

# Overview of Rheumatoid Arthritis-Associated Interstitial Lung Disease and Its Treatment

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## Abstract

Interstitial lung disease (ILD) is a common pulmonary complication of rheumatoid arthritis (RA), causing significant morbidity and mortality. Optimal treatment for RA-ILD is not yet well defined. Reliable prognostic indicators are largely byproducts of prior ILD progression, including low or decreasing forced vital capacity and extensive or worsening fibrosis on imaging. In the absence of validated tools to predict treatment response, decisions about whether to initiate or augment treatment are instead based on clinical judgment. In general, treatment should be initiated in patients who are symptomatic, progressing, or at high risk of poor outcomes. Retrospective data suggest that mycophenolate mofetil, azathioprine, and rituximab are likely effective therapies for RA-ILD. Abatacept is also emerging as a potential first-line treatment option for patients with RA-ILD. Further, recent data demonstrate that immunosuppression may be beneficial even in patients with a usual interstitial pneumonia (UIP) pattern on imaging, suggesting that immunosuppression should be considered irrespective of imaging pattern. Recent randomized controlled trials have shown that antifibrotic medications, such as nintedanib and likely pirfenidone, slow forced vital capacity decline in RA-ILD. Consideration can be given to antifibrotic initiation in patients progressing despite immunosuppression, particularly in patients with a UIP pattern. Future research directions include developing tools to predict which patients will remain stable from patients who will progress, discriminating patients who will respond to treatment from nonresponders, and developing algorithms for starting immunosuppression, antifibrotics, or both as first-line therapies.

## Keywords

- ▶ rheumatoid arthritis
- ▶ interstitial lung disease
- ▶ usual interstitial pneumonia
- ▶ treatment
- ▶ management
- ▶ mycophenolate
- ▶ azathioprine
- ▶ rituximab
- ▶ abatacept

Rheumatoid arthritis (RA) is an autoimmune disease characterized by inflammatory arthritis that has a worldwide prevalence of <1%.<sup>1</sup> RA is linked to excess mortality, and respiratory conditions are important contributors, likely exceeding cardiovascular disease as an underlying cause of death in RA.<sup>2–4</sup> RA can lead to various pulmonary complications. The most common of these include interstitial lung disease (ILD) and airways disease, which can manifest as bronchiectasis and bronchiolitis.<sup>5–9</sup> Additional manifestations include rheumatoid nodules, pleural disease, and vasculitis, outlined in ▶ **Table 1**.<sup>10–12</sup>

Among the variety of pulmonary manifestations in RA, RA-associated ILD (RA-ILD) is the most common pulmonary manifestation and is most associated with increased morbidity and mortality.<sup>3,13,14</sup> In recent years, there have been several advancements in our understanding of RA-ILD treatment. Importantly, the first randomized controlled trial specific to RA-ILD was published.<sup>15</sup> Additionally, we now have large, multi-center studies examining treatment outcomes specific to patients with RA-ILD that help inform our treatment decision-making.<sup>16,17</sup> In this article, we present a timely review of

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**Table 1** Common pulmonary and thoracic manifestations of RA

	Pulmonary manifestation	Clinical signs and symptoms	Physiologic, radiologic, and/or pathologic manifestations	Treatment
Parenchymal involvement	Interstitial lung disease	Dyspnea, cough, fatigue	PFT: restriction and impaired diffusion HRCT: reticulation, ground glass opacities, traction bronchiectasis, and/or honeycombing, subcategorized into UIP, NSIP, OP, or HP patterns	Immunosuppression and consideration of antifibrotics
	Rheumatoid nodules	Dyspnea, cough, chest pain	HRCT: multiple subpleural/peripheral nodules on imaging FDG-PET with low-level metabolism Histopathology: necrotizing granulomas with central fibrinoid necrosis surrounded by palisading macrophages	Uncomplicated nodules require no specific therapy <sup>10</sup>
Airways involvement	Follicular bronchiolitis	Dyspnea	PFT: nonspecific—can be normal, restrictive, obstructive, or mixed HRCT: bronchiolar nodularity and bronchial wall thickening	Variable response to inhaled glucocorticoids and bronchodilators, oral corticosteroids, or other immunosuppressants; can consider macrolides <sup>3</sup>
	Constrictive bronchiolitis (obliterative bronchiolitis)	Dyspnea	PFT: airway obstruction HRCT: mosaic attenuation/air trapping and pulmonary nodules	Generally not responsive to prednisone and immunosuppressants <sup>6,7</sup>
	Bronchiectasis	Chronic cough and sputum production	PFT: obstruction, decreased FVC, and impaired diffusion HRCT: bronchial dilation, bronchial wall thickening, mucus impaction, mosaic attenuation/air trapping	Airway clearance, prophylactic antibiotics for frequent or severe infections. Risk/benefit consideration of immunosuppression <sup>8</sup>
	Cricoarytenoid arthropathy	Hoarseness, odynophonia and odynophagia, voice deficiency, stridor, and dyspnea	PFT: extra-thoracic obstruction HRCT: changes in joint space, density, ankylosis, erosion, subluxation, and soft tissue swelling Laryngoscopy: edema of the arytenoids and interarytenoid mucosa	Glucocorticoids locally into the cricoarytenoid joint or systemically; securement of the airway in the setting of airway obstruction; surgery as radical therapy <sup>9</sup>
Vascular disease	Rheumatoid vasculitis	Cutaneous vasculitis and vasculitic neuropathy, less commonly eye and pericardial involvement	Histopathology: mononuclear or neutrophilic infiltration of the small- and medium-sized vessel walls in association with features of vessel wall destruction (necrosis, leukocytoclasia, and disruption of the elastic laminae)	Immunosuppression, historically with high-dose glucocorticoids and cyclophosphamide <sup>11</sup>
Pleural disease	Pleural effusions and pleuritis	Dyspnea, pleuritic chest pain	Imaging: generally unilateral pleural effusion Cytology: exudative pleural effusion, low glucose, low pH, high RF titer with cytology showing elongated macrophages and multinucleated giant cells alongside granulomatous debris	Small and asymptomatic effusions generally resolve spontaneously; thoracentesis for symptomatic effusions; rarely corticosteroids and chest drainage for sterile empyematous exudate <sup>12</sup>

Abbreviations; FDG-PET/CT, fluorodeoxyglucose-positron emission tomography; FVC, forced vital capacity; HP, hypersensitivity pneumonitis; HRCT, high-resolution computed tomography; NSIP, nonspecific interstitial pneumonia; OP, organizing pneumonia; PFT, pulmonary function testing; RA, rheumatoid arthritis; UIP, usual interstitial pneumonia.

evidence informing RA-ILD therapies, offer our management approach, and pose critical research questions for the coming years.

