Revista Română de Reumatologie
Romanian Journal of Rheumatology

REVIEW

Rheumatoid Arthritis-Associated Interstitial Lung Disease

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Abstract

Rheumatoid arthritis (RA) is a systemic autoimmune disease affecting 1% of the population, characterized primarily by joint involvement but also by extra-musculoskeletal manifestations, among which interstitial lung disease (ILD) is the most clinically significant. RA-associated ILD (RA-ILD) may precede articular symptoms or remain subclinical for years, and is a leading cause of morbidity and mortality in RA, with median survival of 3-7 years after diagnosis. Risk factors include male sex, older age, smoking, high disease activity, autoantibody positivity, and genetic variants such as MUC5B rs35705950. Pathogenesis involves autoantibody formation, citrullination of lung proteins, and environmental triggers, with smoking acting as a major driver. Diagnosis relies on high-resolution computed tomography (HR-CT), pulmonary function tests (FVC, DLco), and multidisciplinary evaluation. Common HR-CT patterns include usual interstitial pneumonia (UIP) and nonspecific interstitial pneumonia (NSIP), with UIP conferring a worse prognosis. Screening strategies and risk scores are under development to facilitate early detection in high-risk patients. Management of RA-ILD remains challenging. Immunomodulatory therapies such as methotrexate and mycophenolate may slow progression, while antifibrotic therapy with nintedanib has demonstrated efficacy, significantly reducing annual FVC decline. Ongoing clinical trials are evaluating novel agents, including pirfenidone, JAK inhibitors (e.g., tofacitinib in the PULMORA and RAILDTo studies), PDE4B inhibitors (FIBRONEER-ILD), and anti-IL6 biologics. Retrospective studies suggest that tocilizumab may stabilize or improve lung function in a subset of patients. Optimal management requires early identification, regular monitoring, and close collaboration between rheumatologists and pulmonologists. Future research should clarify prognostic markers, refine screening strategies, and expand therapeutic options to improve outcomes in RA-ILD.

Keywords:. rheumatoid arthritis; interstitial lung disease; autoimmune disease; pulmonary involvement; connective tissue disease.

Introduction

Rheumatoid arthritis (RA) is a systemic, progressive autoimmune disorder, characterized by both symmetrical bilateral joint involvement, with erosive bone destruction, especially in the small joints of the hands and feet, although it can also involve large joints (shoulders, elbows, hips, knees, ankles), and by extra-musculoskeletal involvement. RA affects about 1% of the general population in developed countries. A common extra-musculoskeletal target in RA is the lung, but multiple other disorders may occur, including rheumatoid nodule formation, vasculitis, cardiac or neurological involvement. Pulmonary manifestations in RA can involve the lung parenchyma, airways, pleura or pulmonary vessels and most often they appear after longstanding joint involvement, but in certain circumstances they can represent the first manifestation of RA, in which case they define a very aggressive form of RA [1]. The 2013 classification of idiopathic pulmonary fibrosis (IPF) according to the American and European Thoracic Society specifically emphasizes histopathological changes in interstitial lung disease (ILD), many of which are found in association with RA [2]. These changes may show chronic immune activation, increased susceptibility to infections (frequently associated with immunosuppressive medication), or direct toxicity of treatment with conventional synthetic, biological or targeted synthetic disease-modifying antirheumatic drugs (cs/b/tsDMARDs). The prognosis depends on the type and severity of lung involvement [3, 4].

The pathophysiological changes underlying the development of ILD in patients with RA are still poorly understood. Data from the studies available to date suggest the existence of several environmental factors, but also genetic factors. Of these, the presence of the HLA-B54, HLA-DQB1*0601, HLA-B40 and HLA-DR4 genes was associated with the development of RA-associated ILD [2, 5-7]. Studies hypothesize that RA begins in the lung [8]. In line with this hypothesis, there are studies that have demonstrated the existence of citrullinated proteins in the bronchoalveolar lavage fluid of smoking patients, but without a diagnosis of RA, and specific RA antibodies have been identified in the sputum of patients at risk for developing RA [9, 10].

