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Interstitial lung disease in rheumatoid arthritis

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ABSTRACT

Rheumatoid arthritis (RA) is a systemic inflammatory disorder mainly involving joints but almost 50% of the patients develop extra-articular manifestation, one of the most common being lung involvement. While essentially any of the lung compartments can be involved, interstitial lung disease (ILD) is associated with significant morbidity and mortality. In this review, we discuss main current concepts in the screening, diagnostic and monitoring strategies of RA-ILD as well as therapeutic recommendations.

Keywords: rheumatoid arthritis, systemic inflammatory disorder, extra-articular manifestation, lung involvement, interstitial lung disease, RA-ILD

INTRODUCTION

Rheumatoid arthritis (RA) is a systemic inflammatory disorder that affects an estimated 1% of the population worldwide [1]. One of the most common extra-articular manifestation of RA is lung involvement, which can affect more than half of patients during the disease course [2]. RA can essentially affect any lung compartment including: the parenchyma, manifesting as interstitial lung disease or rheumatoid nodules; pleura, resulting in pleural inflammation and/or effusions; small and large airways (cricoarytenoiditis, constrictive or follicular bronchiolitis and bronchiectasis); and pulmonary vasculature (vasculitis and pulmonary hypertension) [2]. Although there is extensive heterogeneity among prevalence studies of lung manifestations in RA depending on criteria for diagnosis, as well as the method and frequency of radiographic imaging, ILD has the greatest estimated prevalence, followed by airway disease, pleural effusion and rheumatoid nodules (Table 1).

EPIDEMIOLOGY AND RISK FACTORS

The 20 years-cumulative incidence of RA-ILD varies based on the definition used between 15,3% symptomatic patients and 60% if HRCT is used for diagnosis [2]. Although RA is more common in fe-

TABLE 1. Prevalence of rheumatoid arthritis-associated lung diseases [1]

Disease phenotype	Prevalence
Parenchymal lung disease	
Usual interstitial pneumonia	8–66%
Nonspecific interstitial pneumonia	19–57%
Organizing pneumonia	0–11%
Others (e.g. LIP or DIP)	Rare
Rheumatoid nodules	<1% radiographically, 30% autopsy
Caplan's syndrome	<1%
Airways disease	
Upper	
Cricoarytenoiditis	32–75% via laryngoscopie,54–72% CT
Lower	
Bronchiectasis	HRCT in ~30%, usually clinically silent
Bronchiolitis (constrictive or follicular)	Lung function tests or CT: 8–30%
Pleural disease	
Pleural effusions	Symptomatic 3–5%, 70% autopsy

UIP: usual interstitial pneumonia; NSIP: nonspecific interstitial pneumonia; LIP: lymphocytic interstitial pneumonia; DIP: desquamative interstitial pneumonia; CT: computed tomography; HRCT: high-resolution computerized tomography

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males, RA-ILD occurs more frequently in males, with a male-to-female ratio as high as 2:1 [3]. Although it was for a long-time considered a late complication, recent data suggest that RA-ILD can appear anytime during the disease course, 10-20% of the patients even develop RA-ILD before articular symptoms [3]. The mean survival is 5-8 years, and it is the second-leading cause of death in patients with RA, following cardiovascular disease [4]. Risk factors for RA-ILD are: age>65 years, smoking, late RA diagnosis, intense RA activity, male sex, high titers of rheumatoid factor (RF) and anticitrullinated antibodies (ACPA), subcutaneous rheumatoid nodules and genetic background [3,4].

Among the investigated environmental risk factors, substantial evidence exists supporting cigarette smoking as a major risk factor for development of RA-ILD. This relationship between RA and smoking was first described over 30 years ago and has been reported in numerous subsequent studies [5]. Smoking can induce protein citrullination, emphysema, a more rapid decline of lung function tests and reduced rate of survival [5]. Numerous other environmental factors, such as silica dust, atmospheric pollutants, oxidative stress, infection and gastroesophageal reflux disease induce inflammatory stimulation in alveolar epithelial cells leading to alveolar and peribronchial wall proliferation and an abnormal fibrotic repair process [4].