## Diagnosis and Prognosis of RA-ILD

### Epidemiology and Risk Factors

ILD is an increasingly recognized complication of RA. Estimates of overall incidence within RA cohorts are variable, due to inconsistent diagnostic techniques and high rates of subclinical ILD. It is estimated that approximately 30% of patients with RA have subclinical ILD noted on high-resolution computed tomography (HRCT),<sup>18,19</sup> but clinically significant disease is present in approximately 10% of patients with RA.<sup>3</sup> The presence of ILD is associated with significant health care use and costs, as well as high morbidity and mortality in patients with RA.<sup>14,20–22</sup> Risk factors of RA-ILD development include

older age, male sex, smoking, and the presence of rheumatoid factor and anticyclic citrullinated peptide antibodies.<sup>23–28</sup> More recently, genetic risk factors have also been identified in RA-ILD, including the *MUC5B* promoter variant and various rare variants in telomerase.<sup>29,30</sup>

### Diagnosis and Screening

For a patient diagnosed with RA and experiencing pulmonary symptoms (e.g. dry cough and exertional dyspnea), HRCT of the chest is the cornerstone of ILD diagnosis. While pulmonary function testing may show restriction and chest radiography may show evidence of fibrosis, these modalities are not adequately sensitive for ILD diagnosis.<sup>31,32</sup> Further, though some recent work has demonstrated the promise of blood biomarkers in detecting ILD in patients with RA, these have yet to be validated for clinical use.<sup>24,33,34</sup> To achieve an accurate diagnosis of ILD, the detailed images afforded by HRCT are

essential in detecting and subcategorizing the pattern of pulmonary fibrosis. In some cases, ILD may precede the diagnosis of RA. Therefore, it is crucial for pulmonologists diagnosing ILD to thoroughly assess for articular signs and symptoms and incorporate serologic screening for RA. Timely and accurate diagnosis enables early collaboration between pulmonologists and rheumatologists. Additionally, the diagnosis of RA-ILD typically obviates the need for a surgical lung biopsy, as the histopathological pattern rarely impacts management when the clinical diagnosis of RA is already established.

In a patient with RA without pulmonary symptoms, screening for early signs of ILD is a nuanced decision. Screening should be considered after shared decision-making with the patient, considering the ILD risk factors as outlined above. As with diagnosis, HRCT is the modality of choice for ILD screening. Once an HRCT is obtained, RA-ILD can be subcategorized into various imaging patterns. Usual interstitial pneumonia (UIP), nonspecific interstitial pneumonia (NSIP), organizing pneumonia (OP), and patterns consistent with hypersensitivity pneumonitis (HP) can be seen in patients with RA.<sup>35</sup> UIP, characterized by honeycombing, traction bronchiectasis and reticulation, is most associated with the prototypic ILD idiopathic pulmonary fibrosis (IPF), but is found in about half of patients with RA-ILD.<sup>36</sup> Meanwhile, NSIP, characterized by bibasilar ground glass opacities, reticulation, and traction bronchiectasis, comprises smaller proportions of RA-ILD cases.

### Natural History and Prognosis

RA-ILD has a significant impact on survival. The risk of death for RA patients with ILD is higher than in patients without ILD, with RA-ILD patients experiencing increased death from pulmonary complications as well as all-cause mortality compared to RA patients without ILD.<sup>14,20</sup> Median survival in RA-ILD varies but has been reported to range from 2 years to 10 years depending on the population studied.<sup>14,28,37,38</sup> While death from RA is decreasing over time, reported trends of mortality rates from RA-ILD are mixed, with some studies reporting an increase in RA-ILD mortality among older patients.<sup>3,39</sup>

Lung function emerges as a consistent predictor of mortality in this population, with low forced vital capacity (FVC) and diffusing capacity (DLCO) portending worse survival in several cohorts.<sup>36–38,40,41</sup> Moreover, percent predicted FVC and DLCO constitute major components of the gender, age, physiology (GAP) model, a validated risk prediction model for mortality in ILD.<sup>42,43</sup> Morisset and colleagues found that the GAP model has good mortality prediction in patients with RA-ILD across four international academic centers, with a concordance index of 0.746.<sup>44</sup> Similar test performance characteristics were reported in the Mayo Clinic cohort, with a concordance index of 0.71.<sup>36</sup> Taken together, low FVC and DLCO signal worse survival.

The presence and extent of fibrosis also play a significant role in prognosis. The presence of fibrosis on histopathology portended a twofold risk of mortality in a group of 48 patients with RA-ILD confirmed by surgical lung biopsy.<sup>45</sup>

Similarly, fibrosis by visual assessment on HRCT is associated with worse survival, with extent of traction bronchiectasis and honeycombing as known predictors of mortality in RA-ILD.<sup>41</sup> Using a visual simple staging system of HRCT, ILD extent  $\geq 20\%$  was associated with a 3.78-fold increased risk of death in RA-ILD cohorts evaluated at the Royal Brompton Hospital and Edinburgh Royal.<sup>40</sup> Similarly, in a Korean cohort of 153 patients with RA-ILD, a visual scoring of fibrosis extent totaling  $\geq 20\%$  of total lung was associated with a 4.5-fold risk of death in multivariable analysis.<sup>46</sup> Further, radiomics, a technique that quantifies computed tomography imaging features, can be used to assess the extent of fibrosis in ILD, facilitating automated analysis to improve objectivity and reproducibility. Oh and colleagues applied a quantitative lung fibrosis score to HRCT images of 144 patients with RA-ILD and found that fibrotic extent predicted worse 5-year mortality. At a cutoff of 12% of total lung volume, higher quantitative lung fibrosis scores predicted survival similar to patients with IPF.<sup>47</sup>

