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Identification, monitoring and management of rheumatoid arthritis-associated interstitial lung disease

Running head: Identification, monitoring and management of RA-ILD

Disease category: Rheumatoid arthritis

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Abstract

Interstitial lung disease (ILD) is a frequent complication of rheumatoid arthritis (RA) that is associated with a significant increase in mortality. Several risk factors for the development of ILD in patients with RA have been identified, but ILD can still develop in the absence of these risk factors. Screening tools for RA-ILD are required to facilitate early detection of RA-ILD. Close monitoring of patients with RA-ILD for progression is crucial to enable timely implementation of treatment strategies to improve outcomes. Patients with RA are commonly treated with immunomodulatory therapies, although their efficacy in slowing the progression of RA-ILD remains the subject of debate. Clinical trials have shown that antifibrotic therapies slow decline in lung function in patients with progressive fibrosing ILDs, including patients with RA-ILD. The management of patients with RA-ILD should be based on multidisciplinary evaluation of the severity and progression of their ILD and the activity of their articular disease. Close collaboration between rheumatologists and pulmonologists is essential to optimize patient care.

Key words: interstitial lung disease, outcome measures, pulmonary, rheumatoid arthritis

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Introduction

Interstitial lung disease (ILD) is a frequent but under-recognized complication of rheumatoid arthritis (RA) associated with significant morbidity and mortality (1-6). ILD can occur at any point in the course of RA. The most common patterns evident on high-resolution computed tomography (HRCT) or histology are usual interstitial pneumonia (UIP) and non-specific interstitial pneumonia (NSIP) (4,7). The clinical course of RA-ILD is variable (8-10). Some patients with RA-ILD develop progressive pulmonary fibrosis (PPF), characterized by an increasing extent of fibrotic abnormalities on HRCT, decline in lung function, worsening symptoms, and premature mortality (9-13). Although RA-ILD may have a substantial impact on prognosis, there are insufficient data to inform evidence-based recommendations on screening and monitoring. In this review, we discuss the impact of ILD in patients with RA and strategies for its detection, monitoring and management.

Prevalence and risk factors for RA-ILD

The reported prevalence of RA-ILD ranges between 10% and 61% depending on the definition used (2,14-26). Symptomatic or clinically significant ILD (based on abnormal HRCT findings, abnormalities in pulmonary function tests [PFTs] and premature mortality) has been reported in 10% to 18% of patients with RA (2,14,17,21,25). Risk factors for the development of RA-ILD include older age, male sex, tobacco exposure, active synovitis, seropositivity for rheumatoid / anti-cyclic citrullinated peptide, and polymorphisms in MUC5B (1,7,23,26-33). However, patients with RA who lack these established risk factors can still develop ILD.

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Diagnosis of RA-ILD

Evaluation for suspected RA-ILD typically includes PFTs, imaging, and sometimes bronchoalveolar lavage. The gold standard for the diagnosis of ILD is an HRCT scan. HRCT is not only useful to characterize the pattern and severity of ILD, but also to exclude alternative diagnoses such as infection, drug-induced pulmonary toxicity and malignancy. UIP, the most common pattern, has features of fibrosis including reticulation, traction bronchiectasis and honeycombing. NSIP is less common and has reticulation along with predominately inflammatory features, such as ground-glass opacities (34,35). Other patterns, such as organizing pneumonia, are also seen (4,9,24,27). As a UIP pattern on HRCT predicts underlying histopathology (36), surgical lung biopsy is usually reserved for patients with atypical patterns on HRCT (e.g., asymmetric disease, nodules/cavitation).

Screening for RA-ILD

Early detection and assessment of RA-ILD are important to enable timely initiation of treatment. Patients may already have severely impaired lung function by the time RA-ILD is diagnosed. A seminal study conducted in 167 patients found that at the time of diagnosis, 14% of patients with RA-ILD had a forced vital capacity (FVC) <50% predicted and 29% had a diffusing capacity of the lungs for carbon monoxide (DLco) <40% predicted (11). A recent study found that a delay in the diagnosis of RA-ILD was associated with increased mortality (37). However, there is no consensus as to which patients with RA should be screened for ILD and no published guidelines for screening.

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Rheumatologists have a key role to play in screening patients with RA for ILD. All patients with RA should be screened for symptoms of lung involvement (i.e., exertional breathlessness, dry cough) and have lung auscultation at every clinic visit. Rheumatologists should have a low threshold to image patients with new or progressive respiratory symptoms and should image all patients with abnormal findings on chest auscultation such as "Velcro" crackles (38). Abnormalities on imaging should prompt referral to a pulmonologist, preferentially one specializing in ILD.

Although dyspnea and cough may develop in patients with RA-ILD (16), some patients remain asymptomatic (17,39,40). In addition, joint disease may limit mobility and mask findings of breathlessness with exertion. This means that limiting screening to symptomatic patients would result in a significant proportion of cases being missed. However, a recent international survey of 354 rheumatologists found that 44% did not think screening was necessary in patients with RA who had risk factors for ILD but no respiratory symptoms (41).

