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Does a window of opportunity for rheumatoid arthritis-associated interstitial lung disease exist?

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ABSTRACT

Rheumatoid arthritis (RA) is an autoimmune disease characterized by chronic inflammatory synovitis, eventually leading to joint destruction. Remarkable advancements in the emergence of molecular targeted therapies and the treatment strategy based on treat-to-target have made it possible for patients to lead their daily lives without disabilities. Specifically, early diagnosis and appropriate treatment without missing a 'window of opportunity' are crucial for improving joint outcomes. On the other hand, interstitial lung disease (ILD) is an extra-articular complication of RA and has an impact on life prognosis. Importantly, it has become evident that achieving remission of arthritis is critical not only for joint outcomes but also to prevent the irreversible progression of pulmonary fibrosis in RA-ILD. Therefore, a 'window of opportunity' may exist not only for joints but also for RA-ILD. However, within RA-ILD, there are cases that progress from an NSIP pattern or airway involvement to a UIP pattern, while there are cases without progression, suggesting that their disease behavior may be diverse. Thus, accumulating evidence is necessary to accurately determine the disease behavior of RA-ILD. This review provides an overview of clinical and radiological features and treatment strategies for RA-ILD, incorporating the latest findings.

1. Introduction

Rheumatoid arthritis (RA) is a representative autoimmune disease characterized by progressive joint destruction, with a prevalence of approximately 1.0% in developed countries [1,2]. It has been significant advancements in drugs and therapeutic strategies for RA in recent years. Alongside conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) like methotrexate, molecular targeted therapies such as biologics and a Janus kinase (JAK) inhibitors have become available [3]. It has become evident that joint deformation due to joint destruction progresses most rapidly within the first two years of onset. During this 'window of opportunity,' appropriate therapeutic interventions can improve joint prognosis [4]. Consequently, the concept of early diagnosis, early treatment, and tight control in line with clear treatment goals has been established as a treatment strategy for RA [3].

On the other hand, when interstitial lung disease (ILD) complicates RA as an extra-articular manifestation, it has a significant impact on life prognosis. In fact, the survival rate for RA-ILD has been reported to be as low as that of idiopathic pulmonary fibrosis [5,6], underscoring the importance of establishing specialized treatment strategies for RA-ILD to improve life prognosis. In this review, we propose the concept that a 'window of opportunity' for RA-ILD may also exist, emphasizing the importance of early diagnosis and stabilization of arthritis activity to prevent irreversible pulmonary fibrosis. Furthermore, the course of RA-ILD may be diverse, and identifying factors to predict the disease behavior of RA-ILD and clarify which cases have a 'window of opportunity' is an important future challenge. We provide an overview of clinical and radiological characteristics, monitoring, and treatment for RA-ILD, taking into account the latest findings.

2. Relationship between imaging findings and clinical features in RA-ILD

The frequency of ILD in RA patients is generally reported to be around 10% to 20% [7,8]. ILD can show various clinical onset, including ILD-preceding pattern prior to RA onset, concurrent ILD pattern with the RA onset, or newly emergent ILD pattern during RA course [9,10]. Risk factors for ILD development include older age, male gender, smoking

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history, poorly controlled arthritis activity, and high levels of rheumatoid factor (RF) and anti-citrullinated protein (CCP) antibodies [10–12].

High-resolution computed tomography (HRCT) is essential not only for assessing the imaging patterns and extent of ILD lesions but also for excluding infections and lung cancer. RA-ILD presents various subtypes in the patterns of imaging findings on HRCT. Usual interstitial pneumonia (UIP) pattern accounts for over half of RA-ILD patients and is the most frequently observed imaging pattern, followed by non-specific interstitial pneumonia (NSIP) pattern [13]. Of note, unclassifiable pattern other than UIP, NSIP, and organizing pneumonia (OP) is also characteristic in RA-ILD, observed in approximately 6% of cases [14].