In patients with RA-ILD, several mutations have been found in telomere-related and surfactant-related genes, similar to findings in patients with familial pulmonary fibrosis[6]. Several genetic predispositions, such as the expression of human leukocyte antigen (HLA) genes, MUC5B, SFTPC, RTEL1, and TERX, are associated with RA-ILD [7]. Recent studies have also suggested that several HLA variants, including HLA-DRB1*15 and HLA-DRB1*16, are associated with an increased risk of RA-ILD [4]. MUC5B polymorphism is associated with the abnormal production of surfactant protein C and the secretion of pro-inflammatory and pro-fibrotic mediators secreted from type 2 alveolar epithelial cells [6,8]. The functional MUC5B rs35705950 promoter variant has been identified as a risk factor for RA-ILD, whereas it was not associated with RA without ILD; it is also related with the risk of progression [7-8]. A large observational study showed a more than 10-fold elevated risk of ILD, especially for UIP pattern, when having both the MUC5B promotor variant and RA when compared with the general population [8]. Based on these results, it was suggested to use the MUC5B rs35705950 promotor variant for genomic risk stratification in patients with RA MUC5B rs35705950 promoter variant.

CLINICAL ASPECTS OF RA-ILD

The diagnostic approach to patients with ILD in the setting of known or suspected RA requires a collaborative multidisciplinary approach: radiology, pathology, rheumatology and pulmonology, evaluating for other potential causes of ILD (hypersensitivity pneumonia, pneumoconiosis), other connective tissue diseases or iatrogenic causes such as drug toxicity. The main clinical symptoms of RA-ILD are exertional dyspnea, chronic dry cough, fatigue, and general weakness [2]. However, these symptoms are nonspecific, appear late, may be overlooked or masked by musculoarticular involvement, anemia, cardiac disease of physical deconditioning. Although rare, pulmonary crackles and digital clubbing should be checked through lung auscultation and physical examination.

In clinical practice, usually the evaluation of symptomatic patients continues with pulmonary function testing (PFT). PFT may reveal a restrictive pattern with normal or low total lung capacity, normal or low forced vital capacity and increased ratio between forced vital capacity and forced expiratory volume. Decreased DLCO is considered the earliest change of lung function tests [9].

In particular, advances in imaging examinations play an important role in RA-ILD diagnosis. However, plain chest radiography is disadvantageous because it has low sensitivity and is limited in the detection of early ILD[2]. In recent times, studies have attempted to diagnose ILD using ultrasound and reported that findings of multiple B lines, irregularities of the pleural line, or pleural nodules on ultrasound might suggest ILD [10]. The gold standard for screening and early diagnosis of RA-ILD is high resolution computerized tomography (HRCT) [10]. Four major HRCT patterns of disease were identified: usual interstitial pneumonia (UIP) (37%), nonspecific interstitial pneumonia (NSIP) (30%), obliterative bronchiolitis (17%), and organizing pneumonia (OP) (8%) [11]. The UIP pattern is characterized by subpleural, basal predominant, reticular abnormalities with honeycombing, and traction bronchiectasis with a relative absence of ground-glass opacities and air trapping on exhalation (Figure 1) [12]. NSIP is characterized by basilar predominant, ground-glass opacities and absence of honeycombing (Figure 2) [12]. Additional patterns less commonly seen in RA include: diffuse alveolar damage, lymphocytic interstitial pneumonia and desquamative interstitial pneumonia. Combined pulmonary fibrosis and emphysema has also been demonstrated on HRCT scans in patients with RA [12].

The role of bronchoalveolar lavage and lung biopsy, unpleasant or invasive procedures, is considered limited due to nonspecific information provided. They may be useful in case of differential diagnosis