With regard to HRCT pattern, it has been hypothesized that patients with RA and a UIP pattern may experience worse survival than those with an NSIP or indeterminate pattern. In 2010, Kim and colleagues reported that a UIP pattern was seen in 24% of patients with RA-ILD, and these patients showed worse survival, with a similar disease trajectory to patients with IPF.<sup>41</sup> Since then, multiple studies have found an association between a UIP pattern on HRCT and higher mortality.<sup>17,36,41,46</sup> In a retrospective cohort of 137 patients with RA-ILD whose baseline HRCT either showed an NSIP or UIP pattern, patients with a UIP pattern had shorter survival time than patients with NSIP.<sup>37</sup> However, in several multivariable models controlling for key confounders including baseline lung function, UIP was no longer independently associated with an increased risk of death.<sup>37</sup> Instead, baseline FVC and evidence of FVC decline were independent predictors of worse survival in these models. It remains unclear what additional prognostic information UIP pattern on HRCT provides in the clinical setting.

Further, evidence of worsening ILD reliably portends worse survival. A decline in FVC of 10% is a consistent predictor of death, associated with worse mortality in a retrospective RA-ILD cohort, as well as a large non-IPF ILD cohort consisting of 125 patients with RA-ILD.<sup>37,48</sup> In this non-IPF ILD cohort, radiologic progression of fibrosis, alone and in combination with symptomatic decline or physiologic decline, was also a strong predictor of subsequent FVC decline.<sup>49</sup>

Other clinical markers have been evaluated as prognostic markers in RA-ILD. In multivariable analyses, older age has been shown to be a consistent risk factor for death.<sup>37,40</sup> Male sex, lower socioeconomic status, higher disease activity score, and higher erythrocyte sedimentation rate value have been associated with worse survival, though these associations have been inconsistent across studies.<sup>40,50</sup> Taken together, the best prognostic markers for mortality are byproducts of progression and severity of fibrosis—evidence of worsening lung disease, low FVC and DLCO, and high fibrotic extent. It seems clear that patients who have experienced progression, either by physiology or imaging, are at higher risk of experiencing more progression and worse mortality.

## Treatment of RA-ILD

Currently, we have limited tools to predict treatment response in patients with RA-ILD. While we are unable to predict who will best respond to therapy, we can rely on the prognostic markers described above to offer treatment initiation or augmentation to the patients most likely to experience poor outcomes.

Immunosuppression is generally used as the mainstay of treatment for ILD complicating RA. The use of immunosuppression is primarily extrapolated from randomized controlled trials of patients with systemic sclerosis-associated ILD, which have shown that cyclophosphamide and mycophenolate mofetil (MMF) can improve lung function.<sup>51,52</sup> The data specific to RA-ILD treatment are primarily observational and retrospective in nature, though there has been one recent randomized controlled trial specific to RA-ILD suggesting antifibrotics may be of benefit.<sup>15</sup> Still, the optimal treatment strategy has not been well-defined. Here, we review the commonly used medications in RA-ILD and present data supporting their use as RA-ILD therapies.

### Immunosuppression

#### Corticosteroids

Corticosteroids are often the first used therapy in RA-ILD, though data supporting this approach are scarce. One retrospective study showed that in patients with RA with a UIP pattern, treatment with glucocorticoids alone or in combination with other immunosuppressant medications improved or stabilized disease in half of 84 patients.<sup>53</sup> In another cohort of 26 patients with connective tissue disease-associated ILD (CTD-ILD), 11 of whom had RA-ILD, two courses of pulse dose methylprednisolone therapy followed by 1 year of corticosteroids and tacrolimus were well-tolerated and led to significantly improved FVC and DLCO at 12 months.<sup>54</sup> Corticosteroids may be particularly effective in patients with an OP pattern on imaging, with one group reporting symptomatic and imaging resolution in 12 patients receiving glucocorticoids.<sup>55</sup> However, prolonged treatment with corticosteroids is discouraged given the toxic side effect profile, including the risk of infection and osteoporosis.<sup>56–58</sup> Corticosteroids, if needed, should ideally be used as a bridge to a steroid-sparing agent.

#### Mycophenolate Mofetil

MMF is a prodrug of mycophenolic acid, which decreases the synthesis of guanine nucleotides and reduces T and B lymphocyte proliferation and antibody formation.<sup>59</sup> Historically, MMF has been used for the treatment of RA-ILD, based on its efficacy in improving lung function in systemic sclerosis-associated ILD.<sup>51</sup> Two retrospective cohort studies have additionally shown that MMF stabilizes FVC in all-comers with CTD-ILD. In a retrospective cohort study of 125 patients with CTD-ILD treated with mycophenolate, 18 of whom had RA-ILD, patients showed significant improvements in percent predicted FVC after MMF initiation.<sup>60</sup> Similar findings were observed in a separate CTD-ILD cohort, where MMF was associated with FVC and DLCO stability.<sup>61</sup>

Recently, Matson et al conducted a multi-site, retrospective study with 212 patients with RA-ILD treated with either MMF, azathioprine, or rituximab.<sup>16</sup> All three treatments resulted in an improvement in FVC and DLCO when compared to the potential response that would have been observed based on the pretreatment trend. Patients receiving MMF, azathioprine, or rituximab had a 3.9% increase in percent predicted FVC and a 4.5% increase in percent predicted DLCO at 12 months, compared to the counterfactual change that would have been expected had treatment not been initiated. Additional data from 18 UK centers suggest that all-cause mortality tended to be lower among RA-ILD patients treated with MMF compared to anti-tumor necrosis factor therapies, though the numbers were small.<sup>39</sup>

However, it is crucial to note that MMF has not proven effective in addressing the inflammatory joint disease in RA. In fact, a randomized clinical trial was prematurely terminated when MMF was no better than placebo at improving the primary endpoint of the American College of Rheumatology 20% responder index (ACR20), which accounts for joint disease, global disease activity, and acute phase reactants.<sup>62</sup> Further, nearly 8% of patients treated with MMF in the Matson study needed additional therapy for progression of joint disease,<sup>16</sup> further underscoring MMF's lack of joint disease efficacy.