There has been little discussion to date on whether this pattern classification truly reflects the pathophysiology and disease stages of RA-ILD. We observed that these imaging patterns may potentially reflect the disease stages of RA-ILD [10]. Specifically, some cases with RA-ILD initially exhibit an NSIP pattern, transformed into a UIP-like pattern as the disease stage progressed, and ultimately evolved into a UIP pattern (Fig. 1). In addition, the frequent occurrence of airway involvement is a characteristic feature of RA-ILD on imaging, with particular emphasis on small airway lesions. Importantly, as small airway lesions progressed, structural damage to the lung tissue also advanced, ultimately transitioning into a UIP pattern (Fig. 2). Therefore, a UIP pattern may represent the most advanced stage of RA-ILD on imaging, comprising two components in its development: i) interstitial inflammation observed in an NSIP pattern and ii) small airway inflammation observed in bronchiolitis (Fig. 3). This progression of imaging-based disease stages in RA-ILD can be closely related to the stages of joint destruction (Fig. 1), indicating that inadequate control of arthritis may lead to both irreversible joint damage and pulmonary fibrosis. In fact, recent research has shown that achieving remission of arthritis can reduce the risk of the development and progression of RA-ILD itself [12,15]. Therefore, early stages of RA-ILD on HRCT patterns such as an NSIP pattern and small airway lesions may be a `window of opportunity' for intervention to prevent the irreversible progressive pulmonary fibrosis (Fig. 3). However, we should also note that while there are some cases with progression from a NSIP pattern or small airway involvement to a UIP pattern, some cases without progression also exist. In addition, there are some UIP cases without NSIP. Therefore, one of the crucial issues in the diagnosis and treatment of RA-ILD is elucidating the 'disease behavior' of RA-ILD that requires the accumulation of sufficient evidence for future resolution.

The progression of RA-ILD based on the HRCT findings described above likely involves pathophysiologically driven overformation of bronchus-associated lymphoid tissue (BALT). BALT is inconspicuous in normal lungs, whereas BALT is particularly prominent in peripheral bronchial regions of RA-ILD [10,16–19]. BALT in RA-ILD consists of T cells, B cells, and follicular dendritic cells, and generates various cytokines, chemokines, and even RF and anti-CCP antibodies, contributing to local tissue damage in peripheral bronchial regions [10,18,19]. Furthermore, although the mechanism remains unclear, RA-ILD exhibits localized upregulation of the JAK-STAT pathway in the affected areas compared to idiopathic pulmonary fibrosis [20]. It has been previously reported that T peripheral helper (Tph) cells induced by type I interferons are increased in RA-ILD lesions, suggesting a potential contribution of type I interferons to the upregulation of the JAK-STAT pathway [21–23]. It is believed that in the early stages, these inflammation and cellular infiltration within the bronchioles and alveoli wall progressively disrupt the alveolar structure, ultimately leading to the formation of cysts in the end-stage (Fig. 3).

When presenting with UIP or NSIP patterns on HRCT, patients are often asymptomatic but develop symptoms such as dry cough and exertional dyspnea as the disease progresses. Conversely, cases exhibiting an OP pattern often show a good response to moderate-dose glucocorticoid treatment, with complete resolution of imaging shadows, and tend to have a higher risk of relapse [24] (Fig. 4). Therefore, it is important to differentiate the pathophysiological and clinical characteristics between cases of RA-ILD presenting with UIP or NSIP patterns and those presenting with an OP pattern. Interestingly, serum concentrations of interferon-α, interleukin (IL)-1β, IL-6, IL-8, and interferon-γ-inducible protein 10 showed a significant correlation with the onset of OP pattern [25].

3. Prognosis of RA-ILD

Early detection and assessment of RA-ILD are crucial for initiating appropriate treatment and improving prognosis. Recent studies have shown that delays in the diagnosis of RA-ILD are associated with increased mortality rates [26]. Patients with RA-ILD have been reported to have a mortality risk approximately 2 to 3 times higher than RA patients without ILD [27]. When considering HRCT patterns, a UIP pattern is associated with poor prognosis [6]. In a multicenter, prospective RA cohort study, the risk of mortality was significantly associated with either uncontrolled disease activity (moderate/high DAS28-ESR) or forced vital capacity (FVC) impairment (<80% predicted) [28].