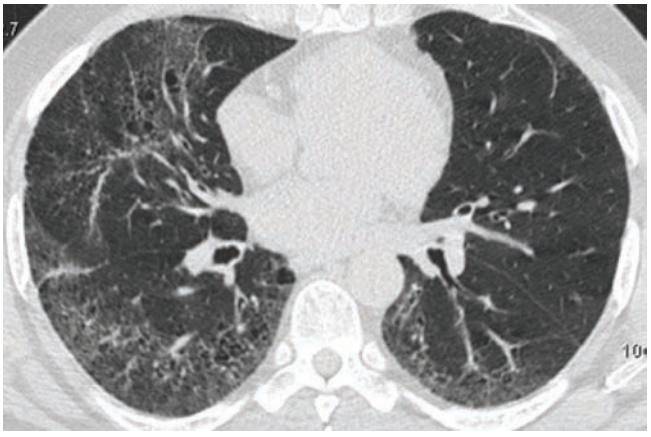

FIGURE 1. HRCT – nonspecific interstitial pneumonia

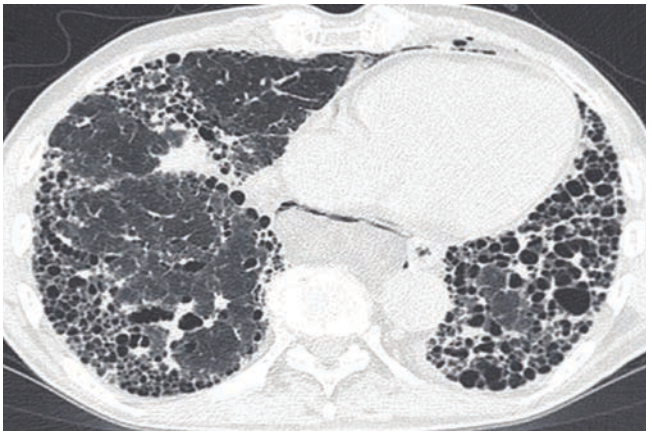

FIGURE 2. HRCT – usual interstitial pneumonia

with infections, drug induced lung disease, patients with ILD but no articular symptoms [2].

SCREENING AND EARLY DIAGNOSIS

Early diagnosis of RA-ILD can be challenging given that clinical symptoms are delayed and PFT show late changes. HRCT is considered the gold standard for early diagnosis but performing lung HRCT for a disease that has a prevalence of 1% is not feasible. Using a probability prediction score to select the patients could prove invaluable. Several models have been proposed, we mention in this review one of the easiest to apply, proposed by Koduri et al in 2023. Multivariate logistic regression models were used to form a scoring system for categorizing patients into high and low risk on a scale of 0–9 points and a cut-of score of 5 [13]. The score includes four simple clinical variables: age, anti-cyclic citrullinated peptide antibodies, rheumatoid factor and smoking (Table 2).The scoring system has a sensitivity of 86% and a specificity of 58% [13]. High-risk patients should be considered for investigation with HRCT and monitored.

TABLE 1. The Variables used for RA-ILD probability score

	0	**1**	**2**
Age at RA onset	<40	40-70	>70
Smoking	never	Ex-smoker or current	
RF titer	negative	Weak positive	Positive
ACPA titer	negative	Weak positive	positive
DAS28	>3,2		

RF rheumatoid factor, CCP cyclic citrullinated protein, DAS28 disease activity score

MANAGEMENT OF RA-ILD

Nowadays there is no consensus on therapeutic recommendations for the treatment of RA-ILD. In the absence of controlled studies, the therapeutic approach to RA-ILD is still debated and based on empirical approaches dependent on retrospective studies and case series. Therapeutic options for RA-ILD are even more complicated by the possible pulmonary toxicity of many disease modifying anti-rheumatic drugs (DMARDs) and by their unclear efficacy on pulmonary disease. Therefore, joint and lung involvement should be evaluated independently of each other for treatment purposes.

The severity and progression of disease are two major factors to consider when deciding whether to initiate or augment ongoing treatment in patients with RA-ILD. Symptoms worsening, PFTs decline or radiologic extension indicate disease progression. Other individual factors such as age, comorbidities, HRCT patterns, and patient wishes should be taken into account. In asymptomatic patients with non-progressive ILD, a "wait and see" approach is usually recommended [3].

Immunomodulating agents

Treatment with immunosuppressive agents is generally used regardless of the pattern of fibrosis, though research is much needed to address whether this is the best strategy [2]. Still, patients with RA-ILD with nonspecific interstitial pneumonia (NSIP) or organizing pneumonia (OP) patterns could have a more favorable response to immunosuppressive therapy than the UIP pattern.

Data on the efficacy of glucocorticoids are somewhat controversial: steroids appear to stabilize the lung function in some studies, while others emphasize their increased infectious [14,15]. In the British Thoracic Society for RA-ILD treatment, dating back to 2008, the first-line treatment involves the use of prednisone 0.5 mg/kg/ day for 1–3 months, subsequently tapered up to 10 mg/day or less, possibly combined with a DMARD. In case of steroid failure, the addition of an immunosuppressant, such as cyclosporine, azathioprine, and cyclophosphamide, is recommended [16]. Of note, high doses of steroids should be used for inflammatory subtypes of RA-ILD with acute or subacute presentation (i.e, cellular NSIP and OP), but not in fibrotic subtypes typical

of advanced and chronic forms (i.e, fibrosing NSIP and UIP) [3].

