILD. Neutrophil and macrophage dominance are characteristic in RA-ILD [20]. Although BAL may be useful to exclude infection, is not necessary for diagnosis of RA-ILD.

Surgical lung biopsy is the best method for histopathologic diagnosis. However, due to the potential risks associated with the method, many patients are diagnosed without surgical biopsy and pathologic confirmation. Video-Assisted Thoracoscopic Surgery (VATS) is often preferred for open lung biopsy. Transbronchial biopsy for diagnosis is limited, and not necessary in patients with typical clinical and radiological findings [19].

Studies of biomarkers that can be used to confirm the diagnosis and evaluate the treatment response are still in progress. Recently a serologic marker known as KL-6 (Krebs von der Lungen-6, proliferating type 2 pneumocytes and high molecular weight glycoprotein expressed in epithelial cells) is focused. KL-6 is elevated in interstitial pneumonia, hypersensitivity pneumonitis, tuberculosis, sarcoidosis and pulmonary alveolar proteinosis. It is also elevated in RA-ILD [34,35]. KL-6; reflects the extensity of HRCT lesions, grade of alveoli is, active and progressive pulmonary disease detection in RA-ILD, and severity of pulmonary fibrosis however may not be very sensitive in early stage pulmonary disease [35]. Oyama et al reported that KL-6 was elevated in 88.9% of patients with active ILD, and only 0.6% of patients without active ILD [36].

Recently, studies have been published that transthoracic ultrasonography is a useful method in the diagnosis of early stage ILD. In a study involving patients with RA, systemic sclerosis and systemic lupus erythematosus, a significant proportion of patients with ILD on HRCT reported pathological changes in transthoracic ultrasonography [37].

18-fluorodeoxyglucose positron emission tomography/computed tomography (18 FDG PET-CT) is one of the modalities that can be used in the diagnosis of ILD. In a recent study evaluating patients with connective tissue disease, findings during deep breathing may contribute to the diagnosis of ILD by 18F-FDG PET / CT was reported [38].

Treatment of Interstitial Lung Disease Associated with Rheumatoid Arthritis

Unfortunately, there is no consensus in the treatment of RA-ILD today. Management must be multidisciplinary and should be planned privately for the patient; both of supportive treatments and medical treatments should be emphasized. The promotion of smoking cessation comes at the beginning of supportive therapies, which is considered to play a pivotal role in the pathogenesis of RA, and also is known to increase both joint symptoms and lung damage. Patients are advised to have pneumococcal and influenza vaccines. Patients with low oxygen saturation should be administered oxygen supplementation [39,40].

RA-ILD treatment is becoming more complicated and challenging as there are reports that almost all medications used in RA treatment can cause ILD or that they have already mediated ILD. Hence, treatment depends on the severity of the illness and patient's

condition. At this point, radiological findings and functional capacity of the lung are as important as the patient's clinic. There are cases without disease symptoms, such as breathlessness and/or cough that incidentally detected with radiologic imaging of ILD findings, these patients do not need additional treatment if they are functionally stable [41]. These patients are recommended to be followed up with respiratory Function Test (PFT) every three months, HRCT and PFT/DLCO every 6-12 months for the first two years, if symptoms progress. Treatment of asymptomatic RA-ILD patients without progressive disease should be continued as usual, and at this level the use of any DMARD which controls joint symptoms is not contraindicated.

During follow-up periods, patients with progression according to clinical, radiological or pulmonary function test findings should be given additional treatment for ILD. Despite the lack of controlled studies in RA-ILD treatment, corticosteroids are considered as first-line therapy. The initial dose is usually 0.5-1mg/kg prednisolone (usually 40-60 mg/daily). Once the response to corticosteroids is achieved, the dose is reduced gradually to the lowest possible dose. The response of some ILD species, such as NSIP and OP, to corticosteroids is better than other subtypes. When corticosteroids are reduced, additional immunosuppressive agents may be needed. For this purpose, corticosteroids may be combined with azathioprine, cyclophosphamide, or Mycophenolate Mofetil (MMF) [42,43].

Since the risk of respiratory failure, patients with a rapidly progressive ILD pattern should be approached aggressively. High dose corticosteroid (prednisolone at 10mg/kg/day) and intravenous pulse cyclophosphamide (6 cycles at 15mg/kg) every 3-4 weeks are recommended for these patients. At the end of the cyclophosphamide treatment, MMF or azathioprine therapy is recommended as an indwelling therapy [42]. Cyclophosphamide has been reported to be useful in active-rapidly progressive disease [42], although there are no randomized controlled trials of its use in RA-ILD and limited efficacy has been reported.