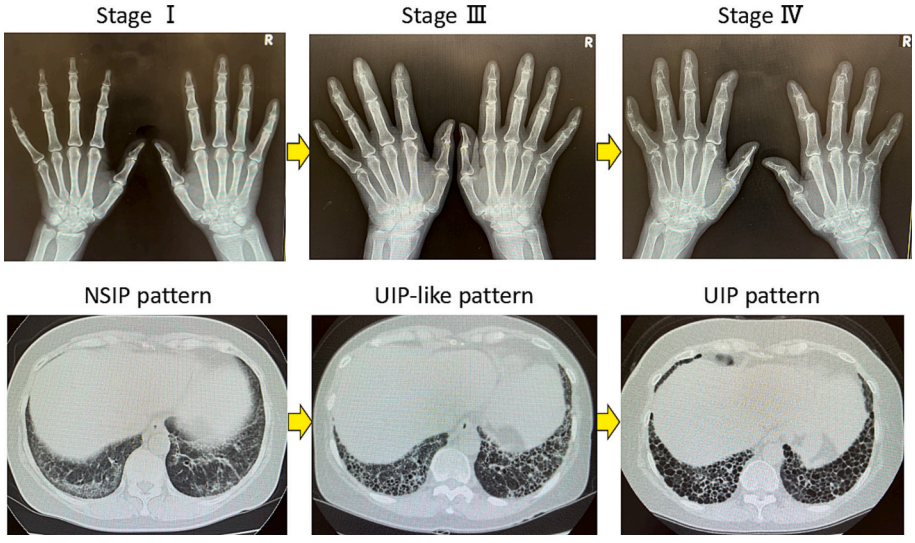

Fig. 1. Poor control of arthritis in RA can lead to progressive fibrosis of RA-ILD.
A case of RA in which joint destruction progressed due to poorly controlled arthritis, resulting in progressive lung destruction from the NSIP pattern through the UIP-like pattern to ultimately develop into the UIP pattern.

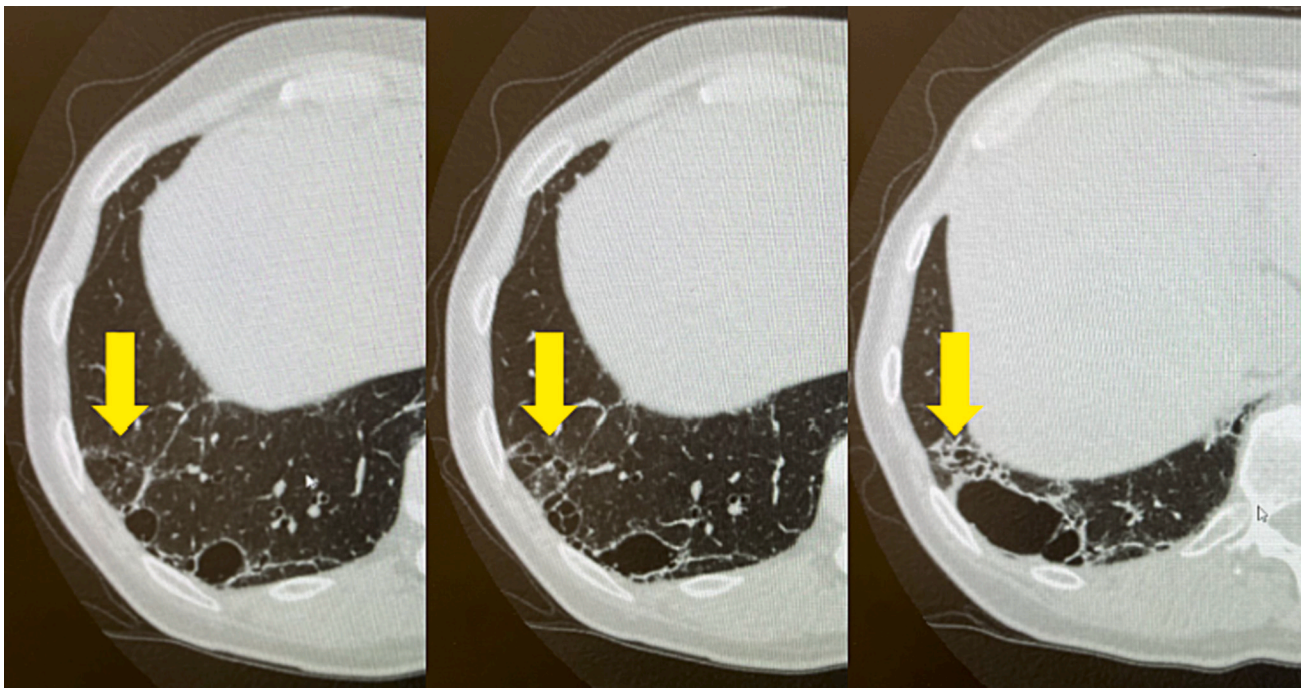

Fig. 2. The destruction of lung structure due to RA bronchiolitis contributes to the formation of RA-ILD.
A case of RA in which bronchiolitis contributes to peripheral ground glass opacities, peribronchial infiltrates, and destruction of lung parenchyma, leading to cysts of RA-ILD.