Screening based only on PFTs would also result in cases of RA-ILD being missed, as many patients with RA-ILD on HRCT have an FVC % predicted that is close to normal (42,43). Chest X-ray has poor sensitivity and specificity for ILD. HRCT is the gold standard for screening for ILD, but it is not feasible that all patients with RA-ILD can undergo HRCT, nor that HRCT could be repeated at frequent intervals. In addition, HRCT may detect interstitial abnormalities, in the absence of symptoms, which are of

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unclear clinical significance. There is an increasing body of evidence that lung ultrasound could be a useful tool to detect the presence of ILD (44-46) and to improve the timing of HRCT to avoid exposing patients to high radiation doses over time. Early screening for ILD is one of the settings in which ultrasound might be used (46,47), but confirmation of the sensitivity of ultrasound to detect ILD in a large cohort of patients with RA is needed and it cannot be regarded as a replacement for HRCT.

Rheumatologists should have a high index of suspicion for lung involvement in patients with risk factors (38,48). Several screening tools for RA-ILD, based on risk factors, have been developed but all require further validation. Compared with HRCT, a predictive score based on sex, age at RA onset, RA disease activity score using 28 joints with erythrocyte sedimentation rate (DAS28-ESR) score and the MUC5B rs35705950 risk allele had 75% sensitivity and 85% specificity for identifying RA-ILD (15), but this tool may be difficult to apply in clinical practice. A risk score based on sex, smoking status, extra-articular manifestations, a clinical disease activity index score and ESR had 90% sensitivity and 64% specificity for identifying RA-ILD (49). A model based on sex, smoking status, rheumatoid factor, C-reactive protein and matrix metalloproteinase-3 had a C-index of 0.826 for accuracy to detect RA-ILD compared with assessment by multidisciplinary team (50). A Delphi panel in Spain proposed screening for ILD in patients with RA with normal auscultation and without respiratory symptoms using a risk score based on sex, smoking status, age, RA duration, family history of ILD, rheumatoid factor or anti-cyclic citrullinated protein antibodies, and DAS28-ESR (51). The VECTOR algorithm, which detects the presence of “Velcro” crackles in sounds recorded by an

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electronic stethoscope, reported 93% sensitivity and 77% specificity for identifying ILD on HRCT in patients with RA (52), but such equipment is not widely available. The ideal screening tool will be one that is easy to use in a clinic setting, applicable in areas with limited resources and directs those with the highest risk of ILD towards HRCT. An ongoing multi-national cross-sectional study, ANCHOR-RA, will develop a multivariable model for predicting the presence of RA-ILD on HRCT, based on risk factors, which might facilitate screening for RA-ILD in clinical practice.

Clinical course and prognosis of RA-ILD

RA-ILD has a variable course (43). Lung function remains stable or even improves after diagnosis in some patients, while others experience decline that is often slow but can be rapid (Figure 1). RA-ILD is associated with a significant increase in mortality (1-3,9,53,54). In a US study of 582 patients, the risk of death over the follow-up period was almost 3-fold greater in patients with RA-ILD than in patients with RA alone (hazard ratio: 2.86 [95% CI: 1.98, 4.12]) (1). In a prospective population-based study of 679 patients with RA-ILD and 11,722 matched patients with RA and no ILD, 10-year mortality was 60.1% (95% CI: 52.9, 66.5) in the patients with RA-ILD compared to 34.5% (95% CI: 32.8, 36.1) in the patients with RA and no ILD (Figure 2) (3). Based on insurance claims from over 500,000 patients with RA in the USA, the hazard ratio for mortality was 1.66 (95% CI: 1.60, 1.72) in patients with RA-ILD compared to those with RA alone, after adjusting for age, sex, smoking history, comorbidities, and immunosuppressive therapy (54). Some studies have reported that mortality in patients

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with RA-ILD and a UIP pattern is as poor as in patients with idiopathic pulmonary fibrosis (IPF) (55,56).

Lower FVC and DLco (4, 9,11,57,58) and their decline over 6 months (11) are associated with greater severity of RA-ILD. A DLco <54% predicted has shown 80% sensitivity and 93% specificity for predicting a significant deterioration in PFTs with increased extent of ILD on HRCT, or death as a result of respiratory failure, over two years in patients with RA-ILD (59). Older age, male sex, higher DAS28 score, a UIP pattern or a greater extent of ILD on HRCT, and elevated blood levels of KL-6, rheumatoid factor, or anti-cyclic citrullinated peptide have also been shown in various studies to be predictors of RA-ILD progression (4,10,11,27,35,40,43,55,57,58,60-64). Models based on demographic factors, clinical characteristics, and HRCT features have shown potential for predicting mortality. The GAP model, based on age, sex and % predicted values for FVC and DLco, appears to predict mortality with similar accuracy in patients with RA-ILD as in those with IPF, the population in which it was developed (65). A risk prediction model developed using age ≥60 years and HRCT variables (extent of fibrosis ≥20%, UIP pattern, emphysema) performed well in predicting 5-year mortality in patients with RA-ILD (66). However, at present, it is not possible to make an accurate prediction of the course of RA-ILD in an individual patient.