Respiratory symptoms in RA can be caused by a series of lung disorders (parenchyma, pleura, airways,

vascularization; Table 1), which are generally nonspecific, manifested by dyspnea on progressively greater exertion, dry cough, fatigue. Complications can occur directly due to RA or indirectly through immunosuppression induced by the medication used for the treatment of RA. Most respiratory symptoms occur in the first 5 years after the diagnosis of RA [3]. However, most patients are asymptomatic and at the time of the appearance of symptoms the ILD is already prevalent, which implies the need for a screening protocol for patients with RA at high risk of developing lung damage in the in order to diagnose it before the onset of symptoms. In 10-20% of cases, respiratory symptoms may precede the onset of joint manifestations [4]. In addition, they can be masked due to functional disability secondary to joint damage through chronic inflammation and destruction of cartilage and subchondral bone [11].

Table 1. *Pulmonary manifestations in RA [84]*

Parenchymal involvement
Interstitial lung disease (UIP – *usual interstitial pneumonia,* NSIP – *non-specific interstitial pneumonia,* acute interstitial pneumonia, OP – *organizing pneumonia)*
Pleural involvement
Pleurisy, pneumothorax, bronhopleural fistula, trapped-long syndrome
Airway damage (obstruction)
Obstructive (constrictive) cricoarytenoid arthritis, bronchiectasis, follicular bronchiolitis, bronchiolitis
Nodules
Rheumatoid nodules, Caplan syndrome
Vascular damage
Rheumatoid vasculitis, pulmonary hypertension
Others
Drug toxicity, infections, neoplasms, pulmonary thromboembolism

Interstitial lung disease (ILD)

ILD is the most common and important pulmonary manifestation associated with RA, despite the fact that its prevalence is not fully established, depending on the characteristics of the studied population and on the method of diagnosis [12, 13]. A study conducted on an Australian cohort of patients with RA with less than 2 years after onset showed that 58% of them had ILD diagnosed by either plain chest X-ray, high-resolution computed tomography (HR-CT), respiratory function tests or bronchoalveolar lavage. Of these, 76% were asymptomatic [14]. At present, it is estimated that approximately 30% of patients with RA have subclinical ILD diagnosed by HR-CT. While, with the discovery of new therapies and treatment schemes for RA, the incidence of other extra-musculoskeletal manifestations has decreased significantly, the incidence of ILD has remained stable or even increased, both through the awareness of its importance and effects by rheumatologists, pulmonologists and imaging specialists, as well as through easier access to diagnostic imaging methods, performed on asymptomatic patients, but who have high risk factors associated with the development of ILD [15, 16]. ILD is considered one of the leading causes of death in RA patients, with an estimated median survival of between 3 and 7 years after its diagnosis. In addition, the association of pulmonary and joint involvement contributes to a significant decrease in the quality of life of patients, to chronic progressive disability and to the use of significant resources of the medical system [17-19]. It is estimated that between 2 and 10% of patients with RA are associated with manifest clinical ILD, but as mentioned above, the percentage of subclinical interstitial lung involvement is probably significantly higher and requires new screening criteria for high-risk patients [20, 21].

Risk factors for the development of ILD associated with RA

The evolution of ILD associated with RA is extremely varied, some of the patients having progression to clinically manifest pulmonary distress and with significant ventilatory dysfunction. The onset of clinical symptoms is associated with an increased risk of mortality and morbidity, with an average survival of between 3 and 8 years [22, 23].

In the case of patients in whom the diagnosis of RA-associated ILD is suspected due to the appearance of clinical manifestations, pulmonary HR-CT is indicated for screening and diagnostic confirmation, but also for the description of the pattern of ILD and for quantitative determination of the extent of interstitial pulmonary fibrosis. In the case of asymptomatic patients who have a particular risk to develop ILD, screening for ILD becomes a challenge. Under these conditions, the identification of methods to determine the risk of progression to ILD in asymptomatic patients may be of great importance, especially due to the current existence of antifibrotic therapies that can reduce the deterioration of lung function [24-26].

Risk factors for the development of ILD in patients with RA have been identified in retrospective studies in patients with diagnosed ILD. The main risk factors are: male gender, advanced age at diagnosis, smoking,

high disease activity (RA) quantified by composite indices (DAS28, CDAI), seropositivity (rheumatoid factor – RF, anti- anti-cyclic citrullinated peptide – anti-CCP antibodies), presence of bone erosions, presence of other extra-musculoskeletal manifestations and long duration of the disease (RA) [27, 28]. A major risk factor associated with the development of RA-associated ILD has been identified in recent studies, namely, the genetic factor MUC5B rs35705950 [29].