#### Azathioprine

Azathioprine is a pro-drug of 6-mercaptopurine that inhibits purine synthesis and is commonly used for RA-ILD.<sup>59</sup> In a retrospective, single-center cohort study of patients with CTD-ILD treated with azathioprine and MMF, the authors find that patients taking azathioprine had a significant yearly increase in FVC and DLCO.<sup>61</sup> However, these findings were limited to patients who could tolerate azathioprine. A higher proportion of patients discontinued azathioprine compared to MMF due to side effects. Similarly, in the multi-center, retrospective study described above, patients taking azathioprine experienced more side effects than patients taking MMF or rituximab and 13% had to stop azathioprine because of an adverse effect.<sup>16</sup> Azathioprine does appear to have some benefit for tender joints,<sup>63</sup> though 5.4% of patients taking azathioprine needed additional therapy for joint disease in this study.<sup>16</sup>

#### Rituximab

Rituximab is a monoclonal antibody against B-cell marker CD20, known to be efficacious in treating RA alone and in combination with other disease-modifying anti-rheumatic drugs (DMARDs).<sup>64</sup> Retrospective data suggest that it is also effective in treating RA-ILD. Several cohort studies have shown that RA-ILD patients treated with rituximab show lung function stability or improvement.<sup>16,65,66</sup> A registry study including 290 patients across 18 UK centers additionally showed that rituximab is associated with a 48% reduction in all-cause mortality compared to RA-ILD patients receiving antitumor necrosis factor therapies.<sup>39</sup>

Further supporting the use of rituximab is a recent trial evaluating combination rituximab and MMF in patients with

NSIP by biopsy or imaging.<sup>67</sup> Patients from 17 academic French centers with ILD refractory to immunosuppressive treatment were included, including three patients with RA-ILD. Rituximab and MMF led to a significant improvement in 6-month percent predicted FVC and progression-free survival compared to placebo and MMF. As expected, patients who received rituximab and MMF had more frequent infections.

### Abatacept

Abatacept is a soluble fusion protein that inhibits T-lymphocyte co-stimulation and is used in RA to treat joint disease, improve physical function, and reduce disease activity and pain.<sup>68</sup> Several case series and retrospective studies show that RA-ILD patients treated with abatacept experience stable or improved lung function and chest imaging while treated.<sup>69–71</sup> Large database studies suggest that patients treated with abatacept may have a lower incidence of ILD exacerbations compared to TNF inhibitors, but this did not reach statistical significance.<sup>72</sup> The most compelling data for abatacept come from a large multicenter observational study of 263 patients with RA-ILD treated with abatacept, finding stable or improved pulmonary function in 90% of patients and stable or improved radiologic appearance in 77% of patients over a 12-month time frame.<sup>73</sup> This was accompanied by a significant reduction in median glucocorticoid dose and significant improvement in joint disease activity. Eleven percent of patients had to discontinue abatacept due to an adverse event, the most common of which was serious infection. More evidence will guide the use of abatacept in the coming years, as there is a phase 2 study currently evaluating the effect of abatacept on lung function in RA-ILD (NCT03084419).

### Cyclophosphamide

Cyclophosphamide is an alkylating antineoplastic agent widely used for the treatment of cancer patients and rheumatologic diseases.<sup>74</sup> Its efficacy in improving lung function has been demonstrated in randomized controlled trials in systemic sclerosis-associated ILD,<sup>51,52</sup> and additionally, cyclophosphamide has been shown to treat tender or swollen joints in RA.<sup>75</sup> The data specific to RA-ILD are very limited. One retrospective study found that patients treated with cyclophosphamide had no worse mortality compared to other treatments, despite having worse baseline lung function.<sup>39</sup> Due to its serious toxicities including hemorrhagic cystitis, gonadal failure, and bladder malignancy, cyclophosphamide is not routinely used as first-line therapy in RA-ILD but can be considered in refractory disease. It is occasionally used for acute exacerbations, though we note that it has not been shown to show a survival benefit in patients with acute exacerbation of RA-ILD in propensity-matched analysis.<sup>76</sup>

### Other Immunosuppressant Therapies

In addition to the aforementioned treatments, various therapies employed for RA are being explored for their potential effectiveness in managing RA-ILD. Among these, tocilizumab, a humanized anti-interleukin 6 antibody, and Janus kinase (JAK) inhibitors show promise.<sup>77,78</sup> Still, the available

data on their efficacy in RA-ILD are limited and warrant further investigation. Ongoing research includes a phase 4 study underway to compare the JAK-inhibitor tofacitinib with methotrexate treatment (NCT04311567). This study aims to evaluate the efficacy and safety of tofacitinib in both subclinical and clinical RA-ILD.

## Antifibrotics

### Nintedanib

Nintedanib is a tyrosine kinase inhibitor that has been shown to slow FVC decline in patients with IPF.<sup>79</sup> Recently, the INBUILD trial evaluated the effect of nintedanib in patients with non-IPF ILD who showed evidence of ILD progression in the 24 months prior to enrollment despite usual care.<sup>80</sup> More than a quarter of these patients had autoimmune ILD, including 98 patients with RA. Post-hoc analyses from the INBUILD trial showed that the effect of nintedanib on reducing the rate of FVC decline was consistent across ILD subgroups and autoimmune subtypes, with a difference in annual FVC change of 118.2 mL/year favoring nintedanib over placebo within the RA-ILD subgroup.<sup>81</sup> It should be noted that the INBUILD trial did not allow background immunosuppression—excluding patients treated with azathioprine, MMF, rituximab, cyclophosphamide, or glucocorticoids. Consequently, it is challenging to know whether nintedanib would augment immunosuppressive therapy for patients with RA-ILD. Extrapolating from the SENSICIS trial, which allowed background immunosuppression and demonstrated that nintedanib slowed FVC decline in patients with systemic sclerosis associated ILD,<sup>82</sup> it seems plausible that nintedanib similarly slows decline in patients with RA-ILD who are progressive despite concurrent immunosuppression.