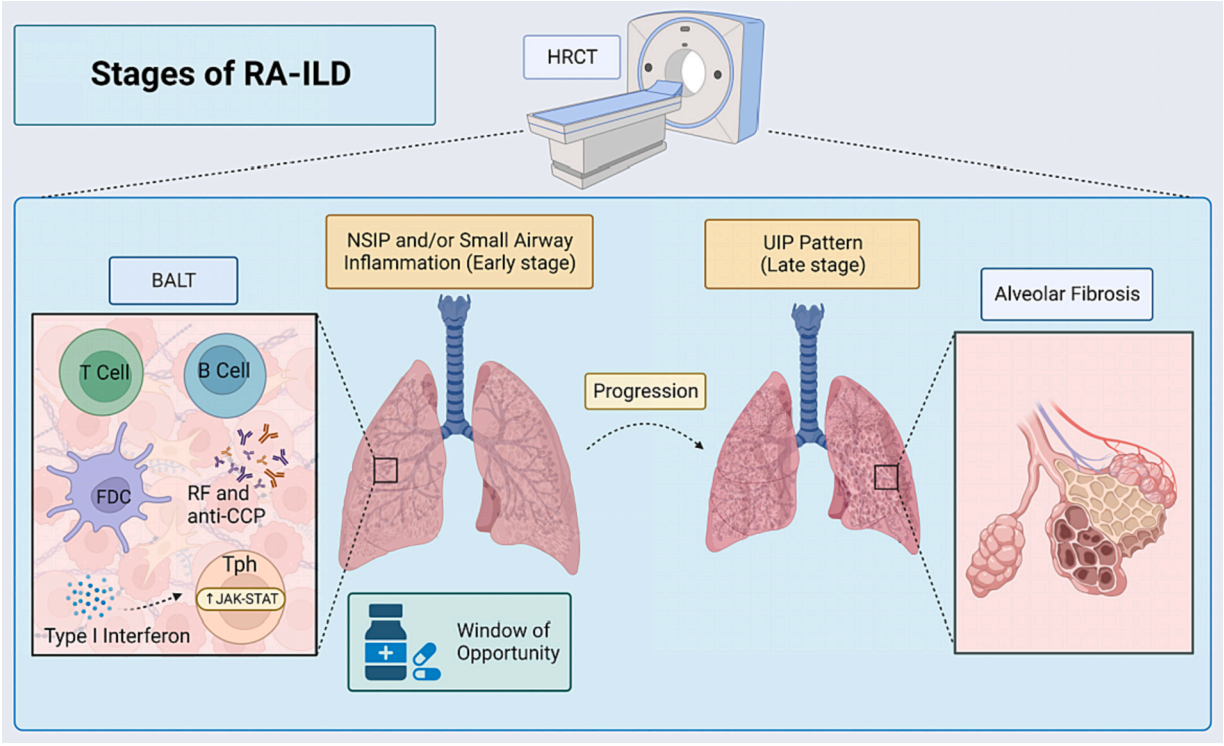

Fig. 3. Window of opportunity in RA-ILD.
In RA-ILD, early stages reveal NSIP pattern and bronchiolitis, with histologically noted lymphoid follicle formation, suggesting immunological involvement. This period is considered the 'window of opportunity,' during which achieving remission of arthritis through anti-inflammatory therapy can prevent progression to irreversible lung structural damage, such as the UIP pattern.

Furthermore, individuals with both moderate/high disease activity and FVC <80% predicted had the highest mortality risk [28]. Additionally, an important prognostic factor in RA-ILD is the occurrence of acute exacerbations of ILD [29] (Fig. 5). Acute exacerbations of ILD pose a highly urgent condition that threatens life prognosis. We have reported that poorly controlled arthritis is a risk factor for causing acute