Thus, the identification of patients with RA with multiple risk factors to develop ILD, who could benefit from pulmonary HR-CT screening at an early, subclinical stage, is a need that is still unmet in the current medical practice. It is necessary to prioritize this need, to develop and validate a risk score for the development of ILD in patients with RA.

Pathogenic mechanisms in RA-associated ILD

The mechanism underlying the occurrence of pulmonary fibrosis in RA-associated ILD is not fully known. Patients with RA generally have circulating autoantibodies, the most important being RF and anti-CCP antibodies. They can be detected in the serum of patients many years before the clinical manifestation of synovitis. Both RF and anti-CCP antibodies have been associated with the development of ILD, especially when present in high titers [30, 31]. There is increasing evidence to support the hypothesis that a subgroup of patients with seropositive RA (RF and/or anti-CCP antibodies) initially developed lung damage, which preceded the clinical onset of arthritis. This theory is supported by the identification in these patients of reactive lymphoid structures of the bronchi-associated lymphoid tissue (BALT) type and is associated with the local production of proinflammatory cytokines and the presence of anti-CCP antibodies [32, 33].

Smoking appears to play an important role in inducing autoantibody formation and it has been associated with higher RF titers [34, 35]. Also, smoking can contribute to the appearance of RA-associated ILD by promoting the citrullination of lung proteins, thus favoring the formation of anti-CCP antibodies. This phenomenon is more common in patients carrying the shared epitope HLA-DRB1. A large case-control study conducted in Sweden demonstrated a 21-fold higher risk of developing RA in anti-CCP-positive patients who smoked and carried two copies of the gene for the shared epitope, compared to non-smokers who did not have this genotype [36, 37]. Citrullination is hypothesized to increase peptide binding to shared epitopes, thereby enhancing the immunogenicity of these proteins. A Japanese study looked at the association between RA-associated ILD and HLA-DRB1 subtypes. While some alleles showed a significant association, others appeared to have a protective effect, and most had no relevant association. This suggests that the shared epitope has a role in the pathogenesis of RA, but not necessarily in the development of ILD [38]. In addition to de novo changes, treatments used for joint manifestations of RA can also contribute to the development of IDL.

Diagnosis of RA-associated ILD

The diagnosis, clinical and paraclinical evaluation of ILD associated with RA, are recommended to be made through a standardized management protocol, within a multidisciplinary team that must include a pulmonologist, a radiologist and a rheumatologist [39, 40].

Medical history and clinical examination

The symptoms of RA-associated ILD occur when the evolution of the disease is already at an advanced stage and patients present with dyspnea on exertion ad dry cough. In the case of pulmonary fibrosis associated with RA, the symptoms associated with them will also be taken into account, such as joint pain or muscle damage [41, 42]. Medical history will identify factors of professional or private environment (feathers, industrial substances), previous and current medication (e.g. amiodarone, chemotherapy), smoking/non-smoking status, family history, as well as the onset of the disease. From the point of view of clinical examination, auscultation is essential for the identification of bilateral basal crackling rales. They are a predictive factor for the evolution of fibrosis [42, 43].

Laboratory analysis

Laboratory tests are recommended for diagnosis, including blood count, evaluation of liver and kidney function, evaluation of acute phase reactants, as well as tests to exclude cardiac damage (CK, CK-MB, troponin, BNP, myoglobin, aldolase) [42, 44, 45].

A prospective multicenter study aimed to evaluate the association between plasma concentrations of matrix-metalloproteinases (MMPs) and ILD in patients with RA. The diagnosis of ILD was validated by the patients' treating physicians by imaging methods, and the plasma concentrations of MMP1, 7 and 9 were measured from blood samples of selected patients. Of the 2312 patients, 284 were diagnosed with prevalent ILD, and 79 developed ILD during 9750 person-years of follow-up (crude incidence 7.5/1000 person-years). Patients with the highest concentrations of MMP7 had a 4-fold higher risk of ILD prevalence (95% CI: 2.33-6.15; p=0.005) and a more than 2-fold increased risk of ILD incidence (95% CI: 1.35-4.02). MMP1 and MMP9 concentrations also correlated with ILD prevalence and incidence, but to a lesser extent. Among patients with RA-associated ILD, higher values of forced vital capacity on respiratory function samples were negatively associated with MMP 7 levels, suggesting a relationship between disease severity and MMP expression. In conclusion, the study argued that MMPs may have a potential pathogenic role in RA-associated ILD and suggested that their determination could facilitate risk stratification for patients [46].

