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Management Issues in Rheumatoid Arthritis-Associated Interstitial Lung Disease

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Abstract

Purpose of review: Summarize recent evidence on the identification and management of rheumatoid arthritis-associated interstitial lung disease (RA-ILD).

Recent findings: Clinical and sub-clinical ILD are frequent extra-articular manifestations of RA. Better means of identifying and treating RA-ILD are needed to improve the prognosis, with a median survival of only 3–7 years after diagnosis. Several serum biomarkers are currently being evaluated for their ability to detect RA-ILD. Thorough evaluation and multidisciplinary discussion remains the gold standard for establishing the diagnosis of RA-ILD. Management is challenging with most RA disease-modifying anti-rheumatic drugs (DMARDs) linked to pneumonitis. Methotrexate is typically avoided in clinically significant ILD, although alternative therapies including leflunomide and biologic DMARDs also carry risks in RA-ILD. Anti-fibrotics appear to slow the progression of ILD, and a large phase II trial exclusively in RA-ILD is underway. Additionally, smoking cessation, pulmonary rehabilitation, oxygen therapy, managing comorbidities, and lung transplantation evaluation are vital to improving patient outcomes in RA-ILD.

Summary: With little high-quality evidence to guide the management of RA-ILD, multidisciplinary teams with expertise in RA-ILD are highly valuable for diagnosing and treating RA-ILD. Clinical and translational research in RA-ILD is needed to fill the many evidence gaps.

Keywords

rheumatoid arthritis; interstitial lung disease; pulmonary fibrosis

Introduction

Interstitial lung disease (ILD) is an extra-articular manifestation of rheumatoid arthritis (RA) first reported by Ellman and Ball in 1948 (1). In this review, we summarize recent evidence on the identification and management of RA-ILD.

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Epidemiology and outcomes of RA-ILD

Between 5–10% of patients with RA will develop clinically significant ILD (2, 3), and another 20–30% may have subclinical involvement (4). Risk factors for RA-ILD include male sex, older age, tobacco use, higher RA disease activity, extra-articular disease features (e.g. subcutaneous nodules), and seropositivity for RA autoantibodies (rheumatoid factor [RF] and anti-citrullinated protein antibodies [ACPAs]) (2, 3, 5–7). While the median survival has been reported to be <3 years (2), two recent observational studies found the median survival to be 7 years after diagnosis (8, 9). In addition to its impact on survival, RA-ILD places a tremendous burden on healthcare systems with mean total 5-year healthcare costs exceeding $170,000 per patient (8).

Two of the most important prognostic factors in RA-ILD are the pattern of ILD and ILD severity. The most common patterns of RA-ILD are usual interstitial pneumonia (UIP), characterized radiographically by honeycombing and traction bronchiectasis, and non-specific interstitial pneumonia (NSIP), characterized radiographically by diffuse ground glass opacities and the absence of honeycombing (2, 10, 11). A meta-analysis of 10 cohort studies including 1,256 patients with RA-ILD estimated a 1.6-fold higher risk of death for those with a UIP pattern compared to other patterns (12). While radiographic appearance is clearly important, several studies have found that pulmonary physiology (e.g. forced vital capacity [FVC]) is more prognostic than ILD pattern. Severity of ILD by pulmonary physiology and high-resolution computed tomography (HRCT) is strongly associated with progression (physiologic and radiographic) and mortality in RA-ILD (13–15).

Identifying RA-ILD

Because the initial manifestation may be inflammatory arthritis (85–90% of cases) or ILD in patients who develop RA-ILD (3, 5), both rheumatologists and pulmonologists have roles in its detection and evaluation (Figure 1).

Identifying ILD in RA

The high prevalence of sub-clinical ILD on HRCT in patients with RA demonstrates that screening approaches relying on clinical signs and symptoms will be poorly sensitive for detecting ILD (4, 16). To improve on the sensitivity of clinical findings, an algorithm to detect Velcro rales in recorded breath sounds from an electronic stethoscope was developed. In 137 RA patients who underwent HRCT, electronic breath sounds had a sensitivity of 93.2% and specificity of 76.9% for detecting ILD and outperformed clinical symptoms, exam findings, chest x-ray, and PFTs (17). Validation in regular clinical settings is needed.