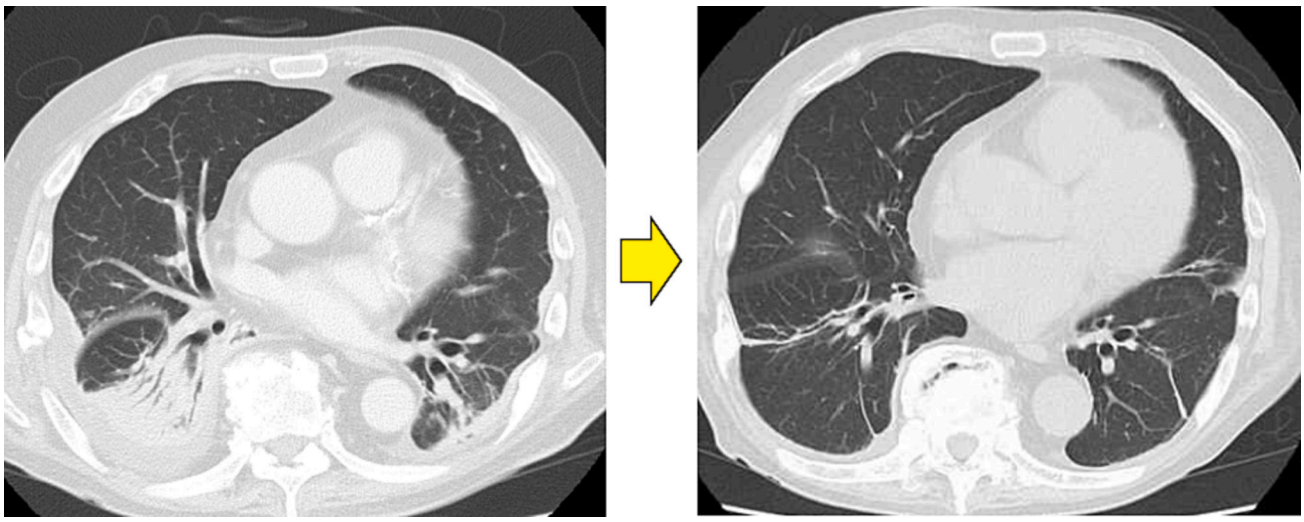

Fig. 4. HRCT findings of RA-OP.
RA-OP has clinical characteristics distinct from RA-NSIP or RA-UIP. On HRCT images, RA-OP exhibits infiltrative shadows. As in the presented case, a favorable treatment response is achieved with moderate-dose prednisolone, resulting in the disappearance of infiltrative shadows. In this case, the addition of sarilumab during prednisolone tapering has also maintained good control of arthritis, and RA-OP has not relapsed.

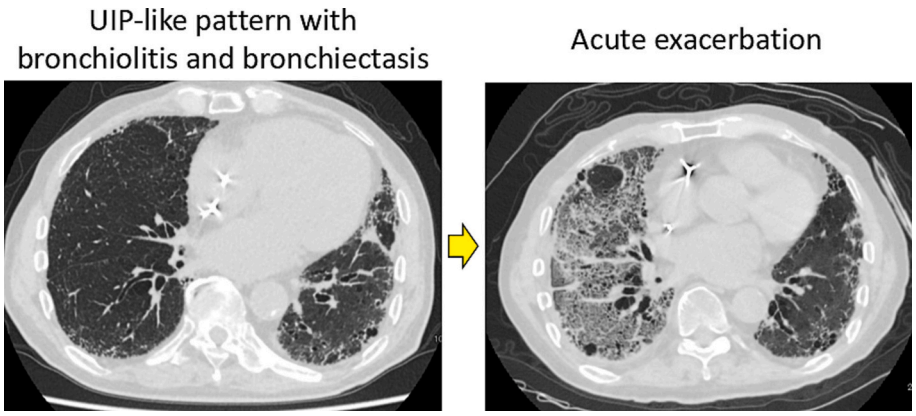

Fig. 5. HRCT findings of acute exacerbation of RA-ILD.
A case of acute exacerbation of RA-ILD is presented. Poor control of arthritis preceded acute exacerbation of RA-ILD. On HRCT images, newly appeared ground glass opacities were acutely observed in RA-ILD with UIP-like pattern, bronchiolitis, and bronchiectasis.

exacerbation of RA-ILD [30]. After acute exacerbation, the mortality risk is higher in severe cases with a baseline FVC of <60% or a P/F ratio of 200 or less at the onset of acute exacerbation [31].