Numerous other serological biomarkers have been studied in patients with RA-associated ILD, but there

are not enough data to support their usefulness in routine clinical practice. Research on these biomarkers has started from the hypothesis that RA-associated ILD shares common characteristics with idiopathic pulmonary fibrosis (IPF), which is why biomarkers present in IPF that could be associated with RA-associated ILD have been studied (Table 2).

Table 2. Identified and experimental biomarkers in RA-associated ILD [47]

Name	Source	Scientific data (evidence)	Utility in RA-ILD
RF	Serum, saliva, BAL	Low specificity, higher titers associated with lung damage in RA	Diagnosis
ACPA	Serum, saliva, BAL	High specificity for RA diagnosis; higher titers associated with lung damage in RA	Diagnosis
PAD	Synovial tissue	Possible involvement in synovial inflammation	Diagnosis
HSP90/70	Serum, BAL	Increased levels in RA-associated ILD; is not present in RA patients without ILD	Diagnosis
MMP7	Serum	Increased levels in RA-associated ILD and in idiopathic pulmonary fibrosis	Diagnosis
CXCL 10 (IP-10)	Serum	Increased levels in RA-associated ILD; is not present in RA patients without ILD	Diagnosis
KL-6/MUC1	Serum	Correlated with RA-associated ILD severity; higher values in fibrotic ILD	Severity
LOXL2	Serum	Correlation with ILD severity associated with RA, but does not differentiate between RA with and without ILD	Severity
Anti-CEP-1	Serum	Marker for RA-associated ILD in RA and UIP pattern on HR-CT	Diagnosis (specificity)
MUC5B	Genotyping	Increased risk of RA-associated ILD, associated with UIP pattern on HR-CT	Diagnosis

Abbreviations: RR – rheumatoid factor, ACPA – peptide-cyclic citrullinate antibodies, PAD – peptidilarginine deiminase, HSP90/70 – shock proteins term 90/70, MMP7 – matrix metalloproteinase 7, CXCL10 (IP-10) – chemokine CXC; KL-6/MUC1 – glycoprotein associated with lung damage, LOXL2 – lysyl-oxidase like 2, anti-CEP-1 – antibodies to citrullinated peptide of alpha-enolase, MUC5B – mucin 5B, BAL – broncho-alveolar lavage, PIU – usual interstitial pneumonia, HR-CT – high-resolution computed tomography.

Imaging (X-rays, CT, ultrasound)

Lung or chest X-ray is the first imaging investigation that will be performed on a RA patient suspected of lung involvement. Conventional radiology cannot give a specific diagnosis, but it can guide the differential diagnosis (for example, cardiac decompensation) or it can give clues about the severity of the disease [46]. The diagnosis of RA-associated ILD is based entirely on HR-CT which also provides information about the anatomy, imaging pattern, evolution over time and clues related to the underlying disease [47]. The patterns found on HR-CT images in patients with RA-associated ILD are:

- reticulated pattern and/or "ground glass" opacities that may be accompanied by peripherally localized traction bronchiectasis;
- "honeycomb" lesions [48];
- UIP pattern (usual interstitial pneumonia) characterized by peripheral subpleural and basal reticulations, with "honeycomb" and traction bronchiectasis;
- NSIP pattern (non-specific interstitial pneumonia) characterized by "ground glass" opacities, condensations and reticulated pattern in the basal areas bilaterally, which may be accompanied by traction bronchiectasis [46, 49].

HR-CT can provide, apart from an accurate diagnosis, data on the prognosis of the disease: UIP with typical "honeycomb" lesions and traction bronchiectasis has a poor prognosis, while the "ground glass" pattern within an NSIP, associated with condensation and reticular pattern, have a good response to immunosuppressive therapy [46, 50, 51].

Last but not least, it is necessary to mention the fact that HR-CT imaging data will always be corroborated with the medical history and the clinical and laboratory data, as well as with those obtained from the evaluation of the pulmonary function, in order to establish the diagnosis, the optimal treatment and the prognosis. There are complex programs based on artificial algorithms that can quantitatively evaluate fibrotic lesions, but they are not currently available in current practice, especially due to the prohibitive price [46, 52].