### Pirfenidone

Pirfenidone is the other antifibrotic approved for treatment of IPF after randomized trials demonstrated its efficacy in reducing the rate of FVC decline.<sup>83,84</sup> Trials evaluating pirfenidone in progressive non-IPF ILD have suffered from poor enrollment and issues with home spirometry monitoring, but the data suggest that pirfenidone is also effective in slowing FVC decline in non-IPF ILD.<sup>85,86</sup> In the first randomized, double-blind, placebo-controlled trial of patients with RA-ILD, the TRAIL1 Network investigators sought to examine the effect of pirfenidone on the progression of lung disease in patients with RA-ILD.<sup>15</sup> Patients from 34 academic ILD centers with at least 10% lung fibrosis and restrictive physiology were included. Patients could not have started or had a dose alteration of corticosteroids or immunosuppression within 3 months of screening. Unfortunately, the trial was stopped early due to slow recruitment and there was no significant difference found in the composite primary endpoint (10% decline in percent predicted FVC or death) between the pirfenidone and placebo groups. However, the investigators did find a slower rate of FVC decline over 52 weeks in the patients receiving pirfenidone as compared to placebo (–66 mL vs. –146 mL). Interestingly, this effect was observed in patients with a UIP HRCT pattern, but the effect on FVC change was not seen in patients without a UIP pattern.



### Consideration of Methotrexate in the Setting of RA-ILD

Distinct from the discussion of RA-ILD treatments, we now turn our attention to an important clinical question of whether to continue DMARDs in the setting of fibrotic ILD. While it is thought that nearly all antirheumatic drugs can worsen ILD, methotrexate stands out as particularly notorious for inducing and worsening ILD. In this context, we examine the evidence supporting the safety of continuing methotrexate in a patient with RA-ILD.

Methotrexate is the preferred first-line disease modifying antirheumatic drug in RA management, effectively reducing disease activity, morbidity, and mortality.<sup>87,88</sup> It is well characterized that methotrexate can induce subacute HP with an incidence of about 1%.<sup>89</sup> This presents as dry cough, dyspnea, and fever, has a median time from drug initiation of 9 months, and is characterized by diffuse ground glass opacities on imaging.<sup>90</sup> Treatment of methotrexate-induced HP involves drug discontinuation, glucocorticoids, and avoidance of future methotrexate exposure.

This is in contrast to the issue of whether methotrexate causes or worsens fibrotic ILD in patients with RA. It has long been disputed that methotrexate exposure causes fibrotic ILD, and clinicians are often concerned about starting or maintaining methotrexate in patients with RA-ILD. The most compelling data to answer this question come from a recent large, retrospective study with systematic evaluation of chest HRCT and methotrexate exposure in 410 patients with RA-ILD and 673 patients with RA and no ILD.<sup>91</sup> Juge and colleagues found that the frequency of methotrexate use was lower in RA-ILD patients compared to RA patients without ILD. In other words, patients who were taking methotrexate for their RA were less likely to have ILD than those who were not taking methotrexate. Additionally, ILD detection by HRCT was delayed by 3.6 years in patients exposed to methotrexate as compared to never exposed patients. While this does not prove causality, this suggests that methotrexate exposure may be protective in RA-ILD. The retrospective nature of this study makes it susceptible to confounding by indication—it is conceivable that physicians may have prescribed methotrexate less frequently to patients with respiratory symptoms or signs suspicious of ILD not captured in the study. One way around this is to restrict analysis to incident cases of ILD, which has been done in one prospective study. Kiely et al found that methotrexate was not associated with incident RA-ILD.<sup>92</sup> They also found a trend toward delayed ILD onset in patients exposed to methotrexate. Based on these studies, in a patient whose joint manifestations are treated well with methotrexate, there is no convincing evidence that methotrexate needs to be discontinued in the setting of fibrotic ILD.

## Therapeutic Approach

### Initiating Treatment for RA-ILD

Unfortunately, there are no clinical practice guidelines regarding when to initiate pharmacologic treatment for RA-ILD, leaving the clinician to weigh the risks and benefits of prescribing treatment for RA-ILD (►Fig. 1). Most would