Monitoring of RA-ILD

Monitoring patients with RA-ILD is essential to ensure prompt identification of patients whose ILD is progressing. In practice, this monitoring is conducted mainly by

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rheumatologists at the patient's regular clinic visits. Although there is no consensus on how patients with RA-ILD should be monitored, a reasonable approach is to query about new or progressive respiratory symptoms at every clinic visit, measure FVC and DLco every 3 to 6 months and perform an HRCT yearly (or earlier if there is worsening of symptoms or physiology).

Follow-up HRCT may be useful in detecting progression of ILD, as well as evaluate for complications such as pulmonary hypertension and neoplasms that can have an impact on survival. However, many issues with HRCT scans in RA-ILD have yet to be resolved, including interobserver variation in the interpretation of scans and determining the optimum time interval for follow-up HRCT. There is increasing interest in automated quantification of computed tomography (CT) scans to assess the severity and progression of ILD. Among patients with connective tissue disease-associated ILDs (CTD-ILDs), the extent of fibrosis, extent of reticulation, and pulmonary vessel volume derived using computer-based CT assessment are predictive of mortality (67,68). Other quantitative lung fibrosis scores, based on data-driven textual analysis, have been shown to correlate with changes in lung function in patients with systemic sclerosis-associated ILD (69), but have not been assessed in patients with RA-ILD. A retrospective study of quantitative lung densitometry in individuals with RA demonstrated that the percentage of lung parenchyma with high attenuation areas was linked to several risk factors for RA-ILD (70). However, this study was performed on cardiac CT scan images, which could have missed very early ILD changes and its findings require validation in prospective studies.

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PFTs, particularly FVC and DLco, are the measures most commonly used to evaluate longitudinal changes in patients with RA-ILD and are typically obtained at 3–6-month intervals. PFTs have several limitations. They are effort-dependent and patients with chest muscle weakness or costochondritis may not be able to perform them accurately. The presence of emphysema (which increases measures of lung volume) may impair the ability of PFTs to measure the severity or progression of ILD (71). However, in patients with moderate to severe lung disease, clinical symptoms and PFTs may be more sensitive than HRCT to detect subtle worsening. While the exact roles of HRCT and PFTs is not clear, these modalities are complementary and both are important in the follow-up of patients with RA-ILD.

Management of RA-ILD

While recommendations to guide the management of patients with RA-ILD have been published (72,73), there are currently no guidelines from international scientific societies relating specifically to the initiation or escalation of treatment in patients with RA-ILD. It remains unclear when treatment for RA-ILD should be initiated to alter the course of the disease and whether biologic therapy alters the rate of progression of RA-ILD or outcomes. Therapy for RA-ILD should be individualized to the needs of the patient based on multidisciplinary evaluation of the severity and progression of their ILD, articular disease and other manifestations of RA, and comorbidities. HRCT findings may also be relevant, as inflammatory disease likely responds better to anti-inflammatory/immunosuppressive therapy than fibrotic disease. We present a proposed

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management algorithm in Table 1. Close collaboration between rheumatologists and pulmonologists is essential. Quiescent joint disease should not lead rheumatologists to complacency in the management of ILD as patients may have PPF in the setting of mild RA.

A decline in lung function, increased fibrosis on HRCT, and/or a worsening of respiratory symptoms with no other cause are generally considered evidence of PPF (13,74). A strong case can be made for treating PPF, given its poor prognosis and the recognition that any loss of lung function from progressive fibrosis is irreversible (38,48,75). A clinical practice guideline published by ATS/ERS/JRS/ALAT in May 2022 provided criteria for the definition of PPF (13), but these were not based on robust data and an evidence-based definition has yet to be established. While a UIP pattern on HRCT has been associated with a worse prognosis in patients with RA-ILD (10,62), this pattern may not be predictive in the setting of progressive decline in pulmonary function (58).

Some studies have raised concerns about a link between the use of certain biologics or disease-modifying antirheumatic drugs (DMARDs) and worsening of RA-ILD, or the development of hypersensitivity pneumonitis or lung injury (76-78). These studies did not establish a causal effect but led to unease in using these therapies to treat patients with RA-ILD. Concerns over lung injury have been greatest for methotrexate. However, there is evidence to suggest that methotrexate may actually slow the progression of RA-ILD (79-81). In a retrospective analysis of 40 patients with RA-ILD treated with

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methotrexate, leflunomide and/or azathioprine, FVC improved from 1.47 L to 1.66 L after 6 months' follow up (81). A retrospective analysis of 125 patients with RA-ILD found that use of methotrexate (but not hydroxychloroquine or leflunomide) was associated with a reduced risk of an absolute decline in FVC % predicted of 10% over a mean follow-up of 4.3 years (80). A meta-analysis of randomized controlled trials indicated that leflunomide has no adverse effects on respiratory disease (82). There is also evidence that the risk of developing ILD may be lower in patients treated with methotrexate (83,84). A guideline for the treatment of RA published by the American College of Rheumatology in 2021 included a conditional recommendation for methotrexate over alternative DMARDs for the treatment of inflammatory arthritis for patients with mild and stable airway or parenchymal lung disease who have moderate-to-high disease activity (85).