In addition to the above, RA patients are more prone to developing chronic obstructive pulmonary disease (COPD), as well as other lung diseases [53, 54]. Currently, there are no evidence-based guidelines identifying the optimal way to screen for respiratory symptoms in patients with RA, nor studies evaluating how common patients with RA and respiratory symptoms have ILD compared to the more common diagnosis of COPD. Thoracic ultrasonography (UST) is a radiation-free, easy-to-use imaging method within the reach of any "bedside" sonographer, with promising results both in RA and in other categories of patients with ILD, such as patients with systemic sclerosis. However, it is not validated as a screening

method for the identification of ILD in RA. Thoracic ultrasonography aims to identify B-lines, as well as the thickening and fragmented appearance of the visceral pleura, which has been observed to be associated with the presence of ILD on HR-CT, but not with airway diseases, such as COPD. There are studies that have evaluated the diagnostic accuracy of the use of UST in the detection of ILD in patients with RA and respiratory symptoms, using thoracic HR-CT combined with multidisciplinary discussion as the reference standard for the diagnosis of RA associated ILD [55, 56].

Lung function

The complete evaluation of patients with RA-associated ILD includes the evaluation of lung function, represented by the combination of spirometry, body-plethysmography and DLco, gasometry and a stress test. The most important functional parameters are forced vital capacity (FVC) and DLco [45, 53, 54]. Blood gas analysis must be performed both at rest and during exercise, which provides data on oxygen needs and can highlight early changes in diffusion capacity [41, 55, 56]. The most commonly used exercise test is the 6-minute walk test (6MWT), performed according to a standardized protocol [53, 57].

Bronchoscopy, broncho-alveolar lavage (BAL) and biopsy

Invasive methods such as bronchoscopy, broncho-alveolar lavage (BAL) or biopsy, are necessary if, following all the above clinical and paraclinical investigations, the diagnosis could not be established. BAL is used especially if an inflammatory pathology is suspected and it can help establish the diagnosis. The histopathological examination of the collected fluid can identify granulomatous lesions (sarcoidosis) or lymphocytosis [58]. Also, a high number of neutrophils raises the suspicion of an infection, while moderately elevated values of neutrophils and eosinophils are found in idiopathic pulmonary fibrosis [44, 45].

Lung biopsy is either surgical or by cryobiopsy. Taking into account the fact that the surgical procedure involves certain risks, the decision of its necessity must be taken within the multidisciplinary board, where its benefits and risks in the given situation will be weighed [42, 45]. There is a possibility that the radiological pattern does not coincide with the histological pattern, the former having several different patterns. It goes without saying that the sample will be examined by an experienced pathologist in a specialized center.

Multidisciplinary board

The multidisciplinary board (ILD-board) includes pulmonologists, radiologists, rheumatologists and pathologists and it is responsible for diagnosis and treatment of RA-associated ILD. The ILD-board has already become a standard in numerous clinics [44, 45, 59]. It has already been demonstrated that debating the case of a patient with idiopathic pulmonary fibrosis within a multidisciplinary board increases the accuracy of the diagnosis and has prognostic relevance [45, 60, 61]. In recent years, due to the fact that new therapeutic options have emerged, the attention on ILD associated with connective tissue diseases has increased significantly, which is why the collaboration between pulmonologists and rheumatologists is of particular importance [42, 53, 62].

Screening for RA-associated ILD

Rheumatologists should be highly vigilant in identifying ILD in RA patients with risk factors. Although multiple screening tools have been developed based mainly on risk factors, they all require additional validation in order to be widely applied in clinical practice. Compared to HR-CT, a predictive score that takes into account gender, age at RA onset, disease activity (DAS28), and presence of the MUC5B rs35705950 gene, demonstrated 75% sensitivity and 85% specificity for identifying RA-associated ILD. However, applying this score in clinical practice can be difficult and limited [63].

Another risk score, based on patients' gender, smoking status, presence of extra-musculoskeletal manifestations, disease activity, and ESR value, had a sensitivity of 90% and a specificity of 64% for the identification of RA-associated ILD [27]. A Delphi group in Spain proposed ILD screening in patients with RA, in whom pulmonary auscultation is normal and who had no respiratory symptoms, using a risk score that took into account patients' gender, smoking status, age, duration of disease, family history of ILD, presence of RF or anti-CCP antibodies, and DAS28 [64]. The VECTOR algorithm, which detects the presence of "velcro" rales, recorded by an electronic stethoscope, reported a sensitivity of 93% and a specificity of 77% in the identification of ILD by HR-CT in patients with RA. However, the limited availability of this type of equipment restricts its use in practice. Therefore, an ideal screening tool should be easy to use in the clinical setting, applicable in resource-constrained regions, and able to efficiently identify patients at high risk of ILD, who require additional imaging investigations by HR-CT [65].

