Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/jptcp.v31i5.6416

TACKLING RHEUMATOID ARTHRITIS-RELATED INTERSTITIAL LUNG DISEASE (RA-ILD) WITH CUTTING-EDGE MEDICATION STRATEGIES- A REVIEW ARTICLE

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Abstract

Rheumatoid arthritis (RA) is a chronic autoimmune disorder that primarily targets the joints but also presents significant extra-articular complications, notably interstitial lung disease (ILD). RA-associated ILD (RA-ILD) is a severe complication contributing to increased morbidity and mortality among RA patients. This review systematically examines RA-ILD, including its pathogenesis, clinical manifestations, diagnostic techniques, and current treatment strategies. RA impacts 0.5–1% of the global population, causing chronic joint inflammation and pain, but it also has substantial effects beyond the joints. Among these, ILD is the most common and critical pulmonary manifestation, leading to progressive fibrosis in the lung tissue, which significantly increases morbidity and mortality rates.

RA-ILD predominantly presents in two forms: usual interstitial pneumonia and nonspecific interstitial pneumonia. Recent research has shed light on the epidemiology of RA-ILD and identified several risk factors, including smoking, male gender, specific human leukocyte antigen haplotypes, rheumatoid factor, and anti-cyclic citrullinated protein antibodies (ACPAs). The diagnostic approach combines clinical evaluation, chest examinations, pulmonary function tests, and high-resolution computed tomography (HRCT) of the chest to determine the subtype and extent of the disease.

Managing RA-ILD is challenging due to the lack of large randomized controlled trials providing clear guidance. The therapeutic complexity is compounded by the fact that many effective drugs for joint symptoms, such as methotrexate, leflunomide, and anti-tumour necrosis factor alpha agents, can potentially induce or worsen ILD. Promising treatment options include immunomodulators like mycophenolate and rituximab, as well as newly investigated antifibrotic agents. This review explores the current literature to offer management recommendations for RA-ILD and highlights critical gaps in our understanding of this complex condition.

Keywords: lungs, joints, fibrosis, pulmonary, rheumatoid, arthritis, therapy

Introduction

Interstitial lung disease (ILD) is a progressive fibrotic condition affecting the lung tissue and is a common and significant pulmonary complication associated with rheumatoid arthritis (RA) (Brown,

2007; O'Dwyer et al., 2013). RA-associated ILD (RA-ILD) may result from chronic immune activation and inflammation characteristic of RA, leading to abnormal fibroproliferation, or it may be triggered by medications or infections (O'Dwyer et al., 2013). RA-ILD greatly impacts patients' quality of life, causing progressive chronic disability, high healthcare utilization, and reduced life expectancy, with an average survival of less than three years. The prevalence of ILD in RA patients ranges from 5% to 30%, depending on diagnostic criteria and study population (Hyldgaard et al., 2017).

Managing ILD in RA patients is complex, and while several treatments have been proposed, no large randomized controlled trials have been conducted to provide clear clinical guidance. Traditional disease-modifying antirheumatic drugs (DMARDs) like methotrexate and leflunomide, and biological agents such as tumour necrosis factor (TNF) inhibitors, have shown mixed results regarding their safety and efficacy in RA-ILD patients (Roubille et al., 2015; Poudel et al., 2019). Some studies suggest that methotrexate does not significantly increase ILD risk, while others indicate potential harm (Iqbal et al., 2017). Similarly, TNF inhibitors may exacerbate pre-existing ILD or lead to new-onset ILD in some patients (Macedo et al., 2017).

Recent research has focused on alternative therapies, including immunosuppressive agents like mycophenolate mofetil and rituximab, which have shown promise in small studies and case reports (Fernández-Díaz et al., 2018). Additionally, antifibrotic agents such as nintedanib and pirfenidone, which are approved for idiopathic pulmonary fibrosis (IPF), are being explored for RA-ILD treatment due to similarities between the conditions (Flaherty et al., 2019).