Observational studies in patients with CTD-ILD provide some evidence to support the use of mycophenolate and cyclophosphamide (86-89), but there have been no randomized, double-blind, placebo-controlled trials of these therapies in patients with RA-ILD. There is no evidence to support a benefit of corticosteroids alone in reducing progression of RA-ILD. Recent data suggest that for patients with RA-ILD who require second-line therapy for articular disease after DMARDs have failed, rituximab and abatacept may be a better choice than anti-TNF agents and may improve or stabilize ILD in some patients (90-93). There is some evidence to suggest that Janus kinase (JAK) inhibitors may stabilize or improve lung function in patients with RA-ILD (94,95) but no placebo-controlled trials have been conducted. In a retrospective analysis of 28

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patients with RA-ILD treated with a JAK inhibitor, FVC % predicted remained stable (change of ≤20%) or improved in 89% of patients over a median follow-up of 19 months (95). A retrospective cohort analysis utilizing claims data from 28,559 patients with RA found a lower incidence of ILD in patients treated with tofacitinib compared with adalimumab (96).

Similarities in the pathogenesis and course of disease between IPF and other ILDs led to the investigation of drugs with efficacy in IPF as potential treatments for other fibrosing ILDs. The efficacy and safety of pirfenidone were assessed in 123 patients with RA-ILD in the randomized, placebo-controlled, Phase II TRAIL1 trial. The trial was stopped early due to slow recruitment and was underpowered to detect a difference in the primary endpoint (≥10% decline in FVC % predicted or death over 52 weeks), but the rate of decline in FVC in the pirfenidone group was −66 mL/year compared with −146 mL/year in the placebo group, a relative reduction of 55% (Figure 3) (97). This effect was more pronounced in those with a UIP pattern on HRCT, in whom the rate of decline in FVC was −43 mL/year in the pirfenidone group compared with −169 mL/year in the placebo group. The efficacy of pirfenidone as a treatment for ILDs other than IPF remains unclear and it has not received regulatory approval as a treatment for these ILDs. The efficacy and safety of nintedanib in 663 patients with fibrosing ILDs other than IPF that had progressed at any time within the prior 24 months, despite management deemed appropriate in clinical practice, were investigated in the INBUILD trial (98). Eighty-nine patients in the trial had RA-ILD. Overall, the rate of decline in FVC over 52 weeks was −80.8 mL/year in the nintedanib group compared with −187.8 mL/year in the

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placebo group, a reduction of 57% (98). The trial was not designed to study patients with specific ILD diagnoses, but subgroup analyses suggested that nintedanib had a consistent effect on FVC decline across subgroups based on diagnosis (99,100) (Figure 4) or pattern on HRCT (UIP-like pattern versus other fibrotic patterns) (98,100) and irrespective of the use of DMARDs and/or glucocorticoids at baseline (101). Nintedanib has been approved for the treatment of chronic fibrosing ILDs with a progressive phenotype, as well as for the treatment of IPF and systemic sclerosis-associated ILD, in several countries including the USA, UK and European Union. Long-term data from the open-label extension of the INBUILD trial and other trials of nintedanib in patients with fibrosing ILDs suggest that the efficacy of nintedanib in slowing decline in FVC is maintained over the long term, but that the disease continues to progress (102-104).

Several randomized trials are investigating the effects of drugs on lung function in patient populations including those with RA-ILD. These include a randomized open-label trial of the JAK inhibitor tofacitinib vs methotrexate in patients with pulmonary abnormalities suggestive of RA-ILD (PULMORA; NCT04311567), single-center randomized trials of pirfenidone vs glucocorticoid plus an immunosuppressant in patients with CTD-ILD (NCT05505409) and pirfenidone vs DMARDs in patients with CTD-ILD (NCT04928586), and a multi-center randomized placebo-controlled trial of the phosphodiesterase 4B inhibitor BI 1015550 in patients with progressive fibrosing ILDs other than IPF (FIBRONEER-ILD; NCT05321082). In addition, the safety of tofacitinib in patients with RA-ILD is being investigated in an uncontrolled open-label study (RAILDTo; NCT05246293).

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There has been some interest in the impact of biologic and targeted synthetic DMARDS used in RA on the incidence and progression of ILD but the data are limited (105,106). A retrospective study of 28 patients with RA-ILD followed for 30 months on tocilizumab found that 76% showed stabilization or improvement (105), but these findings would need confirmation in prospective blinded placebo-controlled trials. There is also interest in the potential of inhibiting interleukin 6 (IL-6) or other cytokines as a potential treatment for RA, but no randomized trials of such inhibitors in patients with RA-ILD are ongoing.

Rheumatologists should co-manage patients with RA-ILD with pulmonologists when possible. If co-management with a pulmonologist is not possible, rheumatologists should consider prescribing antifibrotic therapies in patients with PPF, utilizing the well-established dosing and monitoring guidelines for these agents.