Cyclophosphamide (CYC) is used in clinical practice despite its limited efficacy data, especially in the case of rapidly progressive ILD. Some retrospective studies reported a better survival in the group treated with CYC [17]. Since CYC shows little benefit on RA joint involvement, it is usually associated with corticosteroids or other immunosuppressants. A major downside of treatment with CYC is its toxicity, including hemorrhagic cystitis, bone marrow suppression, opportunistic infections, hamatological and solid organ malignancies, limiting its use as a long-term treatment.

Mycophenolate mofetil (MMF) is considered the main alternative to CYC as a first-line agent or a possible maintenance therapy in CTD-ILD, with a lower rate of side effects than CYC. There have been several small case series that have demonstrated stabilisation and/or improvement in symptoms, lung function and imaging in patients with non-UIP pattern and led to stabilization among those with UIP [18]. Still, both CYC and MMF are ineffective for the articular manifestations of the disease.

Historical case reports describe patients with RA biopsy-proven ILD that improved after azathioprine (AZA) administration [26]. More recently, two retrospective studies described RA-ILD-UIP patients treated with corticosteroids and cDMARDs, including AZA, without conclusive results [27,28]. On the other hand, pulmonary toxicity has been also described for AZA [29]. Finally, AZA was compared with MMF, demonstrating a marginally better efficacy but a higher rate of side effects [30].

Other DMARDs, biologics and potential for pulmonary toxicity

While DMARDs and biologic agents are widely used for the joint manifestations of RA, the potential treatment benefits for RA-ILD are unknown Another challenge in treating RA-ILD lies in the fact that many of the therapeutic options for RA such as DMARDs and biologic agents have been linked to pulmonary toxicity (albeit rare). The temporal relationship to onset of new pulmonary manifestations and initiation of therapy is crucial in raising the index of clinical suspicion of drug-induced lung toxicity. This can be quite challenging in patients with pre-existing ILD, though development of new parenchymal abnormalities in these patients in whom the differential diagnosis includes drug-induced lung toxicity should be evaluated further with appropriate diagnostic and therapeutic interventions

Methotrexate MTX is the most common first-line agent used to treat RA. A possible link between this medication and lung disease was first described 40 years ago; since then numerous additional cases have been reported [19-21]. Acute/subacute hypersensitivity pneumonia (HP) has been-described in several observational studies, with a prevalence ranging from 1–2%, with a higher dose more likely to be associated with pulmonary toxicity, typically occurring within the first year of treatment [22-23]. More recent studies have suggested that MTX-lung toxicity is much less common than previously thought; since 2001 no cases have been reported in RCTs of MTX in RA [19]. Furthermore, a meta-analysis including 8584 participants from 22 double-blind, randomized, controlled trials in patients with RA treated with MTX found an increased risk of infectious but not non-infectious pulmonary disease, including ILD [19]. However, it may be appropriate to conduct tight monitoring of lung function in patients with an established diagnosis of ILD in treatment with MTX.

Leflunomide (LEF) has also been associated with rapid onset hypersensitivity pneumonia and new-onset and/or exacerbation of ILD with discordant published data [24] Pre-existing ILD or previous use of MTX were the most important risk factors for LEF-induced ILD [24]. Two systematic reviews found conflicting results. Conway et al. showed no association between LEF and increased risk of total or infectious respiratory adverse events in eight controlled trials [25]; on the contrary, a previous systematic review demonstrated an association between the appearance or worsening of ILD and LEF [26].

In the past decades, several case reports associated sulphasalazine with lung toxicity (interstitial pneumonitis, eosinophilic pneumonia, bronchiolitis obliterans) [24]. Most of the patients improved within a few weeks after drug withdrawal [24,31].

Only small series and few case reports showed an improved lung function in patients with RA-ILD treated with cyclosporine or tacrolimus [32]. However, the use of calcineurin inhibitor is often limited by their side effects and their efficacy in RA-ILD remains undefined and needs more dedicated studies.