This review examines the current literature to evaluate management recommendations for RA-ILD and identifies significant gaps in our understanding of this critical condition. Future research should prioritize large-scale, randomized controlled trials to establish evidence-based treatment guidelines and better understand the pathophysiology and progression of RA-ILD. Additionally, multidisciplinary care involving rheumatologists and pulmonologists is crucial for optimizing patient outcomes (Shaw et al., 2016).

Materials and Methods

A comprehensive search across multiple scholarly databases including PubMed, Embase, and the Cochrane central register of controlled trials was conducted to identify relevant articles. The search strategy involved using specific keywords such as 'rheumatoid arthritis' combined with 'interstitial lung disease' or 'RA-ILD', and further refined by including terms like 'treatment' or 'therapeutics'. Additionally, to ensure thoroughness, the reference lists of key articles were meticulously examined for any additional pertinent literature. This systematic approach aimed to gather a comprehensive pool of research studies and clinical trials addressing the treatment and management of interstitial lung disease in individuals with rheumatoid arthritis.

Pathogenesis of *RA-ILD*

Understanding the underlying mechanisms of RA-ILD remains a challenge, with genetics and environmental factors playing pivotal roles in its development (Brown, 2007; O'Dwyer et al., 2013). Specific variations in human leukocyte antigen (HLA) genes, such as HLA-DRB1, HLA-DR4, and HLA-B40, have been linked to the emergence of ILD in RA patients (O'Dwyer et al., 2013). Smoking, particularly in individuals with certain HLA-DR shared epitope (SE) genes, can initiate immune responses to citrulline-modified proteins, leading to lung damage (O'Dwyer et al., 2013). This damage can enhance protein citrullination in lung cells, triggering an inflammatory cascade characterized by the activation of cytokines, chemokines, and growth factors like TNF, interleukins (IL), and vascular endothelial growth factor (VEGF) (Kelly et al., 2014). Hyperactive matrix metalloproteinases (MMP) and increased deposition of extracellular matrix (ECM) due to fibroblast proliferation ultimately contribute to pulmonary fibrosis and ILD onset (Kelly et al., 2014).

Recent studies have shed light on the role of IL-17 in pulmonary fibrosis development in both RA-ILD and idiopathic pulmonary fibrosis (IPF), suggesting potential treatment implications targeting

fibrosis in these conditions (Distler et al., 2019; Flaherty et al., 2019). Although RA-ILD and IPF share immunological pathways, differences exist, with RA-ILD patients showing higher levels of inducible bronchial-associated lymphoid tissue, indicating a greater impact of immunological dysregulation (Macedo et al., 2017).

Assessing risk factors is critical for RA-ILD management, given its prevalence and impact on mortality and treatment options (Juge et al., 2020). Studies have identified independent risk factors for RA-ILD, including genetic predispositions, male gender, older age at RA onset, higher disease activity scores, elevated C-reactive protein levels, higher body mass index, and longer tobacco use duration (Juge et al., 2020). Additionally, reducing systemic inflammation is theorized to potentially modify the course of RA-ILD development (Sparks et al., 2014).

Extensive evidence supports cigarette smoking as a significant environmental risk factor for the development of seropositive RA and RA-ILD. This relationship, first identified over 30 years ago, has been confirmed by numerous studies since then (Brown, 2007; O'Dwyer et al., 2013; Kelly et al., 2014). In one study, RA patients with a history of more than 25 pack-years of smoking were found to be 3.1 times more likely to test positive for rheumatoid factor (RF) and 2.4 times more likely to experience joint erosions compared to non-smoking RA patients, suggesting that cumulative cigarette smoke exposure may exacerbate the severity of joint manifestations in RA (Brown, 2007).

At a molecular level, smoking and possibly other inhaled pro-inflammatory agents, such as silica dust, have been shown to promote protein citrullination in the lungs, a process driven by peptidyl arginine deiminase enzymes (O'Dwyer et al., 2013). This suggests that smoking can alter self-proteins in the lungs, turning them into autoimmune targets (Kelly et al., 2014). Furthermore, a large case-control study in Sweden found that the combination of smoking history and the presence of double copies of HLA-DR shared epitope genes increased the risk of developing RA by 21-fold compared to nonsmokers without shared epitope genes, indicating that smoking may trigger RA-specific immune responses to citrullinated proteins in the context of these genetic factors (Juge et al., 2020).