Lung transplant

Guidelines recommend that patients who have severe and progressive RA-ILD that has not responded to appropriate treatment and who do not have extrapulmonary contraindications should be considered for lung transplantation (107). Retrospective data from 10 patients with RA-ILD demonstrated a 1-year post-transplant survival rate of 67%, similar to the survival rate of 69% in 53 patients with IPF (108). A larger study of data from 275 patients with ILD associated with CTDs other than systemic sclerosis, of

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whom a quarter had RA-ILD, also found no significant differences in post-transplant survival between these patients and 6346 patients with IPF (109).

Non-pharmacological therapies

Patients with RA-ILD may benefit from non-pharmacological therapies. Pulmonary rehabilitation has been shown to improve exercise capacity, dyspnea, and quality of life in patients with ILD (110). Guidelines issued by the American Thoracic Society recommend the use of supplemental oxygen in patients with ILD with severe chronic resting hypoxemia, and ambulatory oxygen in those with severe exertional hypoxemia, while stressing the importance of education of patients and caregivers on the correct use of oxygen equipment (111). Patients with RA-ILD may benefit from supportive care throughout the course of their disease, including information on their disease and its management, emotional support, and end-of-life care (112). Vaccinations against influenza, pneumonia and COVID-19, and advice on smoking cessation, should be provided. Effective communication with patients with RA-ILD is important to improve patient satisfaction and to enable patients to be active partners in decisions about their treatment.

Conclusions

ILD is a significant cause of morbidity and mortality in patients with RA. Although several risk factors for the development of ILD in patients with RA have been recognized, RA-ILD may develop in patients without these risk factors. Early detection and regular monitoring of RA-ILD are vital. In patients with RA-ILD, the goals should be

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remission of RA and to halt the progression of the ILD, but in practice, therapeutic decisions are often difficult. Immunomodulatory therapies are used in most patients with RA, but their efficacy in slowing the progression of RA-ILD remains unclear. Antifibrotic therapy has been shown to slow the progression of fibrosing ILD and the antifibrotic therapy nintedanib has been approved for the treatment of patients with progressive pulmonary fibrosis due to ILDs, including RA-ILD. The management of patients with RA-ILD should be based on a multidisciplinary approach, involving at minimum a rheumatologist and a pulmonologist, and individualized to the needs of the patient. Questions for future research on the identification, monitoring and management of RA-ILD are summarized in Box 1.

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FIGURE LEGENDS

Figure 1. Clinical course of RA-ILD in the 24 months after RA-ILD diagnosis (9).

Figure 2. Survival in patients with RA-ILD and a matched RA cohort without ILD. Adapted by permission from BMJ Publishing Group Limited (Ann Rheum Dis, Hyldgaard et al, Volume 76, Page 1700-1706, Copyright (2017)) (3).

Figure 3. Estimated rate of change in FVC (mL) with pirfenidone and placebo over 52 weeks in patients with RA-ILD in the TRAIL1 trial (97).

Figure 4. Rate of decline in FVC (mL/year) over 52 weeks in patients with progressive fibrosing ILDs treated with nintedanib versus placebo in subgroups by ILD diagnosis in the INBUILD trial. Reprinted from Lancet Respir Med, Volume 8, Wells AU et al, Nintedanib in patients with progressive fibrosing interstitial lung diseases—subgroup analyses by interstitial lung disease diagnosis in the INBUILD trial: a randomised, double-blind, placebo-controlled, parallel-group trial, Pages 453-460, Copyright (2020), with permission from Elsevier (99).

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Table 1: Proposed management of RA-ILD

	Initial management	Further management	Monitoring	Considerations for all patients with RA-ILD
Asymptomatic	- Smoking cessation - Control RA activity	Wait and watch	Bi-annual PFTs	- Minimize risk - For worsening of symptoms or HRCT, consider infection (e.g., PJP due to immunosuppression) or drug-related toxicity - Use alternative DMARD or biologic where possible in severe or progressive disease - Look for and treat comorbidities such as reflux and OSA - For a disproportionate decline in DLco, consider pulmonary arterial hypertension - Stay up to date with vaccines including influenza and pneumococcal - Consider community palliative care
Mild (<10% fibrosis on HRCT)	- Walk oximetry - Smoking cessation - Control RA activity - Wait and watch	If progressing: 1. NSIP: DMARDs, steroids 2. UIP: consider antifibrotic therapies and medications for RA activity	- Clinical assessment - Review medications - Address RA activity - Bi-annual PFTs - HRCT if worsening clinically or on PFTs	
Moderate (10-25% fibrosis on HRCT)	- Walk oximetry, nocturnal oximetry - Control RA activity - Review DMARDs. <u>Other therapies:</u> 1. NSIP: consider steroids, MMF, abatacept, or rituximab 2. UIP: consider antifibrotic therapies and medications for RA activity	- Use alternative DMARD or biologic where possible if progressing - Refer for lung transplant evaluation	- Clinical assessment - HRCT for stability - PFTs every 3 or 6 months for at least 1–2 years; thereafter, monitoring depends on ILD severity and progression	
Severe (>25% fibrosis on HRCT) or rapidly progressing	- Walk oximetry, nocturnal oximetry - <u>Therapies:</u> 1. NSIP: consider steroids, MMF, abatacept, or rituximab	Refer for lung transplant evaluation	PFTs every 3–6 months for at least 1–2 years; thereafter, monitoring depends on ILD severity	