Tumour necrosis factor-alpha inhibitor (TNFi) may have both profibrotic and antifibrotic effects, the imbalance between these two roles might trigger fibrosis or stabilize ILD [3]. Numerous case reports, retrospective cohort studies, analyses of large national databases have reported newly detected or exacerbated ILDs upon the treatment with TNFi [33-40]; however, so far, data are overall inconclusive. A British national prospective observational study of 367 patients with pre-existing RA-ILD found that the mortality in patients with RA-ILD was not increased by treatment with TNFi compared with cDMARDs [35]. In a prospective study, Detorakis evaluated, in RA patients with or without ILD, the effects of TNFi on lung parameters, observing that the ILD extent score remained unchanged both in the TNFi and cDMARDs

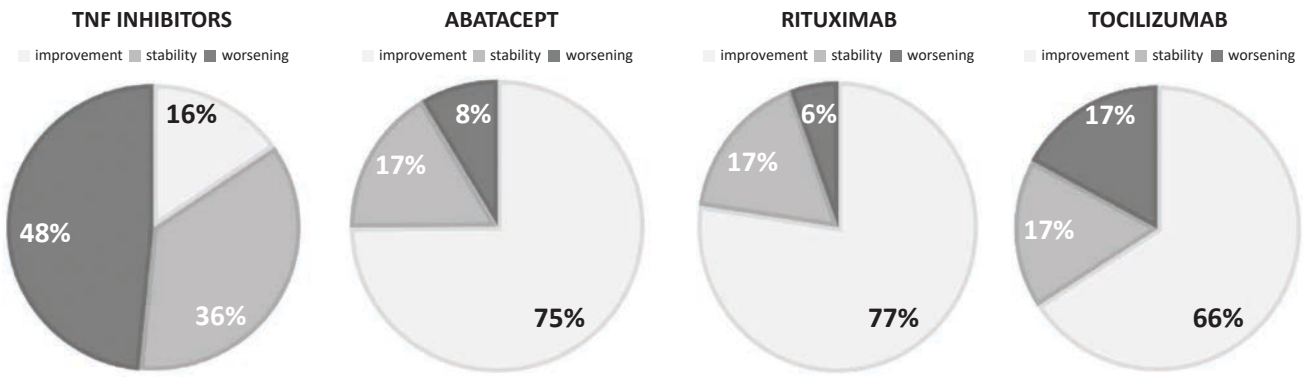

FIGURE 3. Pulmonary effects of different biologics in RA-ILD patients: a review of the literature

groups. There was no exacerbation of ILD, nor new ILD onset in patients without pre-existing ILD [36]. A comprehensive search on the PubMed, Embase, Ovid, Cochrane, China National Knowledge Infrastructure and Wanfang database including 7 original articles and 28 case reports demonstrated the lack of benefit from TNFi treatment in patients with ILD and association with pulmonary adverse events [40].

Case reports and small uncontrolled retrospective studies have broadly shown that the majority of RA-ILD patients treated with abatacept remained stable or improved [41-44]. In an observational multicenter study, 263 patients with RA-ILD were treated with abatacept (ABA) alone or combined with MTX or another csDMARD [42]. All 3 treatment groups experienced the stabilization or improvement of respiratory symptoms, PFTs and HRCT findings. In an Italian multicenter retrospective study; abatacept appeared to be safe, and FVC, DLCO, and HRCT remained stable in 77.8%, 58.3%, and 70.4% of patients, respectively [43]. A recent systematic review including one case series and eight observational studies confirmed the efficacy and safety of abatacept in RA-ILD [44]. The improvement or stabilization of FVC or DLCO was observed in over 85% of the cases, while the improvement or stabilization of ILD imaging was observed in 76.6% and 92.7% of the cases, respectively, regardless of the radiological pattern [44]. Abatacept led to a significantly lower probability of ILD worsening compared to TNFi and csDMARDs, being associated with a 90% reduction in the relative risk of lung function deterioration at 24 months [44]. A preliminary small clinical trial is ongoing to assess the feasibility of a larger controlled study to evaluate the safety of ABA in RA-ILD (APRIL study, NCT03084419).

Rituximab (RTX) is one of the most important biologics for patients with RA-ILD. Numerous case reports, small case series, retrospective observational studies, even open label pilot studies suggested that rituximab (RTX) is a safe therapy for ILD including severe refractory forms [45-55]. Especially patients with OP or NSIP demonstrated improvement or stability of PFTs and HRCT. Regarding patients with UIP pattern, 2/3 of patients had a decline in FVC and half had HRCT worsening [47]. A 10-year study by Yusof et al. assessed the effects of RTX in 700 RA patients, of whom 56 (8%) had a previous diagnosis of ILD; pulmonary involvement improved or remained stable in 68% of cases, while 32% showed a progression of ILD and half of them died because of progressive ILD [48]. Factors associated with ILD progression were radiologic UIP pattern, a previous history of lung progression, and DLCO<46% predicted before the therapy. The incidence of new ILD was 0.4% [48]. In a study of 43 patients with RA-ILD included in the British Society for Rheumatology Biologics Register for RA, the mortality rate was lower in the rituximab group compared to TNFi group [50]. Additionally, several RCTs as EvER-ILD (rituximab with MMF vs placebo) and RITUX-IP (rituximab) are currently underway. However, a meta-analysis of biological therapies in CTD noted that RTX was associated with an increase of non-infectious parenchymal lung disease [54]. In a couple of prospective studies the use of RTX resulted in a DLCO decline, suggesting deaths associated with pneumonia and possible acute progression of ILD and new ILD after RTX [54-55].