4. Monitoring and treatment of RA-ILD

There was strong consensus for clinical symptoms, HRCT and pulmonary function test (PFT) to monitor disease progression [32], but no established consensus on the frequency of HRCT and PFT follow-up for monitoring RA-ILD exists. Typically, PFT is conducted every 3 to 6 months, and HRCT is performed annually, based on the clinical judgment of the attending physicians [27]. It is important to note that in patients with muscle weakness, accurate measurements may be challenging in PFT, and in patients with concomitant emphysema, lung volume measurements may increase relative to the severity of RA-ILD. KL-6 is considered a useful serum biomarker reflecting the radiographic extent and progression of RA-ILD. It also increases during the acute exacerbation of RA-ILD. Therefore, KL-6 holds potential utility as a serum biomarker for detection of disease severity and progression of RA-ILD [33–35].

There are no specialized treatment guidelines for RA-ILD. The four major causes of death in RA-ILD are reported to be acute exacerbation of ILD, respiratory failure due to progressive pulmonary fibrosis, malignancies including lung cancer, and infectious pneumonia [10,13]. Prevention and treatment of these conditions are particularly important for improving the prognosis of patients with RA-ILD.

A monitoring and treatment strategy for RA-ILD is shown in Fig. 6. Firstly, achieving remission of arthritis or at least low disease activity is crucial not only for the joint prognosis but also for preventing the new development, progressive pulmonary fibrosis (PPF), and acute exacerbation of RA-ILD. However, it is often challenging to target remission of arthritis in RA-ILD. For example, RA-ILD patients are typically older, and many have impaired renal function, which may limit the use of methotrexate. As a result, treatment options may be limited, and it may be necessary to use TNF inhibitors (golimumab, certolizumab, or ozoralizumab) or non-TNF inhibitors (abatacept, tocilizumab, sarilumab, rituximab) or JAK inhibitors with proven efficacy even without concurrent use of methotrexate. Non-TNF inhibitors have been suggested to potentially reduce the risk of ILD progression, exacerbation, and mortality compared to TNF inhibitors in RA-ILD patients [10,16,36,37]. Furthermore, recent reports suggest a reduced risk of RA-ILD development when using JAK inhibitors compared to TNF inhibitors [36].