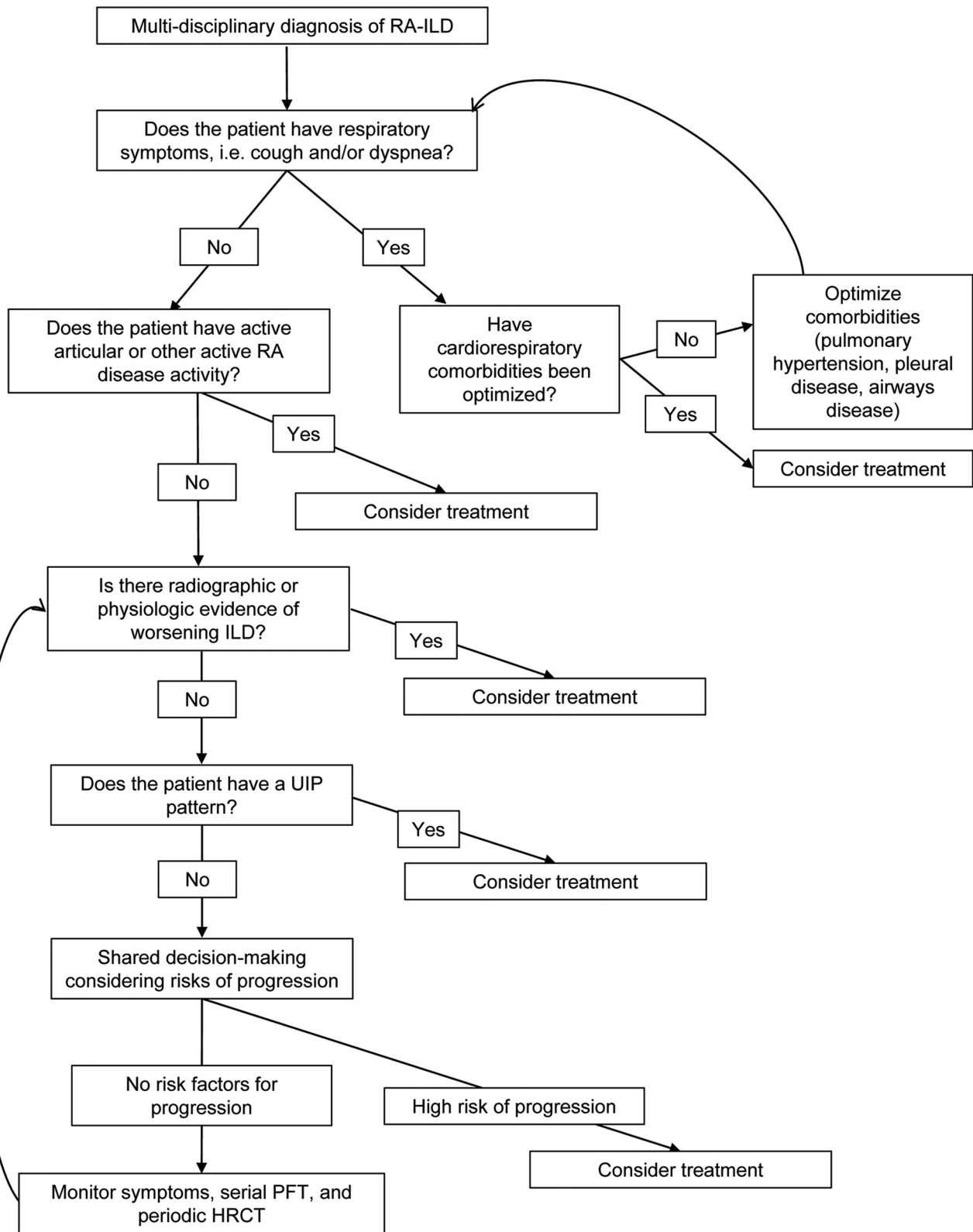
agree that a patient experiencing symptoms of dyspnea and/or cough due to RA-ILD should be offered treatment. Additionally, for RA patients with ILD who have extrapulmonary indications for treatment, such as active articular disease, discussion between rheumatologists and pulmonologists should remain standard of care and preference should be given to a medication that also targets the lung disease. Lastly, we consider patients who have demonstrated prior evidence of ILD progression to be at risk of further progression and recommend treatment in this group.

The decision to initiate treatment becomes more ambiguous when approaching an asymptomatic or stable patient. We simply do not yet have tools to predict treatment response in RA-ILD—that is, we cannot predict which patients will improve on treatment from those who will progress despite treatment. As a surrogate to treatment prediction, we consider risk factors of progressive disease, with the rationale that patients most likely to experience lung function decline and death are also likely to benefit from treatment. For patients with demographic risk factors for progressive disease, including older age, we recommend shared decision-making regarding initiating treatment versus close monitoring. Similarly, as discussed above, patients with low or decreasing FVC and DLCO and extensive or worsening fibrosis, including those with a UIP pattern on HRCT, are likely to benefit from early initiation of treatment.

### Choice of Treatment

Once the decision has been made to initiate therapy, the question becomes whether to start immunosuppression or antifibrotic as first-line therapy. We highlight that, in general, immunosuppressants have been shown to improve or stabilize lung function in RA-ILD. Contrastingly, antifibrotics do not reverse disease or improve symptoms but have instead been shown to slow lung function decline. Given the potential to improve lung function, immunosuppressant therapy should be considered as first-line therapy in RA-ILD.

Next, the question arises whether radiologic pattern should influence first-line therapy—specifically, if immunosuppression should be avoided in patients with a UIP pattern. UIP is most associated with IPF, the prototypic ILD for which it has been shown that a combination of prednisone, azathioprine, and *N*-acetylcysteine leads to increased mortality.<sup>93</sup> This has led to the concern that patients with RA and a UIP pattern share biologic and mechanistic similarities with IPF that would predispose them to similar harm. In the retrospective study comparing azathioprine and MMF in patients with CTD-ILD, patients taking azathioprine were not found to have an increased rate of adverse outcomes compared to patients taking MMF, even when analyses were restricted to patients with a UIP pattern.<sup>61</sup> These data were corroborated by the large multi-site study of 212 patients with RA-ILD treated with azathioprine, MMF, and rituximab, where Matson and colleagues found no impact of radiologic UIP on the effect of immunosuppression on lung function.<sup>16</sup> These data justify the use of immunosuppression as first-line therapy in patients with RA-ILD, irrespective of HRCT pattern.



**Fig. 1** Our approach to initiating treatment for RA-ILD. We suggest treatment for symptomatic patients and patients with progressive RA-ILD. Risk factors for progression and UIP pattern are considered in shared decision-making regarding when to initiate treatment. HRCT, high-resolution computed tomography; ILD, interstitial lung disease; PFT, pulmonary function testing; RA, rheumatoid arthritis; UIP, usual interstitial pneumonia.

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**Table 2** RA-ILD treatment