The proinflammatory cytokine IL-6 shows profibrotic effects antagonizable by IL-6R blockade, suggesting a potential benefit of this therapeutic strategy in RA-ILD. Tocilizumab (TCZ) was found to stabilize or even improve ILD in case-series, case reports and retrospective national multicenter studies [56-59]. On the other hand, adverse lung effects have been also reported after the use of TCZ: the worsening of pre-existing ILD after TCZ infusions and subsequent improvement of symptoms and HRCT findings after its withdrawal [60]. The risk factors for ILD deterioration were advanced age (≥65 years) and previous or concurrent ILD at baseline. On the opposite, Data from real-life post-marketing surveillance show a good safety profile for TCZ in a Japanese population of RA-ILD patients, the incidence rate of new ILD (0.5%) was similar to that recorded for TNFi [61].

Data regarding the possible roles of Jak Inhibitors in the treatment of RA-ILD are limited. In RA clinical development programs of tofacitinib and baricitinib, 0.1% of patients newly developed ILD; however, to-

facitinib was not associated with ILD exacerbation [62].

Antifibrotic therapy

Currently, two anti-fibrotic agents were approved for the management of idiopathic pulmonary fibrosis (IPF), namely nintedanib and pirfenidone. To date, only nintedanib has been studied in a double-blinded RCT in patients with progressive fibrosing ILD, including the cases of RA-ILD. Nintedanib was found to reduce the FVC decline originally in IPF and subsequently in systemic sclerosis-associated ILD [63]. Following these results, the INBUILD trial, an international, double-blind RCT comparing nintedanib to placebo was conducted in patients with progressive fibrosing lung disease (with a baseline extension >10% on HRCT) of different types (of whom 13% were RA-ILD) [64]. Patients treated with nintedanib had a significantly slower FVC decline over 52 weeks with a between-group FVC difference of 104.0 ml/ in favor of nintedanib (95% CI, 21.1–186.9; p < 0.41). The results were significant irrespective of a HRCT pattern [64]. Diarrhea was the major side effect of nintedanib, occurring in 2/3 of the treated patients, which led to a dose reduction in 1/3 of patients and drug discontinuation in 20% of cases [64].

TRAIL1 was a randomized, double-blind, placebo-controlled, phase 2, multicentric study aimed to assess the safety, tolerability, and efficacy of pirfenidone for the treatment of RA-ILD [65]. The trial was stopped early due to slow recruitment and the COVID-19 pandemic. Despite not meeting the composite primary endpoint (decline in FVC% from baseline of 10% or more or death), pirfenidone slowed the rate of decline of FVC over time in patients with RA-ILD (change in absolute FVC -p=0·008 and FVC%- p=0·002). Safety in patients with RA-ILD was similar to that seen in other pirfenidone trials.

When the diagnosis of RA-ILD is made, it is important not to overlook conservative and supportive care in these patients. Conservative intervention involves the prevention of lung infections through antibiotic prophylaxis and vaccinations; the management of comorbidities such as chronic obstructive pulmonary disease or gastroesophageal reflux; the cessation of cigarette smoking; the use of supplemental oxygen in case of desaturation; and pulmonary rehabilitation. Last but not the least, the inclusion of severe and refractory patients on the transplant lists should be considered