Evolution and prognosis of RA-associated ILD

The evolution of RA-associated ILD is variable, lung function may remain stable or even improve after diagnosis in certain cases, while other patients may present a slow of lung function tests. RA-associated ILD is associated with a high degree of mortality. A US study of 582 patients found that the risk of death during the follow-up period was three times higher in patients with ILD compared to those with RA without lung involvement (RR 2.86; 95% CI: 1.98-4.12) [66]. Another prospective study, which included 679 patients with RA-associated ILD and 11,722 control patients with RA without ILD, showed a 10-year mortality rate of 60.1% (95% CI: 52.9-66.5) in the group with ILD, compared to 34.5% (95% CI: 32.8-36.1) in the group without ILD [20]. Approximately 52% of patients with RA-associated ILD evolve in the first 2 years after diagnosis to a progressively fibrosing

form. A relative decline in FVC of more than 10%, a decline in DLco of more than 15%, or worsening of respiratory symptoms or radiological images, are associated with progressive forms of the disease.

UIP has a prognosis similar to the one observed in idiopathic pulmonary fibrosis. Low values of FVC and DLco, as well as their decline within 6 months, are correlated with a higher severity of RA-associated ILD. A DLco below 54% has a sensitivity of 90% and a specificity of 93% to predict worsening of lung damage (assessed by HR-CT) or death due to respiratory failure [67]. Older age, male gender, increased DAS28, UIP pattern or extension of lung involvement on HR-CT, increased serum values of KL-6 protein, high RF and anti-CCP antibodies, are among the factors associated with a negative prognosis [68].

Predictive models that include demographics, clinical characteristics, and imaging are useful for assessing mortality. For example, a model using age over 60 years and imaging variables (fibrosis of more than 20%, UIP pattern, emphysema), has a good ability to predict mortality at 5 years in patients with RA-associated ILD [69].

Monitoring of RA-associated ILD

Monitoring of patients with RA-associated ILD is essential for the early identification of those in whom ILD demonstrates progression. In clinical practice, monitoring is mainly performed by the rheumatologist. Despite the fact that there is still no clear consensus and strategy regarding the monitoring of patients with RA-associated ILD, an integrated approach that includes the evaluation of respiratory symptoms is recommended at each visit, respiratory function tests (FVC and DLco) at intervals of 3-6 months, as well as an annual HR-CT scan or more frequently depending on the clinical evolution. Follow-up HR-CT can highlight disease progression and associated complications, such as pulmonary hypertension or neoplasms, which can significantly influence the prognosis [70, 71].

However, the interpretation of HR-CT raises methodological difficulties related to interobserver variability and to establishing the optimal interval between examinations. In this context, automatic methods for quantifying pulmonary changes on CT images are increasingly studied, especially in associated connective tissue diseases, where parameters such as the degree of fibrosis, reticular pattern, and pulmonary vascular volume are prognostic factors of mortality. The data available so far in RA-associated ILD are still limited, requiring validation by prospective studies [72].

Pulmonary function tests are the standard methods of longitudinal evaluation of lung function, but they have limitations related to the patient's exercise capacity, the ability to comply with instruction given by the technician who performs the tests, as well as the association of comorbidities. The presence of emphysema can influence their accuracy, especially in terms of estimating progression. However, in patients with advanced disease, respiratory function test may be more sensitive than imaging in detecting progression. HR-CT and respiratory function test are complementary and essential in the monitoring of patients with RA-associated ILD [73].

Management of RA-associated ILD

Despite the existence of recommendations regarding the management of patients with RA-associated ILD, in present there are no official international guidelines available that clearly establish the timing of initiation or escalation of treatment. It is unclear whether therapeutic interventions, especially biological molecules, alter the rate of disease progression or the overall prognosis. Therefore, the therapeutic strategy must be adapted individually, depending on the severity of lung damage, the activity of the joint disease and the patient's comorbidities [74].