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	2. UIP: antifibrotic therapies - Look for and treat opportunistic infections			

DLco = diffusing capacity of the lungs for carbon monoxide. DMARDs = disease-modifying anti-rheumatic drugs. HRCT= high-resolution computed tomography. NSIP = non-specific interstitial pneumonia. OSA = obstructive sleep apnea. MMF = mycophenolate mofetil. PJP= Pneumocystis jirovecii pneumonia. PFTs = pulmonary function tests. UIP = usual interstitial pneumonia.

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Box 1. Research questions in the identification, monitoring and management of RA-ILD.

Identification of RA-ILD

- What is the risk of ILD in patients with RA and specific combinations of risk factors?
- Which patients with RA and no respiratory symptoms should be screened for ILD using HRCT? How often should HRCT be repeated in these patients?
- What are the prognostic implications of "sub-clinical" RA-ILD?

Monitoring RA-ILD

- What is the natural history of RA-ILD?
- How often should patients with RA-ILD have repeat PFTs and HRCT?
- Do quantitative CT techniques have a role to play in monitoring the progression of RA-ILD?
- Is exercise testing useful in monitoring patients with RA-ILD?
- What criteria should be used to identify patients with PPF associated with RA-ILD?
- What are the most important risk factors (clinical, radiological, blood-based) for progression of RA-ILD?

Management of RA-ILD

- Are immunomodulatory therapies effective in slowing the progression of fibrosing RA-ILD? Which are most effective?
- Which patients with PPF associated with RA-ILD should receive antifibrotic therapy?
- How should treatment response versus treatment failure be defined in patients with PPF associated with RA-ILD?
- How long should treatment for RA-ILD be continued in patients with apparently stable disease?
- How should dyspnea and cough in patients with RA-ILD be managed?
- When should patients with PPF associated with RA-ILD be evaluated for lung transplant?

CT, computed tomography; HRCT, high-resolution computed tomography; ILD, interstitial lung disease; PFTs, pulmonary function tests; PPF, progressive pulmonary fibrosis; RA, rheumatoid arthritis; RA-ILD, rheumatoid arthritis-associated ILD.

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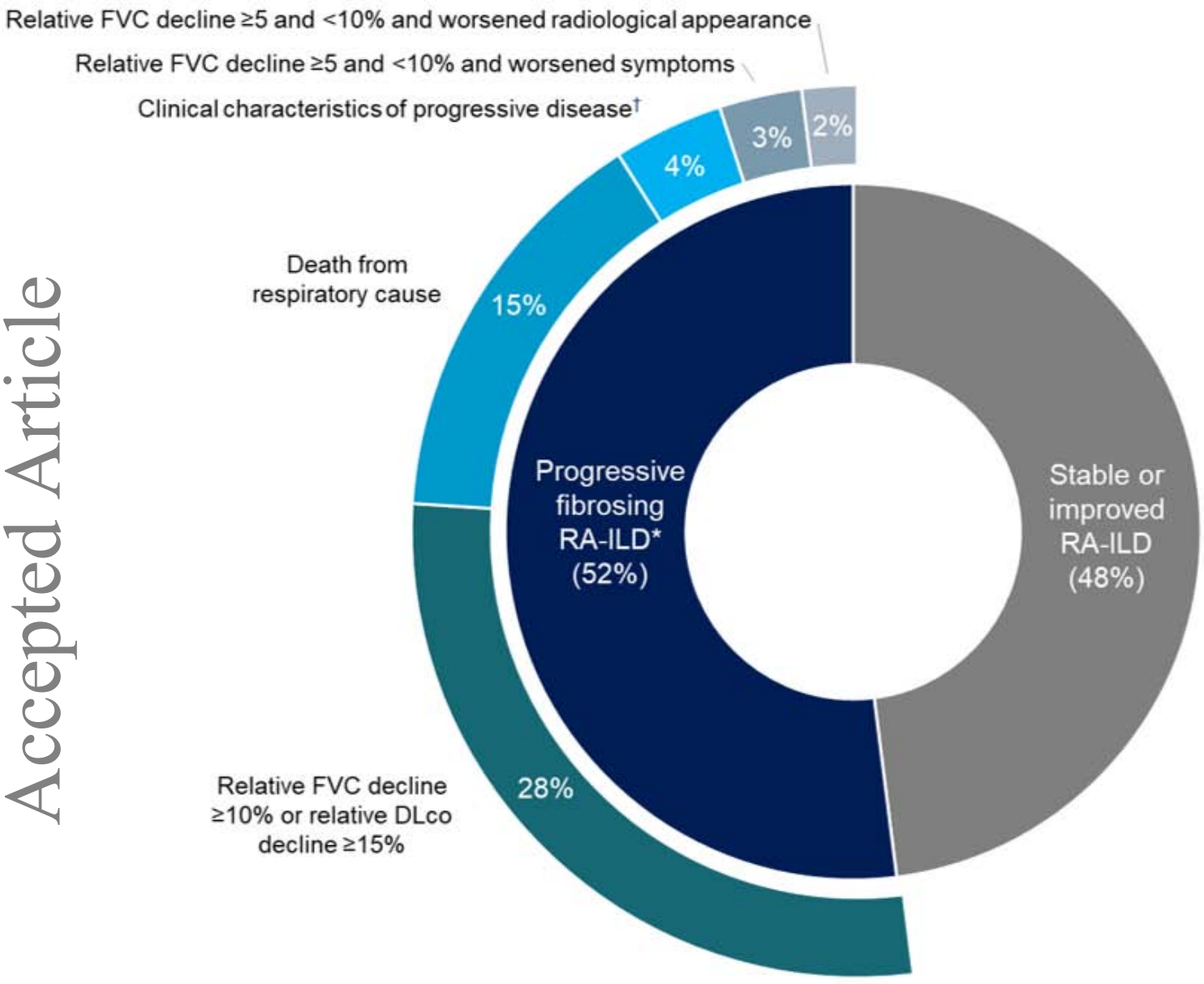