There is substantial interest in identifying serum biomarkers for RA-ILD since early identification may aid in preventing irreversible damage resulting from delays in diagnosis. In a large, international, case-control study, a *MUC5B* promoter variant (rs35705950) was associated with 3-fold higher odds of RA-ILD compared to RA alone (18). Our group performed a multi-center cross-sectional study that found the presence of anti-malondialdehyde-acetaldehyde (MAA) antibodies to be associated with 2-fold higher odds of ILD in RA (19). Other biomarkers that have been previously examined include matrix

metalloproteinase (MMP)-7, surfactant protein D, pulmonary and activation-regulated chemokine, interferon-γ-inducible protein 10, anti-citrullinated heat shock protein 90, antibodies to cross-reactive peptidyl-arginine 3/4, and anti-citrullinated alpha enolase antibodies (20–24). To date, there has not been validation of most of these biomarkers or integration into clinical care.

Identifying RA in ILD.

When ILD is the initial manifestation, providers must differentiate RA as the underlying etiology from other connective tissue diseases (CTD) and idiopathic interstitial lung diseases. In addition to history and exam focused on articular symptoms, testing for RA autoantibodies (RF and ACPAs) should be completed. While ACPAs are highly specific (>95%) for RA in most settings (25), they may also occur in the setting of chronic lung diseases even in the absence of RA (26). Individuals with ACPAs but without inflammatory arthritis appear to be at high risk for developing RA later (27). Many of the biomarkers which show promise for identifying ILD in RA may not be useful for differentiating RA-ILD from other ILD. A recent study of two independent RA-ILD cohorts demonstrated overlap in serum pro-inflammatory cytokines and MMPs in RA-ILD and IPF (28).

Establishing the diagnosis and treatment team in RA-ILD

The gold standard for diagnosing RA-ILD is a multidisciplinary discussion of history, clinical exam, blood testing, HRCT, PFTs, and when performed, lung biopsy. While most multidisciplinary discussion of newly diagnosed ILD includes pulmonologists, radiologists, and pathologists, the inclusion of rheumatologists improves the detection of CTD-ILD (29). Given the correlation between HRCT and pathology findings as well as the morbidity accompanying surgical lung biopsy, biopsy is not typically pursued unless there is uncertainty in the diagnosis. Transbronchial cryobiopsies are a novel, less invasive method to acquire tissue to establish the diagnosis of ILD, though standardization of the procedure and delineation of its role in the diagnostic evaluation are still being determined (30). After establishing the diagnosis of RA-ILD, a multidisciplinary team including support staff (e.g. nurses, pharmacists, and respiratory therapists) is crucial for ongoing management, and referral to specialized centers with CTD-ILD programs should be considered, when available.

Overview of the management of RA-ILD

The authors approach to managing RA-ILD is shown in Figure 2. We begin by assessing disease severity, risk factors, and patient preferences. Supportive interventions are implemented for all patients. In patients with clinically significant or progressive ILD (based on clinical symptoms, PFTs, HRCT), we modify use of RA disease-modifying anti-rheumatic drugs (DMARDs). If RA-ILD progresses, we consider alternative immunomodulatory therapy and anti-fibrotics.

Non-pharmacologic therapies

Smoking tobacco is the strongest environmental risk factor for both RA and ILD, and counseling on smoking cessation is of paramount importance. Ambulatory oxygen therapy is routinely prescribed for patients with a PaO_2 ≤55 mm Hg or SpO_2≤88%. Despite widespread use, oxygen therapy has questionable benefit in regards to dyspnea, exercise tolerance, and mortality (31–33). Even though patients with CTD-ILD appear to benefit less than patients with other forms of ILD (34), pulmonary rehabilitation meaningfully improves exercise capacity, reduces dyspnea, and improves quality of life (35). Lung transplantation evaluation should be considered in all patients with progressive ILD. Patients with RA-ILD that undergo lung transplantation have a similar risk of rejection and mortality as patients with other ILD (36, 37).

Selecting pharmacologic therapies

The outcomes in RA have dramatically improved with aggressive treatment strategies and an expanding armamentarium of DMARDs. Complicating the choice of DMARDs in RA-ILD is that most DMARDs have been linked to drug induced pneumonitis (38). We review the evidence for pharmacologic therapies in RA-ILD (all off-label), focusing on ILD outcomes given the existence of guidelines for the management of articular disease in RA (39, 40).

Glucocorticoids.