The progression of pulmonary fibrosis is usually defined by decreased pulmonary function (FVC), extension of fibrosis on HR-CT, and worsening of respiratory symptoms without any other identifiable cause. The UIP imaging pattern, most frequently identified in RA-associated ILD, was associated with a more reserved prognosis, although its predictive value is controversial in the absence of functional decline [53].

The use of methotrexate in patients with RA-associated ILD has long been controversial due to the suspicion of potential pulmonary toxicity. However, recent evidence suggests that methotrexate not only does not accelerate the progression of lung damage, but may even slow the decline in lung function. Retrospective analyses have shown a reduction in pulmonary functional loss (FVC) in patients treated with methotrexate, leflunomide or azathioprine. The 2021 ACR guidelines support the use of methotrexate in RA with mild ILD or moderate inflammatory activity, in the absence of severe pulmonary contraindications [75, 76].

In cases of ILD associated with connective tissue diseases, there is favorable evidence for the use of mycophenolate mofetil and cyclophosphamide. However, double-blind randomized controlled trials that conclusively confirm the efficacy of these therapies are lacking. Their use is mainly based on observational studies and extrapolation of data from other types of interstitial lung diseases [77].

Nintedanib, an antifibrotic agent approved for idiopathic pulmonary fibrosis and systemic sclerosis-associated ILD, has also demonstrated efficacy in RA-associated ILD, according to data from the INBUILD study. Patients treated with nintedanib had a slower rate of decline in FVC compared to placebo (-80.8 mL/year versus -187.8 mL/year), equivalent to a reduction of 57%. This benefit was observed regardless of imaging pattern or concomitant therapy with DMARDs or glucocorticoids [78, 79].

Several clinically randomized trials evaluating the

effects of therapy on lung function in RA-associated ILD are notable, for instance:

- the PULMORA study (ClinicalTrials.gov ID NCT04311567), comparing tofacitinib (JAK inhibitor) with methotrexate, which was terminated because of low recruitment due to the pandemic and high screening failure rate in particular because of low prevalence of interstitial abnormalities at diagnosis in Sweden;
- single-center trials comparing pirfenidone with immunomodulator-associated glucocorticoids [80, 81];
- the FIBRONEER-ILD study, investigating the phosphodiesterase inhibitor BI 1015550 in patients with non-idiopathic pulmonary fibrosis ILD [82];
- the RAILDTo study (ClinicalTrials.gov ID NCT05246293), which explores the safety of tofacitinib in ILD associated with RA in an open-label design.

There is a growing interest in the potential of biological agents (e.g. anti-IL6 agents) and targeted synthetic DMARDs (tsDMARDs) in influencing the evolution of RA-associated ILD. A retrospective study in 28 patients with RA-associated ILD treated with tocilizumab reported a rate of stabilization or clinical improvement of 76% [83], but the results require confirmation by prospective, randomized, double-blind trials. Also, inhibitors of IL6 or of other pro-inflammatory cytokines are considered promising options for the future.

Conclusions

Interstitial lung involvement is an important cause of morbidity and mortality among patients with RA, which may be due to both the lack of awareness of this condition and the latency of the diagnosis, which leads to late identification of the disease and the presentation of patients in advanced stages, with severe functional impairment. As treatment options diversify, early evidence-based diagnosis is becoming increasingly important for the successful treatment RA-associated ILD. Although several risk factors for the occurrence of ILD have been identified in this context, it can also occur in patients who do not have such factors. Thus, early detection and regular monitoring of RA-associated ILD are essential to prevent severe complications.

In patients with RA-associated ILD, the therapeutic objectives are to achieve remission of joint disease and stop the progression of pulmonary fibrosis. In practice, however, therapeutic decisions are often difficult. Most patients with RA benefit from immunomodulatory therapies, but their effectiveness in controlling the progression of ILD remains uncertain. In contrast, antifibrotic therapy has demonstrated the ability to slow the progression of pulmonary fibrosis, and nintedanib is approved for the treatment of patients with progressive forms of ILD.

Optimal management of patients with RA-associated ILD requires a multidisciplinary approach, involving at least collaboration between rheumatologists and pulmonologists, and must be tailored to the individual needs of the patient. Future research directions should aim to clarify issues related to early identification, effective monitoring and therapeutic management in RA-associated ILD.

Conflicts of Interest: The authors declare no conflicts of interest.

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Received: 10.05.2025

Accepted: 28.06.2025