*Relative decline in FVC ≥10%, relative decline in DLco ≥15%, or worsened symptoms or radiological appearance accompanied by relative decline in FVC ≥5 to <10%.
†Lung transplant or oxygen therapy and severely impaired DLco but insufficient pulmonary function data.

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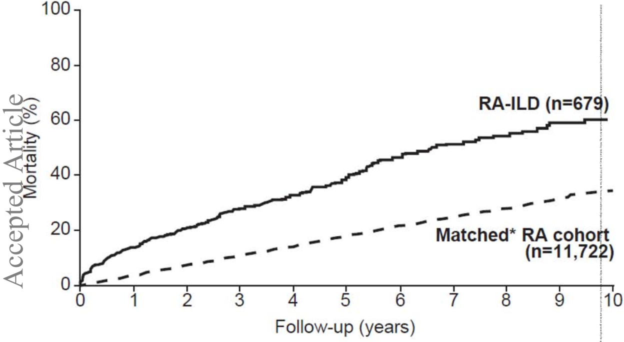
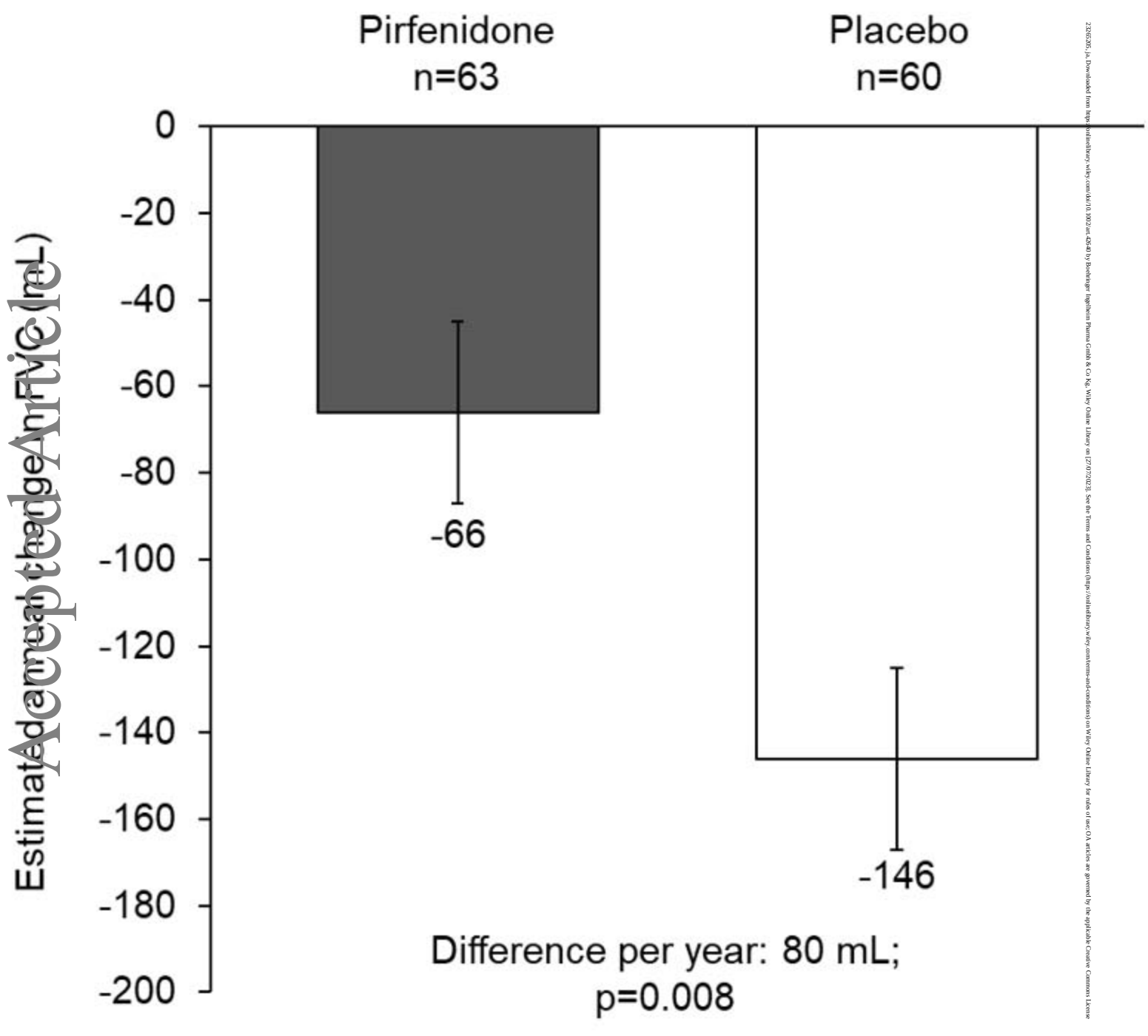