Rheumatoid arthritis-associated interstitial lung disease (RA-ILD) is the most prevalent pulmonary complication in RA patients, being identifiable in up to 60% of these individuals via high-resolution computed tomography (HRCT). Of these cases, approximately 10% are clinically significant, making RA-ILD a major contributor to morbidity and mortality among RA patients (Nannini et al., Turesson et al., Bongartz et al., Olson et al.). Despite RA being more prevalent in females, RA-ILD is more frequently observed in males, with some studies reporting a male-to-female ratio as high as 2:1 (Komiya et al., Saag et al.). The lung disease typically manifests in the fifth to sixth decades of life, around a decade after the onset of joint disease (Nannini et al.).

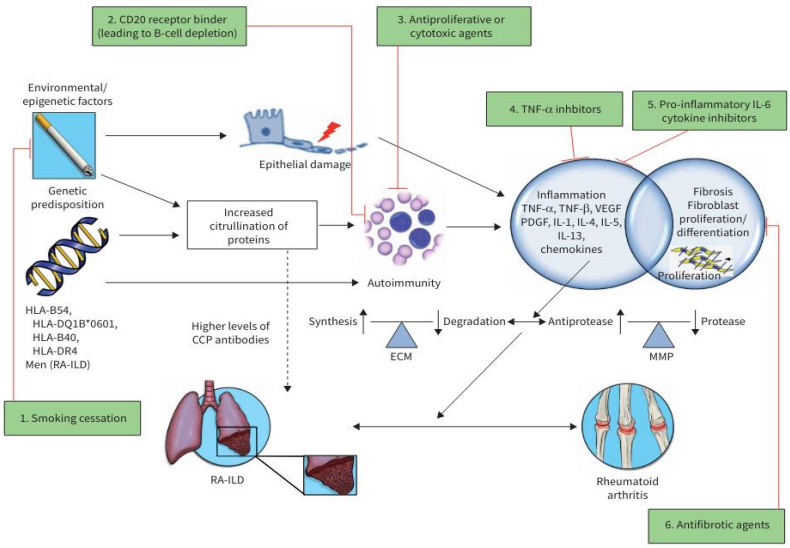

Figure 1. Schematic Illustration of RA-ILD Pathogenesis and Therapeutic Targets

The pathogenesis of rheumatoid arthritis (RA)-associated interstitial lung disease (ILD) involves a complex interplay of risk factors, genetic predisposition, and environmental exposures. Risk factors include smoking history, male sex, and older age, while genetic factors such as the shared epitope HLA-DRB1 also play a role. Environmental exposures causing damage to airway and alveolar epithelial cells can lead to increased protein citrullination. In genetically predisposed individuals, this can trigger an inflammatory process characterized by activation of cytokines, chemokines, and growth factors, such as tumor necrosis factor (TNF), vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and interleukins (IL). This inflammation contributes to fibroblast proliferation and differentiation, increased synthesis and deposition of extracellular matrix (ECM), and heightened activity of matrix metalloproteinases (MMP), leading to the development of ILD and pulmonary fibrosis. Synovial fibroblasts play a similar role in the joint manifestations of RA.
Various therapeutic targets include:

Avoiding exposures like smoking cessation;
Binding CD20 receptors to deplete B-cells (e.g., rituximab);
Using antiproliferative or cytotoxic agents (e.g., cyclophosphamide and mycophenolate);
Inhibiting TNF-α (e.g., adalimumab, etanercept, infliximab);
Inhibiting pro-inflammatory IL-6 cytokines (e.g., tocilizumab);
Employing antifibrotic agents (nintedanib and pirfenidone).

Other therapeutic agents not depicted include corticosteroids, which reduce inflammation by inhibiting prostaglandin and leukotriene synthesis, decreasing circulating monocytes, and inhibiting collagenase and lysosomal enzyme release (King et al.). Additionally, non-biologic disease-modifying anti-rheumatic drugs (cDMARDs) like methotrexate are not pictured. Methotrexate's exact mechanism in RA is unclear but is believed to involve adenosine signaling, increasing adenosine levels and promoting an anti-inflammatory state (Gulati et al.).

Clinical Presentation and Diagnosis

Although rheumatoid arthritis (RA) is often diagnosed before interstitial lung disease (ILD) is identified, some patients may initially present only with pulmonary symptoms. In such cases, a high level of suspicion for RA-ILD is necessary to distinguish it from idiopathic interstitial pneumonias (IIPs). Clinical features resembling those of IIPs, such as chronic dyspnea and cough, are commonly seen in patients with RA and ILD. Physical examination may reveal inspiratory crackles, while pulmonary function tests (PFTs) typically show restrictive physiology, often accompanied by a reduction in diffusing capacity. While high-resolution computed tomography (HRCT) imaging is usually sufficient for confirming ILD diagnosis, surgical lung biopsy may be necessary in a minority of cases (American College of Rheumatology, 2019).

Patients presenting pulmonary symptoms due to rheumatoid arthritis (RA) should undergo chest imaging assessment. While initial evaluation may involve standard chest radiographs, high-resolution computed tomography (HRCT) scans are crucial for identifying patterns and distributions of interstitial pneumonia, airway abnormalities, pleural abnormalities, and other parenchymal abnormalities such as nodules, bronchiectasis, and vascular abnormalities initially and for monitoring disease progression over time. While all patterns of interstitial pneumonia can be observed in RA-associated interstitial lung disease (RA-ILD), the predominant manifestation is the usual interstitial pneumonia (UIP) pattern. A study on patients with RA-ILD identified four major HRCT patterns: UIP (37%), nonspecific interstitial pneumonia (NSIP) (30%), obliterative bronchiolitis (17%), and organizing pneumonia (OP) (8%) (American College of Rheumatology, 2019).
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. NSIP is characterized by basilar predominant ground-glass opacities and the absence of honeycombing. Less common patterns observed in RA-ILD include other types of

interstitial pneumonia such as OP, diffuse alveolar damage, lymphocytic interstitial pneumonia (LIP), and desquamative interstitial pneumonia (DIP)-like patterns. Combined pulmonary fibrosis and emphysema (CPFE) have also been detected on HRCT scans in RA patients. Analysis of HRCT images in patients with a smoking history and either idiopathic pulmonary fibrosis (IPF) or RA-ILD revealed the coexistence of radiographically evident emphysema in nearly 50% of individuals with RA-ILD and 35% of those with IPF, with an association to lower pack-year smoking histories compared to control groups. These findings further support a potential pathogenetic link to smoking in both diseases (American College of Rheumatology, 2019).

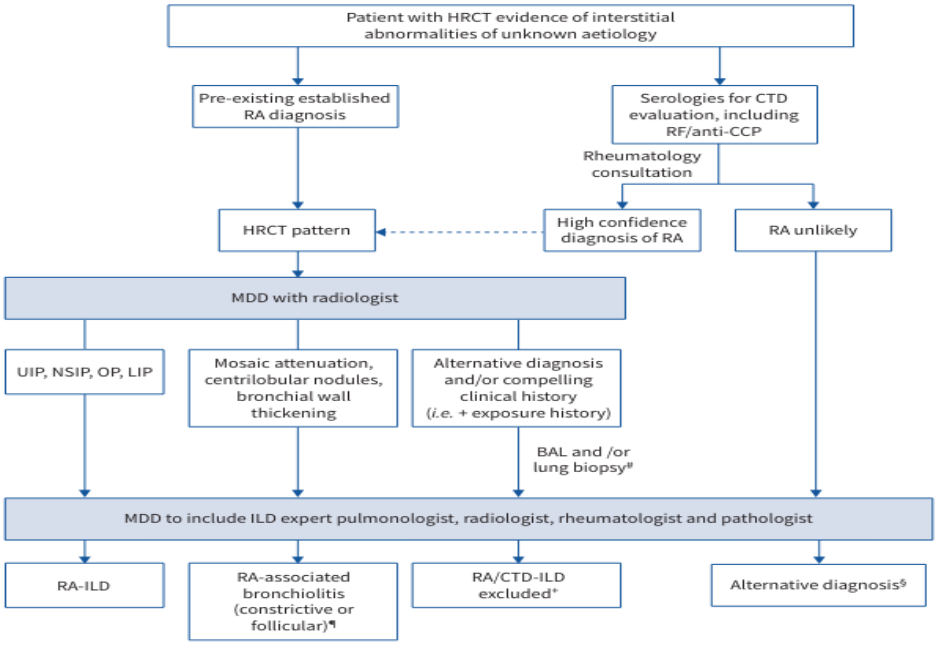

Figure 2. The proposed diagnostic algorithm for identifying rheumatoid arthritis (RA) and/or connective tissue disease (CTD)-associated interstitial lung disease (ILD) is depicted in Figure 1. It outlines a stepwise approach involving various diagnostic modalities and considerations. These include obtaining high-resolution computed tomography (HRCT) scans, assessing serological markers such as rheumatoid factor (RF) and cyclic citrullinated protein (CCP), engaging in multidisciplinary discussions (MDD), and considering further diagnostic interventions such as bronchoalveolar lavage (BAL) or lung biopsies as warranted by clinical presentation and disease severity. It is crucial to acknowledge that certain findings may overlap with other radiographic patterns, and patients should be re-evaluated if clinical symptoms or features of CTD emerge during follow-up. Additionally, alternative diagnoses should be pursued based on the clinical context and established guidelines if warranted, such as idiopathic pulmonary fibrosis, hypersensitivity pneumonitis, or sarcoidosis.

A multidisciplinary approach, typically involving pulmonologists, radiologists, and pathologists, is essential for the differential diagnosis of interstitial lung diseases (ILDs) (American College of Rheumatology, 2018). The 2023 American College of Rheumatology (ACR) guidelines outline recommendations for screening ILD in individuals with systemic autoimmune rheumatic diseases (SARDs), as summarized in Table 1 (American College of Rheumatology, 2019). High-Resolution Computed Tomography (HRCT) is identified as the preferred method for detecting ILD in rheumatoid arthritis (RA) patients due to its high sensitivity (American College of Rheumatology, 2019). Characteristic features of usual interstitial pneumonia (UIP) in RA patients include subpleural, basal-predominant reticular abnormalities with honeycombing, traction bronchiectasis, and a relative absence of ground-glass opacities, along with air trapping on exhale (American College of Rheumatology, 2019). HRCT has shown predictive value for progressive fibrosis in RA-ILD cases,

with a wide distribution of subpleural reticular pattern (RP) and/or interlobular septal thickening and peribronchovascular interstitium (PBVI) thickening identified as indicative of fibrosis progression (American College of Rheumatology, 2019).

A prospective study conducted in Switzerland on 205 systemic sclerosis (SSc) patients demonstrated the reliability and accuracy of a specific, reduced HRCT procedure with nine slices distributed in a basal-apical gradient for identifying ILD in SSc patients. This approach can be seamlessly incorporated into daily clinical practice for early ILD diagnosis and screening, offering the added benefit of lower radiation dosage compared to standard whole-chest HRCT (American College of Rheumatology, 2020). While multiple pulmonary function tests (PFTs) are commonly used in clinical practice for assessing lung restriction, reliance solely on PFTs may lead to underdiagnosis of significant SSc-related ILD (American College of Rheumatology, 2020). Transthoracic lung ultrasonography has emerged as a potential tool for detecting impending pulmonary structural alterations in RA patients, with a study indicating pleural nodules or B-line phenomena in 28% of RA patients, correlating with signs of incipient ILD on CT scans (American College of Rheumatology, 2020).
For monitoring ILD progression, the 2023 ACR guidelines recommend the use of HRCT chest and/or PFTs, with preference given to using both modalities over PFTs alone. In individuals with RA-ILD, PFT monitoring every three to 12 months during the first year is suggested, followed by less frequent monitoring once stability is achieved (American College of Rheumatology, 2020).
A summary of studies highlighting risk factors and diagnostic modalities in RA-ILD is provided in Table 1.

Table 1*:* The 2023 American College of Rheumatology (ACR) Guidelines for Screening ILD in

Screening modality	ACR recommendations
Pulmonary function test	Conditionally recommend screening with PFTs for people with SARDs at increased risk of developing ILD.
High-resolution CT scan	Conditionally recommend screening with HRCT of the chest for people with SARDs at increased risk of developing ILD.
6-minute walk test distance	Conditionally recommend against screening with 6MWD chest for people with SARDs at increased risk of developing ILD.
Chest radiography	Conditionally recommend against screening with chest radiography for people with SARDs at increased risk of developing ILD.
Ambulatory desaturation testing	Conditionally recommend against screening with ambulatory desaturation testing for people with SARDs at increased risk of developing ILD.
Bronchoscopy	Conditionally recommend against screening with bronchoscopy for people with SARDs at increased risk of developing ILD.
Surgical lung biopsy	Strongly recommend against screening with surgical lung biopsy for people with SARDs at increased risk of developing ILD.

Patients with Systemic Autoimmune Rheumatic Diseases

The 2023 American College of Rheumatology (ACR) guidelines recommend the following for screening interstitial lung disease (ILD) in individuals with systemic autoimmune rheumatic diseases (SARDs):

- Regular monitoring of Pulmonary Function Tests (PFTs) to assess lung function.
- Utilization of High-Resolution Computed Tomography (HRCT) for detailed imaging of lung structures.
- The 6-Minute Walk Test Distance (6MWD) is employed to evaluate exercise tolerance and functional status (Fischer et al., 2023).

Pharmacological Management

Immunosuppressants

The efficacy of immunosuppressants in treating usual interstitial pneumonia (UIP) associated with rheumatoid arthritis (RA) or connective tissue disease (CTD) remains uncertain. Retrospective studies indicate that immunosuppressants might be more effective in interstitial lung disease (ILD) types other than UIP. Thus, they could offer more benefits for RA-ILD with nonspecific interstitial pneumonia (NSIP) or organizing pneumonia (OP) patterns rather than UIP (Fischer et al., 2020; Suda et al., 2018). However, lung biopsies can reveal diverse histologic abnormalities within different specimens, and some patients exhibit unclassifiable or mixed patterns on high-resolution computed tomography (HRCT). Unfortunately, there is limited data on medication efficacy and disease progression in these patients over time (King et al., 2019).

Glucocorticoids are often included in the initial treatment regimen for clinically significant RA-ILD due to their effectiveness in CTD-ILD rather than RA-ILD (Kuwana et al., 2017). NSIP and OP ILD patterns are more likely to respond to glucocorticoids than UIP (Kuwana et al., 2017). A retrospective case series published in 2018 on 26 ILD patients with underlying CTD diagnoses reported that prednisone and oral tacrolimus, administered after two courses of pulse-dose methylprednisolone therapy, were well tolerated and showed multifaceted efficacy (Lee et al., 2018). Conversely, there is no evidence supporting the use of steroids as monotherapy in idiopathic pulmonary fibrosis (IPF). Mayo Clinic researchers conducted a retrospective study on survival in 157 IPF patients receiving no medication, 54 receiving maintenance doses of prednisolone alone, 167 receiving colchicine alone, and 71 receiving both colchicine and prednisolone. No statistically significant difference in survival was observed between patients on prednisolone and those receiving no treatment after adjusting for age, sex, and lung function (Ryu et al., 2019). In RA-ILD patients, corticosteroids increased the risk of life-threatening infections. Despite the use of disease-modifying antirheumatic drugs (DMARDs), a higher frequency of infections was associated with a mean daily dose of prednisone greater than 10 mg (Rojas-Serrano et al., 2018). Thus, their optimal use is in the early management of acute exacerbations or until new medications with better long-term safety profiles are available.

Other immunomodulatory treatments such as mycophenolate mofetil (MMF), cyclophosphamide, azathioprine, cyclosporine, and tacrolimus may also be used to treat RA-ILD, but their effects remain unclear. MMF was well tolerated in a large, heterogeneous cohort of 125 CTD-ILD patients (including 18 with RA-ILD), with a low discontinuation rate. Over a median follow-up of 2.5 years, MMF therapy was associated with stable or improved pulmonary function (Fischer et al., 2020).

Despite the lack of controlled clinical trials for cyclophosphamide in RA-ILD and limited efficacy data, it is still used in clinical practice, especially in cases of highly progressive ILD (King et al., 2019). A 2019 retrospective study examined factors related to progression and survival in 266 RA-ILD patients, finding that those receiving cyclophosphamide had a better prognosis (Fischer et al., 2019). Azathioprine is often used as an alternative to methotrexate in RA-ILD. A single-centre retrospective cohort analysis of CTD-ILD patients reported comparable clinical outcomes and longitudinal pulmonary function tests (PFTs) in patients treated with azathioprine and MMF (n = 97, 24% RA-ILD) (Schneider et al., 2017). While these additional immunomodulatory treatments (such as MMF and azathioprine) may be effective for ILD, healthcare professionals must consider potential side effects and their less favorable impact on articular disease (Bongartz et al., 2016; Turesson et al., 2018).

Conventional Disease-Modifying Antirheumatic Drugs (cDMARDs)

Only 0.3% to 0.4% of RA patients using methotrexate develop pneumonitis. Moreover, methotrexate does not increase the risk of RA-ILD. Prospective early RA inception cohorts indicated a tendency for RA patients on methotrexate to have a lower likelihood of developing ILD (odds ratio: 0.54; 95% CI: 0.28-1.06) (Michaud et al., 2020). A study by Rojas-Serrano et al. in 2017 involving 78 patients observed prolonged survival (HR: 0.13, 95% CI: 0.02-0.64) in RA-ILD patients receiving methotrexate compared to those receiving other cDMARDs after adjusting for confounding variables

(Rojas-Serrano et al., 2017). The higher rate of ILD observed with leflunomide treatment may partly be due to the avoidance of methotrexate in patients with or at risk for RA-ILD (Bernatsky et al., 2019). Leflunomide should be avoided or used with caution in patients with previous methotrexate pneumonitis and those with pre-existing ILD (Bernatsky et al., 2019). It should not be used as a substitute for methotrexate in these situations. Pneumonitis has also been reported with sulfasalazine use (Wolfe et al., 2018). Data on the safety of hydroxychloroquine in RA-ILD are limited.

Biological Disease-Modifying Antirheumatic Drugs (bDMARDs)

Anti-tumour necrosis factor (anti-TNF) agents have shown excellent effectiveness in slowing the progression of articular disease and symptoms. However, their increased use has raised concerns about potential pulmonary toxicity. All anti-TNF drugs approved for RA have been associated with new-onset or worsening of existing ILD: infliximab (Tanaka et al., 2021), etanercept (Michaud et al., 2020), and adalimumab (Furst et al., 2018); as well as newer agents like certolizumab (Bongartz et al., 2019) and golimumab (Saag et al., 2017). Some studies have refuted the lung toxicity of TNF inhibitors (TNFi) and demonstrated their potential for stabilizing or improving pulmonary interstitial disease (Michaud et al., 2020; Bongartz et al., 2019; Tanaka et al., 2021). A British national prospective observational trial of 367 patients with pre-existing RA-ILD found that TNFi treatment did not increase mortality compared to cDMARDs, although RA-ILD-related mortality was higher (34%) among those receiving TNFi therapy (Zamora-Legoff et al., 2018). A longitudinal observational trial involving 263 RA-ILD patients indicated that abatacept (ABA) is similarly effective in stabilizing dyspnea, lung function, and radiological deterioration in both UIP and NSIP patterns of the disease. Early ABA administration may halt RA-ILD progression regardless of the radiological pattern (Adams et al., 2019).

A case series of 226 patients on anti-TNF drugs (83% with RA) found that 10% developed ILD after starting anti-TNF therapy (Yamamoto et al., 2018). Anti-TNF-induced ILD has a significant mortality rate, with one-third of patients affected, increasing to two-thirds in those with pre-existing ILD (Yamamoto et al., 2018; Suda et al., 2017). Anti-TNF therapy should be used cautiously in RA-ILD patients. Other factors increasing mortality risk include advanced age (>65 years), a later ILD diagnosis, and increased immunosuppression (Yamamoto et al., 2018).

Rituximab (RTX), a monoclonal antibody targeting the B-cell marker CD20, is approved for treating RA in anti-TNF nonresponders. Follicular B-cell hyperplasia and interstitial plasma cell infiltrates in RA-ILD patients suggest B cell involvement in disease etiology, raising interest in using RTX for RA-ILD treatment (Keir et al., 2019). A retrospective multicenter cohort study in Portugal found RTX to be promising for CTD-ILD patients (61.2% RA patients), with notable efficacy in non-specific interstitial pneumonia patterns (Michaud et al., 2020). However, a meta-analysis of biological treatments for CTD linked RTX use to increased non-infectious parenchymal lung disease (López-Pomares et al., 2018).

IL-6 inhibitors like tocilizumab have shown that IL-6R inhibition counters the profibrotic effects of IL-6, suggesting potential benefits for treating pulmonary fibrosis in RA. A case series of four RA patients observed that tocilizumab monotherapy maintained or possibly improved ILD (Keir et al., 2019). Conversely, some reports noted ILD incidence or progression after tocilizumab use (Bernatsky et al., 2018).

Janus kinase inhibitors (JAKi), particularly tofacitinib (TOF), have shown promising results in clinical trials. A multicenter retrospective study suggested JAKi therapy as a safe option for RA-ILD, stabilizing ILD on HRCT and potentially preventing PFT deterioration (Michaud et al., 2020). A 2023 prospective study involving 28,559 RA patients found that those on tofacitinib had the lowest ILD incidence among patients receiving bDMARDs (Bernatsky et al., 2023).

Anti-fibrotic agents may prevent RA-ILD progression. Currently, pirfenidone and nintedanib are under study for IPF treatment. The INBUILD study compared nintedanib to placebo in patients with progressive, fibrotic lung disease (13% RA-ILD) across 15 countries. The annual decline in forced expiratory volume (FVC) was significantly lower in patients on nintedanib compared to those on

placebo. A common adverse reaction was diarrhea (Flaherty et al., 2019). Pirfenidone showed efficacy in a phase 2 randomized controlled trial enrolling 253 patients with progressive fibrosing unclassifiable ILD; FVC decreased by 87.7 mL in the treatment arm compared to 157.1 mL with placebo (Flaherty et al., 2019).

Other Treatment Considerations

Other treatment considerations not covered in this review include smoking cessation, pulmonary rehabilitation, oxygen supplementation, management of associated pulmonary hypertension, treatment of comorbidities such as abnormal gastroesophageal reflux, and considering lung transplantation when appropriate (Gulati et al., 2018; Raghu et al., 2011; Collard et al., 2016).

Conclusion

RA-ILD represents a significant challenge in the management of RA due to its impact on patient quality of life and survival. While various pharmacological strategies are available, there remains a need for more targeted therapies and clinical trials to establish optimal treatment protocols. Early recognition and a multidisciplinary approach are crucial in managing this complex condition.

Future Directions

Research into the molecular pathways involved in RA-ILD could uncover new therapeutic targets. Additionally, prospective studies and clinical trials are essential to understand better the efficacy and safety of current and emerging treatments in RA-ILD.

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