Treatment	Mechanism	Route and dosing	ILD outcomes (number of RA-ILD patients)	Treats joints	Side effects
Mycophenolate mofetil	Decreases synthesis of guanine nucleotides and reduces T and B lymphocyte proliferation and antibody formation	Oral: 1.0–1.5 g twice daily	Single-center cohort: FVC and DLCO stability ( $n = 18$ ) <sup>60</sup> Single-center cohort: FVC and DLCO stability ( $n = 43$ ) <sup>61</sup> Multi-center cohort: FVC and DLCO improvement ( $n = 77$ ) <sup>16</sup>	No <sup>62</sup>	GI upset, cytopenia, recurrent infections, elevated liver enzymes
Azathioprine	Pro-drug of 6-mercaptopurine; inhibits purine synthesis	Oral 1.5–2 mg/kg IBW once daily, not to exceed 200 mg/day	Single-center cohort: FVC and DLCO improvement ( $n = 54$ ) <sup>61</sup> Multi-center cohort: FVC and DLCO improvement ( $n = 92$ ) <sup>16</sup>	Yes <sup>63</sup>	GI upset, elevated liver enzymes, cytopenia, recurrent infections
Rituximab	Anti-CD20 antibody	IV 1 g once every 2 weeks for 2 doses, repeat every 24 weeks	Multi-center cohort: FVC and DLCO improvement ( $n = 43$ ) <sup>16</sup> RCT: progression-free survival benefit ( $n = 3$ ) <sup>67</sup>	Yes <sup>94</sup>	GI upset, cytopenia, recurrent infections
Abatacept	T-lymphocyte costimulatory inhibitor	SQ: 125 mg once weekly or IV: 500 mg to 1 g every 4 weeks	Multi-center cohort: FVC and DLCO stability, HRCT stability ( $n = 263$ ) <sup>73</sup>	Yes <sup>68,73</sup>	Recurrent or serious infections, cutaneous infusion reaction
Nintedanib	Tyrosine kinase inhibitor	Oral: 150 mg twice daily	RCT: slow FVC decline ( $n = 89$ ) <sup>80,81</sup>	No	Diarrhea, nausea, vomiting, decreased appetite, elevated liver enzymes, weight loss
Pirfenidone	Suppresses TGF- $\beta$ 1, modulates fibrogenic growth factors, and downregulates inflammatory pathways <sup>100</sup>	Oral: 801 mg 3 times daily	RCT: slow FVC decline ( $n = 231$ ) <sup>15</sup>	No	Nausea, headache, anorexia

Abbreviations; DLCO, diffusing capacity for carbon monoxide; FVC, forced vital capacity; ILD, interstitial lung disease; IV, intravenous; RA, rheumatoid arthritis; RCT, randomized controlled trial; SQ, subcutaneous; IBW, ideal body weight.

With regard to which immunosuppressant to start, the most commonly used agents for RA-ILD are MMF, azathioprine, and rituximab.<sup>16,17</sup> These are reasonable first-line therapies, as all three are associated with improved pulmonary function at 1 year compared to pretreatment pulmonary function trend with no significant difference between treatment choice, based on retrospective data.<sup>16</sup> We also find that reasonable evidence exists to support using abatacept as first-line in RA-ILD, particularly for patients with a high articular burden. Several additional considerations exist in the choice of up-front therapy (–Table 2 and –Fig. 2). MMF does not improve articular symptoms, so a patient with RA-ILD and joint symptoms would need an additional DMARD if prescribed MMF. Azathioprine may have some efficacy in treating joint disease,<sup>63</sup> while rituximab or abatacept has consistently documented efficacy in treating articular disease in RA.<sup>68,73,94</sup> Route of administration should also be a consideration, as patients may prefer the oral route of MMF or azathioprine. We note that azathioprine is less tolerated than MMF, with more side effects and higher rates of drug discontinuation. In patients for whom adherence to a daily or twice-daily drug may pose a problem, rituximab is typically administered every 6 months and abatacept can be administered monthly. Of course, patient preferences and values should be considered for every clinical decision.

### Additional Therapy

After initiating therapy, patients should undergo serial pulmonary function testing every 3 to 6 months. Worsening FVC or DLCO, or worsening symptoms of dyspnea or cough, should prompt HRCT to confirm worsening ILD. Unfortunately, a subset of patients with RA-ILD will continue to progress

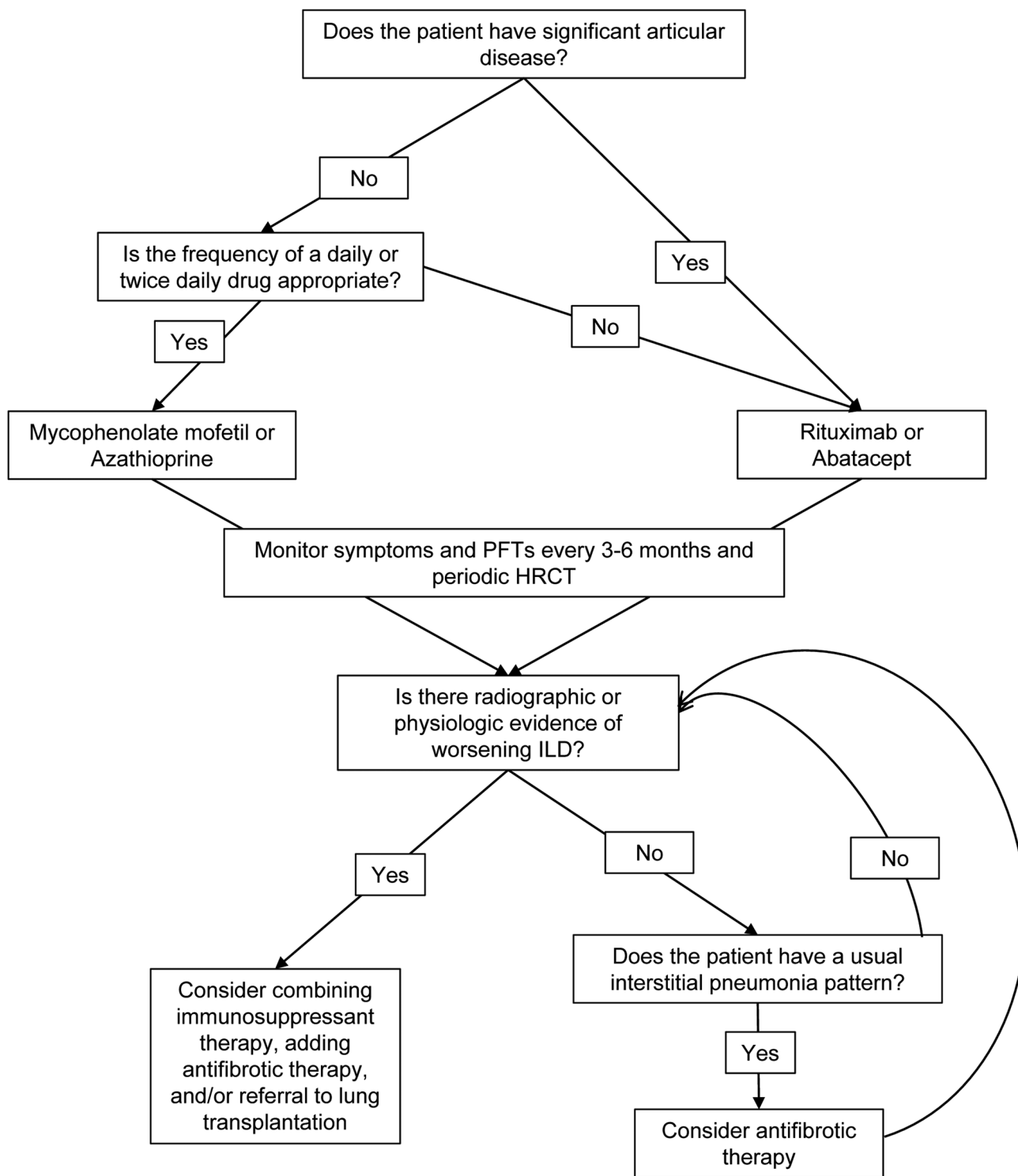
despite immunosuppressant therapy. Based on the INBUILD trial showing nintedanib slows decline in progressive disease<sup>80</sup> and the TRAIL1 trial showing the effect of pirfenidone on the decline in FVC was more pronounced in patients with radiologic UIP,<sup>15</sup> consideration of antifibrotic therapy is warranted in a patient progressing despite immunosuppressant therapy, particularly among those with a UIP pattern.