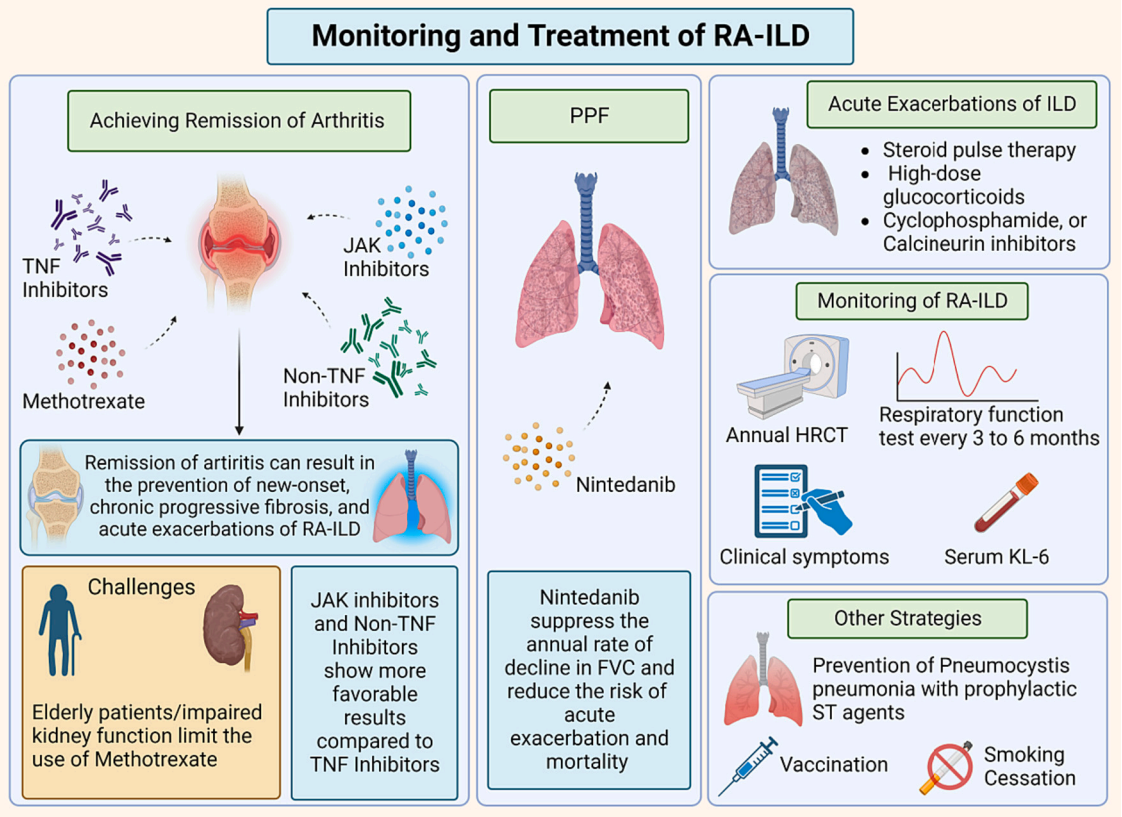

Fig. 6. Monitoring and treatment of RA-ILD.
A conceptual diagram of monitoring and treatment strategies for RA-ILD is presented. Treatment for RA-ILD includes systemic anti-inflammatory therapy used for controlling arthritis, as well as anti-fibrotic therapy for PF-ILD pathology. Additionally, regular imaging assessments to evaluate the presence of lung cancer complications and vaccination for infection prevention, along with prophylactic administration of ST agents, are also crucial.

Additionally, there is an increasing number of studies indicating stabilization or improvement in RA-ILD with the use of JAK inhibitors [38–41]. However, placebo-controlled trials have not been yet conducted.

In cases of acute exacerbations of RA-ILD, a potent induction therapy combining steroid pulse therapy, high-dose glucocorticoids, intravenous cyclophosphamide, or calcineurin inhibitors is required for life-saving purposes [10]. The effectiveness and safety of combination therapy using high-dose glucocorticoids and JAK inhibitors as a treatment for inducing remission in acute exacerbations of RA-ILD represent a future challenge. In any case, upon successful induction of remission, glucocorticoids are gradually tapered, and non-TNF inhibitors or JAK inhibitors are used to maintain arthritis remission.

The efficacy of nintedanib, an anti-fibrotic agent, in PPF was demonstrated in a phase 3 trial (INBUILD trial) that included 89 RA-ILD patients [42,43]. Nintedanib is a low-molecular-weight tyrosine kinase inhibitor that occupies the adenosine 5′-triphosphate binding pocket in various receptors, including platelet-derived growth factor receptor α and β, fibroblast growth factor receptor 1, 2, 3, and vascular endothelial growth factor receptor. Nintedanib was shown to suppress the annual rate of decline in FVC and reduce the risk of acute exacerbation and mortality events. The results for FVC decline were consistent in a subgroup analysis of RA-ILD patients, irrespective of baseline use of DMARDs and/or glucocorticoids. A sub-analysis in RA-ILD patients showed that it gradually demonstrated a suppression effect on the annual rate of decline in FVC compared to the placebo group, starting from six months after initiation of treatment, highlighting the importance of patient compliance for drug effectiveness. There is no established consensus on when to introduce nintedanib in RA-ILD patients. Considering that pulmonary fibrosis is irreversible, introducing nintedanib as early as possible in RA-ILD may be crucial for improving respiratory function prognosis as a ‘window of opportunity’.

Other strategies include smoking cessation, regular screening using HRCT to monitor for the presence of lung cancer, and considering vaccination against *streptococcus pneumoniae*, influenza virus, and COVID-19 to reduce the risk of severe infectious pneumonia. RA-ILD patients are typically older and use biologics or JAK inhibitors, making appropriate prevention of pneumocystis pneumonia, such as with trimethoprim-sulfamethoxazole, essential.

5. Conclusion

RA-ILD is a significant extra-articular complication associated with the prognosis of RA patients. However, in cases of advanced age, renal impairment, or severe pulmonary dysfunction, the use of methotrexate can become challenging, leading to significant limitations in treatment. Nevertheless, previous reports have suggested that achieving remission of arthritis is also crucial to prevent the onset, chronic progression, and acute exacerbation of RA-ILD, making proper control of arthritis highly desirable. In addition, nintedanib, an anti-fibrotic agent, should be considered, as it can independently suppress the annual decline in FVC in RA-ILD patients, separate from anti-inflammatory therapy. A concept that a ‘window of opportunity’ of RA-ILD may exist suggests that early diagnosis and treatment initiation could potentially lead to improved prognosis for pulmonary involvement in some cases. In the future, a more detailed understanding of the pathophysiology and disease behavior of RA-ILD is expected to lead to the establishment of better treatment strategies and improvements in patient life prognosis.

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Declaration of Competing Interest

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Data availability

No data was used for the research described in the article.

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