SUGGESTED ALGORITHM FOR THE ASSESSMENT, MONITORING, AND MANAGEMENT OF RA-ILD

A multidisciplinary discussion should include pulmonologists, radiologists, pathologists and rheumatologists (Figure 4). The monitoring of treatment response in RA-ILD involves the assessment of the activity and severity of both articular and respiratory disease. Baseline evaluation of pulmonary involvement should include clinical examination (including arterial oxygen saturation and a 6-minutes walking test), PFTs, the identification of radiological patterns, and the assessment of disease extension by HRCT. PFTs should be performed in all patients with RA with respiratory symptoms. Baseline FVC <60% of the predicted values and DLCO <40% of the predicted values are poor prognostic factors [3]. A 6–12 month decline in FVC of at least 10% and/or a decline in DLCO of at least 15% is associated with disease progression [3]. HRCT imaging should be indicated for patients with respiratory symptoms, for asymptomatic patients with a DLCO <70% of the predicted values, for patients with a high probability stratification score and for patients with lung ultrasound abnormalities. Individuals with HRCT findings consistent with an UIP pattern and high fibrotic scores have a worse prognosis compared to those with HRCT features indicative of other types.

In the presence of subclinical ILD, a continuation of the DMARD used for controlling arthritis according to the current recommendations for RA management is advised. In the presence of a clinically overt and/or progressive ILD, the discontinuation of DMARDs other than MTX with potential pulmonary toxicity (e.g, leflunomide and sulphasalazine) should be considered, while alternative DMARDs (e.g, CYC, MMF, or AZA), in combination with glucocorticoids, may be preferred. TNFi should be used with caution or reconsidered in patients with RA-ILD. In the presence of clinical, functional, and/or radiological worsening despite treatment, further therapeutic changes are suggested, particularly, the introduction of biologics that have shown to improve or stabilize pulmonary disease (e.g, ABA, RTX or TCZ) or the introduction of anti-fibrotic agents (e.g, nintedanib) in the presence of high fibrotic scores on the HRCT scan [3].

Treatment will be tailored also taking into account the predominance of joint or respiratory symptoms (Figure 5).

CONCLUSION

ILD is one of the most common extra-articular manifestations of RA, unfortunately, often underrated, particularly in its early and subclinical stages. . A comprehensive and multidisciplinary approach is required for early identification of RA-ILD, and timely intervention on progressive and fibrosing forms. Immunotherapies with csDMARDS and/or bDMARDs should be readjusted based on the severity of lung and joint disease and possible comorbidities Ongoing investigations and future RCTs will better clarify the