In a cohort of mixed connective tissue disease with a small number of patients with RA-ILD, mycophenolate mofetil has been reported to contribute for stabilization or improvement in symptomatic healing and PFTs, and useful for reducing of steroid dose as well [44,45]. Despite the fact that positive effects on lung findings have been shown in a small number of studies; due to the lack of healing effect on joint manifestations, the field of use of mycophenolate mofetil is limited, today.

Rituximab is one of the most commonly used drugs in the treatment of RA-ILD in recent years. Rituximab (RTX) is a monoclonal antibody against the B-cell marker CD20 that used to treat RA patients who are unresponsive for anti-TNF or who cannot use these drugs. After the demonstration of follicular B cell hyperplasia and interstitial plasma cell infiltrates in patients with RA-ILD, a potential role for B cell in pathogenesis is suggested. This has caused an increased interest on RTX in the treatment of RA-ILD [46]. Recently, Md Yusof et al., evaluated 700 patients who were diagnosed with RA and used rituximab [47]. 56 of the patients had ILD and 46 of them were appropriately evaluated; it has been reported that in the majority of patients, the disease is stabilized or improved [47].

As with other biological therapies, there is concern about potential pulmonary toxicity with RTX. The reported cases are largely due to

lymphoproliferative diseases. However, there are several reports on the development or worsening of ILD in RA patients using rituximab [48-50].

Antitumor necrosis factor (anti-TNF) agents have been shown to have great efficacy in suppressing RA joint symptoms and improving disease progression, and have been used in many RA patients who have not responded to conventional DMARD therapy in recent years.

However, with the widespread use of these drugs, they have caused concerns about potential pulmonary toxicity. There have been reports of new onset ILD or worsening of pre-existing disease after starting anti-TNF treatment [51-55]. In their study Ramos-Casals et al reported that ILD develops in 10% of 226 patients (83% of RA) who received anti-TNF therapy [56].

On the other handsome studies suggest that there is no correlation between the use of anti-TNF and the development and exacerbation of ILD in RA. A report from the British Society for Rheumatology Biologics Register on patients with RA-ILD taking either anti-TNF agents or traditional DMARDs found no difference in mortality [57]. However, in the same report, ILD mortality was 21% in patients treated with anti-TNF therapy, compared with 7% in conventional DMARDs [57]. In another study, Herrinton et al., compared anti-TNF therapy with non-TNF biologic therapy in their study of more than 8.000 patients; there was no difference in the development of ILD [58].

However, anti-TNF drugs have been shown to have potentially positive effects in stabilizing or ameliorating pulmonary disease [59,60]. Experimental studies indicate that TNF-alpha may have both profibrotic and antifibrotic effects; the imbalance between these two roles may trigger fibrosis or stabilize ILD in vulnerable individuals, but further studies are needed to confirm this hypothesis [61]. Patients with pre-existing RA-ILD should be followed closely and attentively during anti-TNF treatment. Since methotrexate has a potential risk for pulmonary toxicity, the combination of anti-TNF and methotrexate may have a greater risk of developing ILD or worsen the pre-existing disease. Therefore, in patients with ILD, the combination of methotrexate and anti-TNF should not be preferred or should be followed closely in case of necessity.

Despite of non-TNF biological agents such as Tosituzumab and Abatacept are reported to be beneficial in RA patients with ILD, there are some reports that suggest new ILD developments or worsening the pre-existing ILD under these agents [62- 64].

Lung transplantation is recommended as an option for progressive and severe pulmonary disease, despite medical treatment. The results are similar to those of idiopathic interstitial pneumonia; 1-year survival is 68% and 3-year survival is 46%.

Conclusion

RA patients with respiratory complaints should be carefully evaluated for lung involvement. Pulmonary function tests and radiologic imaging techniques should be used in conjunction with clinical evaluation for diagnosis, and appropriate treatment should be initiated urgently. While deciding on the treating agent, the degree of pulmonary involvement and the characteristics of the patient should be considered and the treatment should be customized for

the patient. Non-pharmacologic approaches such as close follow-up, smoking cessation and oxygen supplementation are also important to increase the effectiveness of pharmacological treatment.

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