Further, there is no guidance regarding switching or adding immunosuppressant therapy for progressive RA-ILD, though this is common in clinical practice. After switching between MMF, azathioprine, rituximab, and/or abatacept, if a patient is still showing lung progression, combination immunosuppression may be considered after shared decision-making between the patient, pulmonologist, and rheumatologist. This is done with careful consideration of the risk of severe infection in combining immunosuppressive medications. One additional thought at this point is whether the patient is a lung transplant candidate, as this may preclude the use of certain medications in the peri-transplant period.<sup>95</sup>

### Nonpharmacologic Therapy

Pulmonary rehabilitation, particularly in patients with poor functional status, is likely to lead to improvements in functional exercise capacity, dyspnea, and quality of life in patients with ILD.<sup>96</sup> In addition, while there is no convincing evidence for the use of supplemental oxygen in patients with ILD, most experts agree that oxygen should be offered for patients with severe resting hypoxemia and exertional desaturation, particularly with attributable symptoms or exercise limitation.<sup>97,98</sup> Lastly,





**Fig. 2** Treatment medication choices. Immunosuppressants are considered first-line therapy in RA-ILD, with mycophenolate mofetil, azathioprine, and rituximab consistently shown to improve lung function in RA-ILD in observational studies. Evidence also supports abatacept as a treatment choice, particularly for patients with high articular burden. HRCT, high-resolution computed tomography; ILD, interstitial lung disease; PFT, pulmonary function testing.

lung transplantation results in similar survival rates at 1-year posttransplant in patients with RA-ILD as compared to patients with IPF and systemic sclerosis-associated ILD. Lung transplantation has also been shown to improve quality-of-life scores and dyspnea in those with RA-ILD<sup>99</sup>

### Future Directions and Unmet Research Needs

While there have been strides made in the management of RA, unmet needs remain in the treatment and management of RA-ILD. One pivotal question revolves around the timing of initiating ILD treatment. Accurately predicting which

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patients will maintain disease stability without therapeutic intervention is crucial, as it would allow for close monitoring instead of subjecting these patients to potential side effects of unnecessary medications. Conversely, identifying patients at risk of near-term progression and death is imperative to facilitate informed discussions between patients and clinicians about the initiation of treatment. Notably, the most reliable prognostic indicators are byproducts of severe and/or progressive fibrosis—low lung function, fibrotic extent on imaging, and evidence of worsening disease by physiology and/or imaging. Relying on these prognostic indicators leaves clinicians waiting for overt signs of fibrotic progression before initiating treatment.

Next, an important aspect of RA-ILD management lies in distinguishing patients who will rapidly progress despite treatment from those who will stabilize or improve with treatment. Predicting nonresponders to treatment will be pivotal for tailoring individual patient care, allowing for earlier consideration of combination therapies and timelier referral to lung transplantation. Beyond patient care, identifying nonresponders will optimize clinical trial design through trial enrichment. It will be through randomized trials that we will understand which medications should constitute first-line therapy.

Further, to tailor treatment with a personalized approach, we need to understand which groups of patients with RA-ILD will most likely benefit from immunosuppression, antifibrotics, or a combination of both as the initial therapeutic strategy. Without validated markers to discern between these groups, we currently reach for immunosuppression as first-line given its potential to improve lung function. The ability to predict treatment response will allow for better care of patients with RA-ILD, allowing us to refine our treatment strategies and improve our understanding of this complex disease.

## Conclusion

RA-ILD is a devastating condition, marked by considerable morbidity and mortality. In the absence of validated predictors of treatment response, prognostic markers currently serve as surrogates in deciding when to initiate therapy. Immunosuppression should be considered for RA-ILD, given its potential to improve lung function, even in patients with a UIP pattern. The evidence base, largely based on retrospective observation, supports the use of MMF, azathioprine, and rituximab for RA-ILD. Abatacept is also emerging as an option for RA-ILD treatment. Recognizing that patients may progress despite immunosuppression alone, the addition of antifibrotics should be considered, particularly for patients who progress despite immunosuppression and those with a UIP pattern. This combination holds potential to address the interplay between inflammatory and fibrotic processes. Further research is needed to address several clinical uncertainties. Efforts should focus on developing tools to predict patients who will remain stable from patients who will progress, treatment responders

from nonresponders, and the patients most likely to benefit from immunosuppression and/or antifibrotic therapy.

## Conflicts of Interest

J.V.P. reports no conflicts. J.S.L. reports receiving grants from the NIH and Boehringer Ingelheim, an unrestricted research gift from Pliant, and consulting fees from Blade, Boehringer Ingelheim, United Therapeutics, AstraZeneca, and Eleven P15, outside the submitted work. J.S.L. is/has been on the DSMB for United Therapeutics and Avalyn and is an advisor for the Pulmonary Fibrosis Foundation, outside the submitted work.

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