*Matched by birth year, sex, age at RA diagnosis.



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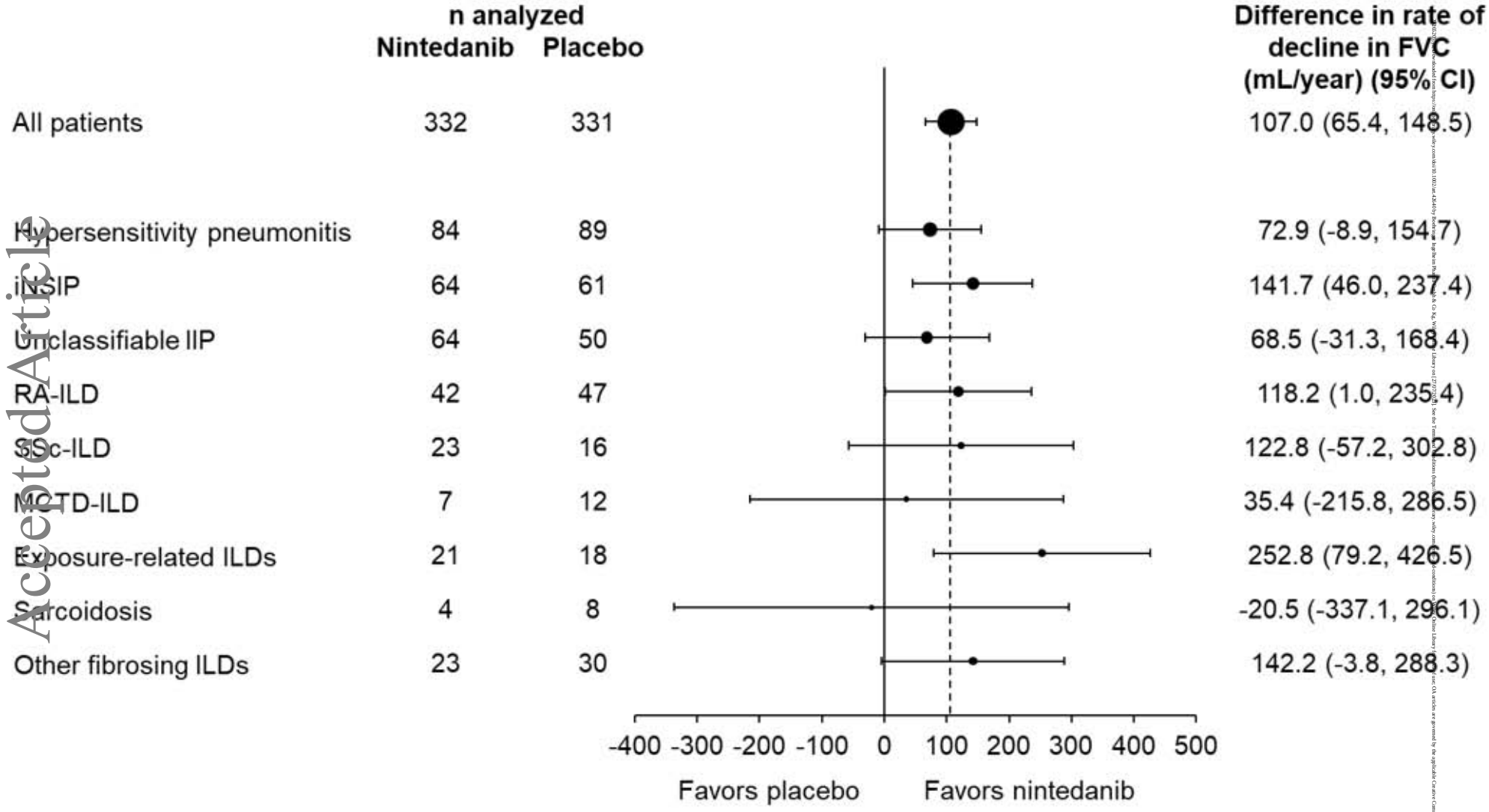

Treatment-by-subgroup-by-time interaction p=0.68.

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