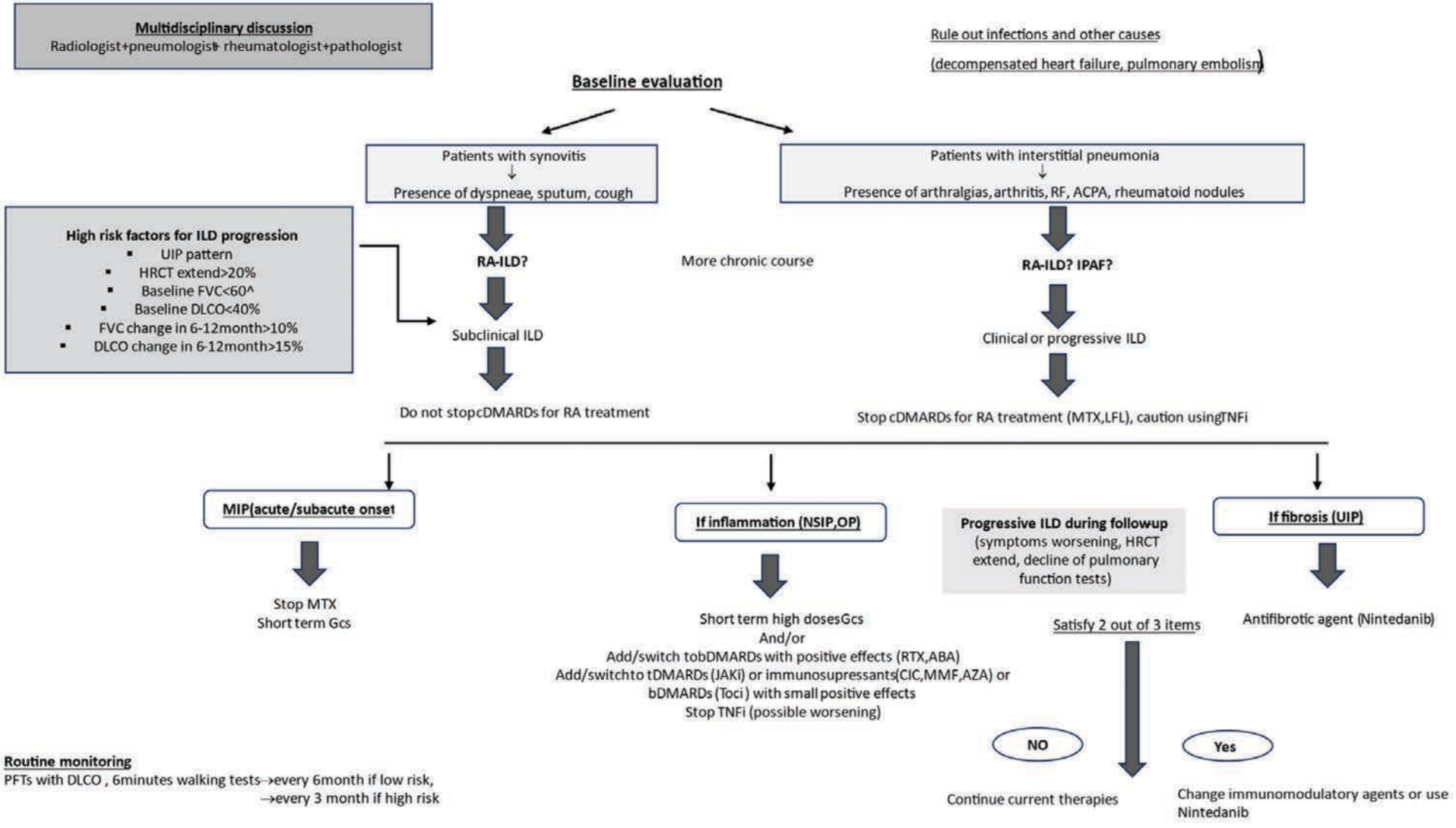

FIGURE 4. The proposed algorithm for assessment, monitoring and management of RA-ILD

ABA, abatacept; bDMARD, biological disease-modifying antirheumatic drug; csDMARD, conventional synthetic disease-modifying antirheumatic drug; ILD, interstitial lung disease; MTX, methotrexate; MTX-pneu, MTX-pneumonitis; RA, rheumatoid arthritis; RTX, rituximab; TCZ, tocilizumab. MIP Methotrexate-induced pneumonia; GCs glucocorticoids.

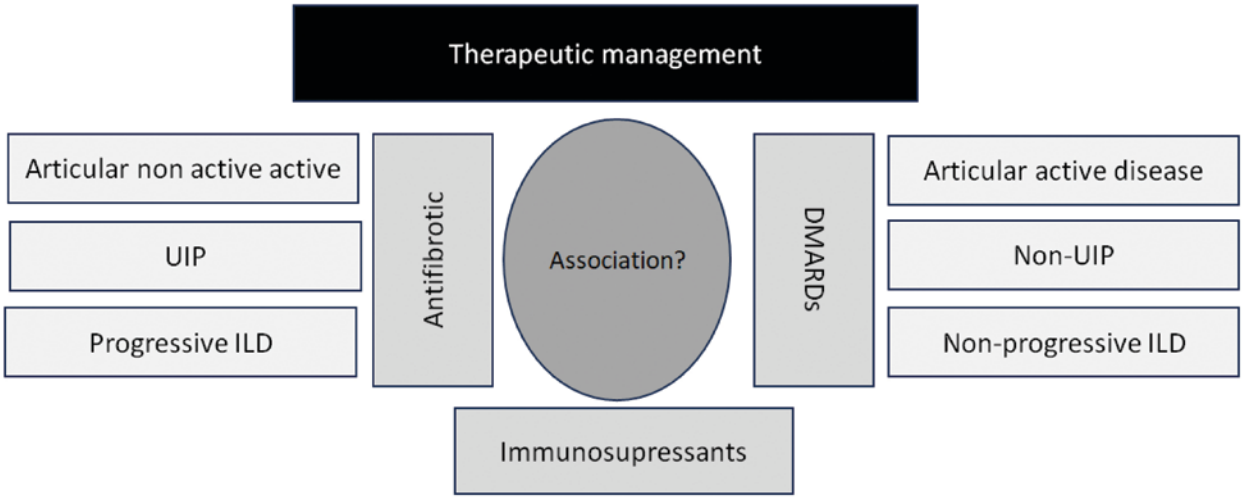

FIGURE 5. Therapeutic management based on the predominance of articular symptoms and HRCT pattern

UIP-usual interstitial pneumonia, ILD-interstitial lung disease, DMARDs-disease modifying active rheumatic drugs

strategies to be put in place for the optimal management of RA-ILD.

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