Glucocorticoids are typically part of the initial treatment regimen for clinically significant RA-ILD, based on experience in CTD-ILD rather than data demonstrating efficacy in RA-ILD (41). NSIP and organizing pneumonia ILD patterns are more responsive to glucocorticoids than UIP (41, 42), though data specifically in RA-ILD are lacking. Glucocorticoids have several dose and duration dependent long-term side effects including infection and osteoporosis (43, 44). Therefore, they are best suited for the initial management or treating acute exacerbations while transitioning to other therapies with more favorable long-term safety profiles.

Methotrexate.

Pneumonitis occurs in only 0.3 to 0.4% of patients with RA treated with methotrexate (45, 46), and methotrexate is not a risk factor for RA-ILD. In fact, results from prospective early RA inception cohorts showed trends towards lower odds of developing ILD in patients with RA treated with methotrexate (odds ratio 0.54, 95% confidence interval [CI] 0.28–1.06) (7). Because pre-existing lung disease is a risk factor for methotrexate pneumonitis (47), the difficulty in distinguishing methotrexate pneumonitis from exacerbations or progression of ILD, and that a lack of pulmonary reserve may predispose to increased mortality if pneumonitis were to occur, many providers discontinue or avoid methotrexate in RA-ILD. While prone to confounding and selection bias, the limited studies evaluating methotrexate use in RA-ILD have not observed worse outcomes with its use (48, 49). We typically avoid the use of methotrexate in clinically significant and/or progressive RA-ILD and engage patients in shared decision making prior to use of methotrexate in RA-ILD. The safety of methotrexate in RA-ILD is a critically important question.

Other conventional synthetic DMARDs (csDMARDs).

Avoidance of methotrexate in those with or at risk for RA-ILD is partially responsible for a higher rate of ILD observed with leflunomide treatment (50). However, pneumonitis is well known to also occur with leflunomide use. Pre-existing ILD and prior methotrexate pneumonitis are risk factors for death in leflunomide pneumonitis (51), suggesting it should not be the standard alternative to methotrexate in these situations. Pneumonitis has also been reported with sulfasalazine (52). There is a paucity of data on the safety of hydroxychloroquine in RA-ILD.

Tumor necrosis factor inhibitors (TNFi).

While several cases of new-onset ILD or exacerbations of ILD have been reported after TNFi use (53, 54), comparative studies are conflicting. In retrospective cohort studies in the British Society for Rheumatology Biologics Register, TNFi were not associated with a higher risk of death compared to csDMARDs in RA-ILD (55), but there were trends towards better survival with rituximab (hazard ratio 0.53, 95% CI 0.26–1.10) compared to TNFi (56). Analyses of large U.S. administrative claims databases have not found significant differences in respiratory events between patients with RA-ILD using TNFi compared to tocilizumab, rituximab, and abatacept (49, 57). However, there were numerically fewer respiratory events among initiators of abatacept compared to TNFi (57). In addition to confounding and selection bias, misclassification of RA-ILD is problematic in these observational studies as demonstrated by extensive testing of the accuracy of administrative algorithms for RA-ILD (58).

Other biologic DMARDs and janus kinase (JAK) inhibitor.

Beyond the aforementioned studies comparing to TNFi (49, 56, 57), there is only limited, uncontrolled data on these agents in RA-ILD. Small, uncontrolled studies generally have shown the majority of RA-ILD subjects treated with rituximab, tocilizumab, or abatacept to remain stable or improved by PFTs (59–62). A small case series did not find exacerbations of ILD with tofacitinib treatment (63), and in the SKG mouse model, tofacitinib effectively treats ILD (64). Biologic DMARDs appear to have a role in other CTD-ILD (65, 66), and several studies are ongoing in CTD-ILD. A double-blind RCT comparing rituximab to cyclophosphamide in CTD-ILD (RA-ILD excluded) is ongoing (67). Phase II RCTs of abatacept in RA-ILD (NCT03084419) and myositis-ILD (NCT03215927) are recruiting.

Other immunomodulatory therapies.

The role of other immunomodulatory therapies such as mycophenolate mofetil (MMF), cyclophosphamide, azathioprine, cyclosporine, and tacrolimus in RA-ILD remains unclear. In a retrospective analysis of 125 CTD-ILD treated with MMF (n=18 RA-ILD), MMF was associated with improvement in lung function in those with a NSIP pattern and stability in those with a UIP pattern (68). Both cyclophosphamide and MMF have demonstrated efficacy in SSc-ILD in double-blind RCTs (69, 70). Azathioprine is often used as an alternative to methotrexate in RA-ILD. A single center retrospective cohort study of CTD-ILD (n=97, 24% RA-ILD) found that patients treated with azathioprine had similar clinical events and longitudinal PFTs compared to MMF (71). There are case reports/series of RA-

ILD improving with cyclosporine and tacrolimus (72–75). While these other immunomodulatory therapies (e.g. MMF, azathioprine) may be effective for ILD, providers must consider their potential for greater toxicities and more modest effects on articular disease (76–78).

Anti-fibrotics.

Currently two anti-fibrotics are FDA approved for the management of IPF, nintedanib and pirfenidone. They both are actively being studied in CTD-ILD. The INBUILD study was an international, double-blind RCT comparing nintedanib to placebo in patients with progressive, fibrotic lung disease (13% RA-ILD) (79). In this study, patients treated with nintedanib had a slower rate of FVC decline over 52 weeks, but there were no significant differences in subjective symptoms or clinical events. Diarrhea was the major side effect of nintedanib, occurring in 67% of treated subjects compared to 24% on placebo. A RA-ILD specific double-blind phase II RCT comparing pirfenidone to placebo is currently enrolling (TRAIL1, NCT02808871) and will illustrate the effects of anti-fibrotics on articular disease in addition to ILD (80). In a mouse model of RA-ILD, nintedanib was effective for both lung and articular manifestations (81). However, in the SENSCIS trial, a large, double-blind RCT comparing nintedanib to placebo in SSc-ILD, less decline in FVC was seen with nintedanib (resulting in FDA approval for SSc-ILD), but it was not effective for the non-ILD manifestation of skin fibrosis (82).

Managing comorbidities in RA-ILD

Chronic obstructive pulmonary disease (COPD).

Even among non-smokers, COPD frequently accompanies RA-ILD. In a multi-center retrospective study, 27% of non-smokers with RA-ILD had emphysema on CT (83). In these individuals, emphysema was independently associated with a UIP pattern and poorer survival. The high prevalence and poor outcomes of concomitant COPD in RA-ILD warrants diligent adherence to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommendations for COPD management (84).

Gastroesophageal reflux disease (GERD).

GERD is common in RA-ILD, with approximately 50% of patients with RA-ILD having a diagnosis of GERD (8). The relationship between GERD and ILD is debated. A recent meta-analysis of 18 case-control studies of GERD and IPF found the existing association to be confounded by smoking (85). Pharmacologic (e.g. proton pump inhibitors, H2 blockers) and non-pharmacologic (weight loss, dietary modification, elevating head of bed) treatments are frequently prescribed in ILD and conditionally recommended in IPF management guidelines (42). Equally as contentious is whether proton pump inhibitors increase the risk of pneumonia (86). Therefore, providers must balance ill-defined risks and benefits of antacid use in RA-ILD.

Monitoring treatment response

Monitoring treatment response in RA-ILD includes both assessment of articular and respiratory disease activity and severity. The American College of Rheumatology (ACR) recently convened a working group to provide recommendations on preferred RA disease activity and functional status measures (87, 88). The five preferred RA disease activity measures were the Disease Activity Score in 28-joints, Clinical Disease Activity Index, Simplified Disease Activity Index, Routine Assessment of Patient Index Data 3, and Patient Activity Scale-II (87). The three preferred functional status measures were the PROMIS physical function 10-item short form, Health Assessment Questionnaire-II, and Multidimensional Health Assessment Questionnaire (88).

The Outcomes Measures in Rheumatology (OMERACT) CTD-ILD working group performed a large Delphi process to identify important domains and outcomes measures for multicenter RCTs in CTD-ILD. The identified core domains and measures (in parentheses) were dyspnea (Medical Research Council dyspnea scale and Dyspnea-12), cough (Leicester cough questionnaire), health-related quality of life (Short Form 36 and patient global assessment), lung imaging (overall extent of ILD on HRCT), lung physiology (FVC and DLCO), and survival (89). These were selected based on relevance to multicenter RCTs, so these should serve as a guide, rather than a mandate, on measures to follow in routine care.

Conclusions

ILD frequently complicates RA, dramatically impacts patients' lives, and places a great financial burden on patients and healthcare systems. Multidisciplinary diagnosis and management is critical to optimizing patient outcomes, especially given the paucity of data to guide treatment decisions. Non-pharmacologic therapies should be universally implemented. The optimal DMARDs and other immunodulatory therapies as well as the role for anti-fibrotics are not well established. International working groups and multi-center RCTs are needed and in place to begin to address the many evidence gaps in RA-ILD management (90).

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Key Points

- Interstitial lung disease is an extra-articular manifestation of rheumatoid arthritis that leads to poor patient outcomes and substantial healthcare costs
- Multidisciplinary discussion of the clinical findings, blood tests, high-resolution computed tomography images, and pulmonary function tests is considered the best approach to diagnose RA-ILD
- Optimal disease-modifying anti-rheumatic drugs and other immunomodulatory therapies in RA-ILD are not known and most have been associated with cases of pneumonitis
- Anti-fibrotics may have an adjunct role in managing progressive RA-ILD
- Quality evidence is lacking for most diagnostic and management considerations in RA-ILD, illustrating the need for clinical and translational research in RA-ILD

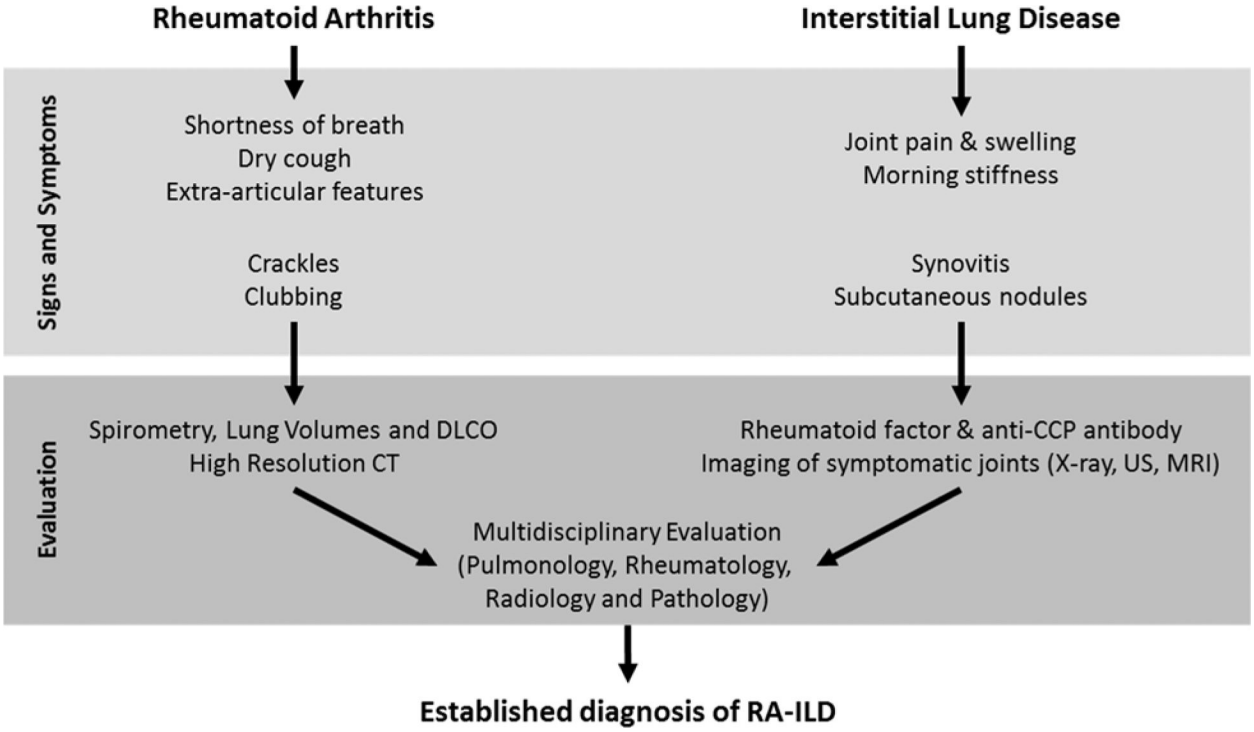

Figure 1. Approach to the identification of rheumatoid arthritis-associated interstitial lung disease.

The initial presentation of rheumatoid arthritis (RA) or interstitial lung disease (ILD) should prompt evaluation for other signs and symptoms attributable to RA-ILD. