Rheumatoid Arthritis (Y Yazici, Section Editor)

# Rheumatoid Arthritis–Associated Interstitial Lung Disease: Current Update on Prevalence, Risk Factors, and Pharmacologic Treatment

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This article is part of the Topical Collection on *Rheumatoid Arthritis*

## Abstract

*Purpose of review* Rheumatoid arthritis–associated interstitial lung disease (RA-ILD) is one of the most serious extraarticular RA manifestations. RA-ILD is associated with worse physical function, lower quality of life, and increased mortality. RA-ILD is comprised of heterogeneous subtypes characterized by inflammation and fibrosis. Diagnosis can be difficult since the presentation of RA-ILD is characterized by non-specific symptoms and imaging findings. Management of RA-ILD is also challenging due to difficulty in precisely measuring pulmonary disease activity and response to treatment in patients who may also have articular inflammation. We provide a current overview of RA-ILD focusing on prevalence, risk factors, and treatment.

*Recent findings* Research interest in RA-ILD has increased in recent years. Some studies suggest that RA-ILD prevalence may be increasing; this may be due to underlying biologic drivers or increases in imaging and recognition. Novel RA-ILD risk factors include the *MUC5B* promoter variant, articular disease activity, autoantibodies, and biomarkers of damaged pulmonary parenchyma. Treatment should focus on controlling RA disease activity, which emerging data suggest may reduce RA-ILD risk. Immunomodulatory and anti-fibrotic drugs may also treat RA-ILD.

*Summary* RA-ILD is an underrecognized and serious manifestation of RA, but important progress is being made in identifying risk factors and treatment.

## Introduction

Patients with rheumatoid arthritis (RA) have excess respiratory mortality compared with the general population [1•, 2, 3]. RA-associated interstitial lung disease (RA-ILD) is one of the most common and serious extraarticular manifestations of RA. Median survival after RA-ILD diagnosis is only 3–7 years, which is markedly reduced compared with RA patients without ILD and the general population [4, 5••, 6]. Patients with RA-ILD have substantial health care costs and interactions; 72% have an all-cause inpatient admission and 76% have an all-cause emergency department visit [7••]. Patients with RA-ILD also have reduced quality of life and physical function, increased respiratory symptoms, and a more severe RA disease as measured by the Multi-Dimensional Health Assessment Questionnaire (MDHAQ) score and total swollen joint count [8].

RA-ILD is distinguished by subtypes by histologic and/or imaging features [9•, 10]. The most common subtype is usual interstitial pneumonia (UIP), characterized by fibrosis, and typically has a more aggressive clinical course [11•]. Non-specific interstitial pneumonia (NSIP) is also common in patients with RA and is typically characterized by parenchymal inflammation [11•]. Some patients have both inflammatory and fibrotic characteristics that may make it difficult to distinguish between UIP and NSIP, and, perhaps, some patients transition from an inflammatory to a fibrotic form of NSIP [11•]. Other less common RA-ILD subtypes include lymphocytic interstitial pneumonia (LIP), acute interstitial pneumonia (AIP), organizing pneumonia (OP), desquamative interstitial pneumonia (DIP), and respiratory bronchiolitis ILD (RB-ILD) [11•]. Since routine chest computed tomography (CT) imaging is becoming more widely utilized, interstitial lung abnormalities (ILA) are commonly detected and may represent a subclinical RA-ILD form that may progress to clinically significant RA-ILD in some [8, 12•]. Besides RA-ILD, patients with RA may have other pulmonary manifestations including airway disease, pleuritis, nodules, pulmonary vascular disease, bronchiectasis, bronchiolitis, and secondary Sjogren's syndrome [9•]. Smoking is an established risk factor for RA development and lung diseases such as ILD and emphysema, and this may explain lung abnormalities in some patients [13••]. Finally, patients with RA may be at an increased risk for pneumonia and drug side effects causing pneumonitis [14]. Therefore, lung abnormalities are a relatively common clinical feature of patients with RA

with significant morbidity and mortality. This review focuses on RA-ILD given increased research interest in identifying risk factors and treatment for this pulmonary manifestation of RA.

Despite the expanding options of biologic and targeted disease-modifying anti-rheumatic drugs (DMARDs), the prevalence of RA-ILD may be increasing [7••]. Rheumatologists, pulmonologists, and other clinicians are confronted with the management of patients with RA-ILD who may have combinations of articular and pulmonary involvement. In this review, we will provide an update on the prevalence, risk factors, and pharmacologic management of RA-ILD.

# Prevalence of RA-ILD

The prevalence of RA-ILD ranges widely in previous research, likely due to varying methodologies in detection [4, 5••, 7••, 12•, 15–17, 18•, 19••, 20–24]. Some studies identified RA-ILD through clinical detection (from any means such as symptoms, screening, or incidental findings), with prevalence estimates ranging from 2 to 8%. However, these methods may only identify the most severe forms of RA-ILD and likely underestimate prevalence [4, 17]. Other studies used administrative databases to identify RA-ILD through billing codes or chest imaging/procedures and estimate prevalence from 8 to 20% [5••, 7••, 25–27]. However, the evaluation of RA-ILD may incur a billing code even in negative cases, thus resulting in erroneously increased prevalence.

The true prevalence of ILD in RA is not established, and estimates vary widely related to inclusion of subclinical ILD in sensitive methods or exclusion of true, but milder cases, in stringent methods. Research reviews of the images of chest CT scans obtained through clinical care are another method to increase sensitivity of detection, with ILA or RA-ILD prevalence of 10–30% [19••, 21]. In these studies, patients with RA-ILD that did not have chest imaging performed would have gone undetected. Conversely, a proportion of those with ILA may never progress to clinically significant lung disease, or the pulmonary presentations may relate to other causes such as infection, drug toxicity, and smoking. Finally, other studies performed prospective recruitment of patients with RA to obtain chest imaging as part of the research protocol to detect RA-ILD in asymptomatic individuals [12•, 15, 16] or among those with high suspicion of lung disease, with RA-ILD prevalence ranging from 10 to 50% [28]. These difficulties in understanding prevalence of RA-ILD may be overcome by a clear consensus on screening strategy and RA-specific classification criteria for clinical practice.

A recent nationwide US study used pharmacy claims data and found that RA-ILD prevalence was increasing [7••]. Prevalence of RA-ILD increased from 3.2 cases per 100,000 in the general population in 2003 to 6.0 cases per 100,000 in the general population in 2014 (denominator of all RA patients was not reported) [7••]. This is in contrast to improvements in survival of RA patients compared with the general population over the same time period following the introduction of biologic DMARDs [29]. Increasing prevalence of RA-ILD may be due to many factors including as follows: a true increase perhaps due to changes in the underlying epidemiology of RA or its treatment, increased recognition or billing practices from clinicians, increase in detection from advanced chest imaging, or increasing longevity of RA patients. Future

investigations should focus on replicating this finding and distinguishing the reasons for possible increased prevalence of RA-ILD. A screening strategy for RA-ILD among those with RA has already been detailed, and investigations concerning screening implementation should be a high research priority [9•].

# Risk factors for RA-ILD

Most studies have examined risk factors for RA-ILD as an overall entity, rather than RA-ILD subtypes. As previously discussed, detection of RA-ILD also varies widely by different research methods. These nuances could explain discrepancies in research studies attempting to identify risk factors for RA-ILD. Nevertheless, there is a growing list of identified RA-ILD risk factors (Table 1).

Demographic factors associated with RA-ILD include male sex and older age [6, 30–32, 33•]. Since most patients with RA are women, the finding of male sex may be somewhat paradoxical, but is not explained by possible confounding factors including cigarette smoking. Men have over a 2-fold increased risk of RA-ILD compared with women [6]. Future studies should focus on characterizing this sex difference within RA. Older age has also been associated with RA-ILD

**Table 1. Currently identified risk factors for RA-ILD**

| Available in clinical care | References | Currently available only in research studies | References |
|---|---|---|---|
| Demographic factors | | Genetics | |
| Older age | [6, 30–32, 33•] | *MUC5B* promoter variant | [34••] |
| Male sex | [6, 30–32, 33•] | *HLA-DR2* and others | [35] |
| Lifestyle | | Autoantibodies | |
| Cigarette smoking | [6, 30, 31, 36] | Anti-CEP1 | [37•, 38] |
| RA clinical characteristics | | Anti-CarP | [39•] |
| Longer RA duration | [40] | Anti-PAD3 | [41•] |
| Higher ACPA titer | [6, 30, 31, 36] | Anti-PAD4 | [41•] |
| Higher RF titer | [6, 30, 31] | Anti-MAA | [42•] |
| Higher ESR level | [31, 32, 33•] | Anti-HSP90 | [43, 44] |
| Prednisone use | [31, 45, 46] | Anti-IL-1α | [47] |
| Rheumatoid nodules | [33•] | Other biomarkers | |
| Moderate/high articular disease activity | [19••] | MMP7 | [30] |
| | | PARC | [30] |
| | | Surfactant protein D | [30] |
| | | Fibronectin | [48•] |
| | | IP-10/CXCL10 | [49] |
| | | IL-18 | [50] |

*Anti-CarP*, anti-carbamylated protein; *Anti-CEP1*, anti-citrullinated alpha-enolase peptide 1; *Anti-HSP90*, anti-citrullinated heat shock protein 90; *Anti-IL-1α*, anti-interleukin-1α; *Anti-MAA*, anti-malondialdehyde-acetaldehyde; *Anti-PAD3*, anti-peptidyl-arginine deaminase 3; *Anti-PAD4*, anti-peptidyl-arginine deaminase 4; *HLA-DR2*, human leukocyte antigen DR2; *IL-18*, interleukin-18; *IP-10/CXCL10*, interferon-γ-inducible protein 10; *MMP7*, matrix metalloproteinase 7; *MUC5B*, mucin 5B; *PARC*, pulmonary and activation-related chemokine

risk. This finding also deserves dedicated research on how immunosenescence, accelerated aging, or telomere shortening may be associated with RA-ILD risk.

Cigarette smoking has also been implicated as a lifestyle risk factor for RA-ILD [6, 30, 31, 36]. As already mentioned, smoking is a risk factor for RA, and it appears that smoking after RA onset and current smoking also impart risk for RA-ILD. While cigarette smoking has long been associated with poor pulmonary outcomes in many diseases, this finding suggests that at least some RA-ILD risk could be modifiable. Research studies may focus on gene-smoking interactions, which could further delineate some of the mechanisms of RA pathogenesis.

Several clinical RA factors are associated with RA-ILD. Elevations of rheumatoid factor (RF) and anti-citrullinated protein antibodies are risk factors for RA-ILD [6, 30, 31, 36]. Seropositivity for these antibodies portends a more severe articular course and higher risk of extraarticular manifestations including RA-ILD. RA severity factors including prednisone use [31, 45, 46] and rheumatoid nodules [33•] are associated with an increased RA-ILD risk, as have elevated erythrocyte sedimentation rate (ESR) [31, 32, 33•] and longer RA duration [40] are additional RA-ILD risk factors. Articular disease activity was recently associated with incident RA-ILD in a prospective study [19••]. Specifically, moderate to high disease activity was associated with a 2-fold increased risk for RA-ILD compared with low disease activity or remission [19••]. This finding suggests that articular involvement may be a marker of not only systemic inflammation but also ongoing pulmonary inflammation, hence suggesting that disease control through a treat-to-target strategy could delay or even prevent RA-ILD onset. However, other prospective observational and interventional studies are needed to confirm these findings. The potential role of DMARDs in RA-ILD onset is discussed later.

Recently, a large multinational study implicated the *MUC5B* promoter variant with RA-ILD risk [34••]. MUC5B is a type of mucin that is secreted and glycosylated into pulmonary mucosa as a key contributor to the lubricating and viscoelastic properties of airways and alveoli. This variant of the *MUC5B* gene (G>T at the rs35705950 single-nucleotide polymorphism) has also been associated with an increased risk for several chronic respiratory diseases, including idiopathic pulmonary fibrosis [51], ILD [52], and chronic obstructive pulmonary disease (COPD) [53]. In individuals with the promoter variant, excess MUC5B secretion impairs mucosal host defense, resulting in overexuberant lung injury from inhaled substances, inflammation, and fibrosis. The *MUC5B* promoter variant increases the risk for ILD by 3-fold among patients with RA and is specific for the UIP subtype of RA-ILD that is most prone to fibrosis and a severe disease course [34••]. While other genes have also been implicated in RA-ILD, none is as strongly associated as the *MUC5B* promoter variant [35]. This important finding may set the stage to understand the role of potential perturbations to pulmonary mucosa at airways, such as microbiome and inhalants. Mechanistic studies related to this gene will deepen the understanding of RA-ILD, and clinical studies should also incorporate this into prediction modeling prior to possible clinical application.

Besides RF and anti-citrullinated protein antibodies (ACPAs), other autoantibodies have been investigated for contributions to RA-ILD risk and are currently only available for research purposes. Fine specificity ACPAs including anti-citrullinated alpha-enolase peptide 1 (CEP-1) [37•, 38] and anti-

citrullinated heat shock protein 90 (HSP90) [43, 44] have been associated with RA-ILD, supporting the role of ACPAs in RA-ILD pathogenesis [36]. Peptidylarginine deiminase (PAD) isozymes catalyze citrullination, and anti-PAD3/4 have recently been associated with RA-ILD [41•]. Carbamylation is a process similar to citrullination except that it involves the irreversible modification of lysine to homocitrulline without involving enzymes [54]. Anti-carbamylated protein (CarP) antibodies have also been associated with RA-ILD risk [39•]. Malondialdehyde and acetaldehyde are products of oxidative stress that are known to be highly immunogenic, profibrotic, and proinflammatory [55, 56]. Anti-malondialdehyde-acetaldehyde (anti-MAA) antibodies were recently associated with an increased RA-ILD risk [42•]. Anti-IL-1α [47] has also been associated with RA-ILD risk. It is possible that dysregulated post-translational modification of proteins may be important in the development of RA-ILD. Future studies should investigate how citrullination, carbamylation, and MAA may impart RA-ILD risk.

Finally, other non-antibody biomarkers such as LDH [57], CA-125 [58], matrix metalloproteinases [30, 49, 59], plasma surfactant protein D [30], interferon-γ-inducible protein 10 (IP-10)/CXCL10 [49], pulmonary and activation-related chemokine (PARC) [30], fibronectin [48•], and IL-18 [50] were found to be associated with an increased risk of RA-ILD among patients with RA. A model that included demographic, clinical risk factors and biomarkers (MMP7, PARC, surfactant protein D) was able to classify presence of RA-ILD with high accuracy [30], and future studies should consider the utility of incorporating these markers into clinical care for RA-ILD screening.

# Treatment of RA-ILD

The treatment of RA can potentially delay or prevent the onset of RA-ILD. We advocate for managing RA articular disease with DMARD therapy, including those with ILD. In patients with progressive ILD despite optimal therapy for RA, one can consider changing the immunosuppressive agent or adding anti-fibrotic therapy.

To date, there are no medications specifically approved by the US Food and Drug Administration (FDA) for treatment of RA-ILD. However, nintedanib is approved for connective tissue disease–associated ILD, which could encompass RA-ILD [60••]. Pirfenidone was recently approved for "unclassifiable ILD," which may also include RA-ILD [61••]. Most of the current evidence available is drawn from observational studies, case reports, and case series. It may be most beneficial to treat patients with RA-ILD presenting with rapid disease progression and higher extent of lung injury in order to stabilize lung function [62]. Next, we outline the treatment options for RA-ILD as well as best available evidence.

## Impact of glucocorticoids and non-biologic and biologic DMARDs on RA-ILD onset

The association of DMARDs with RA-ILD onset is controversial. Some studies identified glucocorticoid use as a risk factor [31, 45, 46], but this could be a marker of RA disease activity, which is also a risk factor for RA-ILD. The possible association of methotrexate with RA-related lung disease is controversial [63]. Pneumonitis is a rare but potentially devastating adverse effect of methotrexate,

typically characterized by acute presentation of fever, cough, and chest imaging abnormalities that often resolves with methotrexate discontinuation [64]. A meta-analysis that included six placebo-controlled trials of methotrexate in patients with inflammatory diseases including RA showed no increased risk of pulmonary adverse events, but the sample size was small (504 respiratory adverse events among 1630 participants) and follow-up was short [65]. Another recent observational study (*n* = 2701) found no evidence that methotrexate was associated with incident ILD in RA, and there was a suggestion that methotrexate may delay the onset of ILD [33•]. A large placebo-controlled trial of methotrexate performed among patients with cardiovascular disease (*n* = 4786) recently showed a statistically significant increased risk for pulmonary adverse events, but most events were not severe, and patients with RA were excluded [66•].

Clinicians are often confronted with conflicting evidence of the potential impact of DMARDs on RA-ILD risk. For example, clinical trials suggested a potential increase of COPD exacerbations for patients with RA treated with abatacept; follow-up studies found no pulmonary safety concerns and other studies suggested potential benefit of abatacept on RA-ILD [67•]. A recent meta-analysis suggested that leflunomide, tumor necrosis factor inhibitors, rituximab, and tocilizumab may induce pneumonitis or worsen preexisting RA-ILD [68]. However, this finding could be subject to confounding by indication since many patients with RA-ILD are treated with rituximab or could be explained by channeling away from methotrexate in patients suspected to have RA-ILD. Given the high prevalence of chest imaging abnormalities in patients with RA, clinicians must weigh how DMARDs may impact possible progression to clinically severe RA-ILD when choosing medications to treat articular inflammation. Therefore, the pulmonary safety of DMARDs should be a high research priority.

Rheumatologists should readily involve pulmonary colleagues when interpreting possible pulmonary imaging or functional abnormalities to risk stratify patients. A multidisciplinary approach is central in patients with RA that may have several organ systems involved in order to accurately assess disease activity, risks and benefits of medications, and response to treatment. Besides rheumatologists and pulmonologists, this may also include primary care providers, pulmonary rehabilitation, chest radiologists, and pathologists among other specialists. Managing patients with RA-ILD can be particularly challenging since patients may have articular inflammation, pulmonary involvement, or both throughout their disease course.

We now focus on treatment of pulmonary manifestations of RA-ILD.

## Immunosuppressive drugs

### Glucocorticoids

Glucocorticoids should no longer be considered a first-line therapy in all patients with RA-ILD. However, they may be considered during severe exacerbations or when quick onset of action is desired. Glucocorticoids are no longer used for fibrotic forms of lung disease based on results in IPF showing worsened outcomes [69]. The inflammatory RA-ILD subtypes of RA-ILD, particularly NSIP and OP, may be steroid-responsive [70]. Glucocorticoid therapy is generally started at a prednisone equivalent of 0.5–1 mg/kg/day, or in the case of

fulminant disease, pulse dose intravenous methylprednisolone 1–2 g per day. Glucocorticoids should be given with careful monitoring and management of side effects, particularly infection given the propensity for pneumonia or other opportunistic infections. Pneumocystis pneumonia prophylaxis should be considered in patients with RA-ILD who will be on glucocorticoids (thresholds of dose/duration of glucocorticoid for staring prophylaxis are not specifically established in RA-ILD) [71]. Studies have shown that glucocorticoids are associated with a 4-fold increased risk of serious infection in older adults with RA [72]. Glucocorticoid-induced osteoporosis is another important adverse event requiring careful screening and follow-up, particularly given that RA itself is a risk factor for osteoporosis [73]. Glucocorticoid treatment is the most common secondary cause of osteoporosis [74].

## Mycophenolate mofetil

Most of the evidence for mycophenolate mofetil (MMF) comes from observational studies in CTD-ILD, particularly systemic sclerosis, in the demonstration of disease stabilization [75, 76]. MMF has also been shown to have a superior safety profile compared with oral cyclophosphamide in scleroderma-ILD [77]. In a small study with CTD-ILD patients ($n = 10$), MMF was associated with symptom improvement and imaging/pulmonary function test improvement (composite of lung volumes or diffusion capacity) [78]. However, these studies are limited by a small sample size; larger controlled studies will be needed to confirm the findings. MMF has relatively poor efficacy for articular manifestations of RA, and a concomitant DMARD may be needed to control disease activity in joints [79].

## Rituximab

Rituximab, a B cell–depleting anti-CD20 antibody, has shown promise in the treatment of CTD-ILD. Small studies demonstrated stable or improved lung function with rituximab therapy in patients with scleroderma-ILD or dermatomyositis-ILD [80, 81]. Rituximab has also been used as rescue therapy for severe and progressive CTD-ILD [82]. In RA patients with ILD, an observational study reporting the experience of using rituximab over 10 years demonstrated that it was relatively safe and did not lead to ILD progression [83•]. A study performed in the British Society for Rheumatology Biologics Register for RA compared outcomes of RA-ILD patients on rituximab ($n = 43$) with those on a TNFi ($n = 309$). This study demonstrated lower mortality in patients treated with rituximab vs. those receiving TNFi [84•]. Rituximab has proven efficacy for articular involvement, so it may be considered in patients with simultaneous inflammatory activity in lungs and joints. Rituximab and mycophenolate mofetil may also be considered in combination for some patients.

## Cyclophosphamide

Cyclophosphamide has been used to treat many types of ILD, with studies demonstrating lung function stabilization of fibrosis [85]. A recent Cochrane systematic review of cyclophosphamide in the treatment of connective tissue disease–related ILD (CTD-ILD), using four trials ($n = 495$), demonstrated that cyclophosphamide led to a small improvement in forced vital capacity (FVC) but not $D_{LCO}$; there was

no difference between cyclophosphamide and MMF. Given the toxicity profile of cyclophosphamide, it is reasonable to reserve it for those with the most rapidly progressing or refractory disease. While not typically considered for articular disease activity due to its side effect profile, it may be considered in patients with severe or refractory inflammation in both lungs and joints.

## Azathioprine

There are no controlled studies of azathioprine in RA-ILD, but there is generally less enthusiasm for use of azathioprine in any type of ILD after the results of the PANTHER-IPF trial. Based on evidence in IPF, the combination of glucocorticoids and azathioprine was thought to improve survival, but results of the PANTHER-IPF trial in 2012 abruptly altered this management approach [86]. The PANTHER-IPF trial was terminated early due to higher mortality and increased hospitalization rates in the combined prednisone, azathioprine, and N-acetylcysteine arm compared with placebo, with many of the complications attributed to pulmonary infection [87]. However, in a retrospective cohort study of CTD-ILD ($n = 54$) in 2016, azathioprine was shown to stabilize pulmonary function over time and comparable incidence of adverse outcomes as occurred in the MMF group in the same study [88]. Azathioprine may still be considered in some, such as articular involvement warranting non-biologic DMARDs and contraindication to other drugs.

## Other immunomodulatory drugs

Tocilizumab is an interleukin-6 receptor (IL-6R) antibody and is approved for the treatment of RA. A small retrospective study of 28 RA-ILD patients receiving tocilizumab demonstrated potential stabilization of pulmonary disease and an acceptable safety profile [89•]. Conversely, early RCTs and case reports have suggested association between incident ILD with tocilizumab treatment [90]. A recent meta-analysis of observational studies among patients with RA suggested a possible relationship with tocilizumab and worsening of RA-ILD [68]. Further large prospective studies would be necessary to elucidate the efficacy and safety of tocilizumab in RA-ILD.

Abatacept is a soluble chimeric fusion protein of cytotoxic T lymphocyte antigen 4 (CTLA-4)-Ig, blocking the T cell co-stimulation in RA. An open-label study of 63 RA-ILD patients in Spain showed that the majority of patients achieved symptom and PFT stability, with 20–25% of patients experiencing improvement [91•]. A phase 2 open-label clinical trial is currently enrolling patients to study the safety of abatacept among patients with RA-ILD (AbatacePt in Rheumatoid Arthritis-ILD [APRIL]) [92].

There are currently inconclusive data on the pulmonary safety of Janus kinase (JAK) inhibitors. Low rates of ILD have been reported from the RA clinical development programs and post-marketing surveillance studies of tofacitinib and baricitinib [93]. A small open-label trial in 18 patients with amyopathic dermatomyositis–associated ILD demonstrated improvement in pulmonary function and survival in the tofacitinib group compared with historic controls [94]. A randomized, controlled, open-label phase IV clinical trial comparing efficacy of tofacitinib vs. methotrexate in RA-ILD (PULMORA) has not yet started recruitment [95].

## Anti-fibrotic drugs

### Nintedanib

Nintedanib inhibits multiple tyrosine kinases and is approved by the US FDA for IPF, systemic sclerosis–associated ILD, and chronic fibrosing ILDs with a progressive phenotype, which could include RA-ILD. Nintedanib has been shown to be efficacious in progressive fibrotic ILDs ($n = 663$) in a randomized, double-blind, placebo-controlled, phase 3 trial (INBUILD trial) with stringent inclusion criteria to demonstrate reduction in disease progression [60••]. This trial included 89 (13%) patients with RA-ILD. Patients in the nintedanib arm had a slower rate of decline in FVC compared with placebo over a 52-week period, with a comparable benefit seen in the treatment of IPF (INPULSIS trial) [96]. Among patients with CTD-ILD, the benefit was more prominent in the UIP subtype vs. other subtypes. Even though there are improvements compared with placebo, the magnitude of clinical benefit is not yet established. Therefore, nintedanib can be considered in patients with RA-ILD. Gastrointestinal side effects may limit its use in some patients.

### Pirfenidone

Pirfenidone, an anti-fibrotic agent with anti-inflammatory properties, has demonstrated efficacy in IPF by ameliorating pulmonary function decline and decreasing mortality in randomized controlled trials [97]. It has been approved by the US FDA for the treatment of mild or moderate IPF and "unclassifiable ILD," which could include IPAF and RA-ILD; it has demonstrated a slower decline in FVC compared with placebo [61••]. Rash and gastrointestinal side effects, such as nausea, are common limiting factors in it use. An open-label, phase 2 study in patients with systemic sclerosis–associated ILD demonstrated tolerability of pirfenidone, even in those taking concurrent MMF [98]. Treatment of RA-ILD using pirfenidone is currently being investigated in an ongoing phase 2 clinical trial (TRAIL1) [99]. Similar to nintedanib, pirfenidone can be considered in patients with RA-ILD, though the magnitude of clinical benefit is unclear, and side effects are common. While not yet directly investigated, it may be reasonable to treat fibrotic subtypes of RA-ILD such as UIP with anti-fibrotic drugs.

## Lung transplantation

Lung transplantation can be considered in patients with end-stage RA-ILD who fail to respond to therapy. There are limited data available for outcomes in lung transplant in RA-ILD patients. In a retrospective review of 10 RA-ILD patients compared with 53 IPF patients who underwent lung transplantation, 1-year survival was comparable between the two groups (67% vs. 69%, respectively). The study also found a significant improvement in quality of life related to respiratory symptoms [100]. The candidacy for lung transplant in RA-ILD needs to be carefully evaluated given common RA comorbidities such as osteoporosis and extrapulmonary manifestations such as atherosclerotic cardiovascular disease.

## Ongoing trials

The ongoing trials evaluating RA-ILD treatment are outlined in Table 2. These include abatacept, tofacitinib, and pirfenidone.

**Table 2.** **Current ongoing clinical trials evaluating pharmacologic treatment of RA-ILD**

| Trial Identifier | Intervention vs. comparison | Primary end point | Clinical trial phase | Current status | Estimated enrollment (*n*) | Follow-up duration |
|---|---|---|---|---|---|---|
| NCT03084419 [92] | Abatacept (single arm) | Change in FVC | 2 | Recruiting | 30 | 28 weeks |
| NCT04311567 [95] | Tofacitinib vs. methotrexate | Change in total interstitial disease score by HRCT | 4 | Not yet recruiting | 48 | 48 weeks |
| NCT02808871 [99] | Pirfenidone vs. placebo | Composite (≥ 10% decline in FVC or death) | 2 | Recruiting | 270 | 52 weeks |

*FVC*, forced vital capacity; *HRCT*, high-resolution computed tomography; *ILD*, interstitial lung disease; *RA*, rheumatoid arthritis

## Conclusions

Pulmonary involvement in RA is relatively common and there has been a growing interest in RA-ILD over the last few years. Many challenges should be acknowledged: lack of a uniform screening strategy that in turn guides the prevalence estimates, unclear natural history in terms of timing of onset and rate of progression, and optimal treatment approaches. Despite these challenges, progress has been made in identifying several novel risk factors. These include the *MUC5B* promoter variant [34••], moderate to high articular disease activity [19••], autoantibodies such as anti-CarP [39•] and anti-MAA [42•], and biomarkers such as MMP7, PARC, and surfactant protein D [30]. While there are many approved DMARDs and biologic agents used to treat RA, the safety and efficacy of many of these agents in RA-ILD still needs to be evaluated. With some encouraging data in large cohorts on rituximab stabilizing lung disease in RA-ILD, and RCT data with the use of anti-fibrotics, a novel approach of combining selected immunosuppressive and anti-fibrotic therapy will need to be evaluated in a larger clinical trial [61••]. While important gaps in the optimal treatment remain, tremendous progress in distinguishing subtypes of RA-ILD, risk factors for its development, pathogenesis, and management have has been made over the last few years.

## Funding

## Compliance with Ethical Standards

**Conflict of Interest**
Dr. Dellaripa reports involvement in a clinical trial funded by Genentech and a study funded by Bristol-Myers Squibb. Dr. Bolster reports clinical trial funding from Cumberland and Corbus; is a consultant to Gilead Sciences; and has stock ownership in Johnson and Johnson. Dr. Khanna is a consultant to Acceleron, Actelion, Amgen, Bayer, Boehringer Ingelheim, CSL Behring, Corbus, Galapagos, Genentech/Roche, GSK, Gilead, Horizon Merck, Mitsubishi Tanabe Pharma, Regeneron, Sanofi-Aventis, and United Therapeutics; and holds stocks in Eicos Sciences, Inc. Dr. Doyle reports research funding from Bristol-Myers Squibb and involvement in a clinical trial funded by Genentech and Bristol-Myers Squibb. Dr. Sparks reports research funding from Bristol-Myers Squibb and Amgen and consultancy to Bristol-Myers Squibb, Gilead, Inova, Janssen, and Optum.

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## References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:
•     Of importance
••    Of major importance

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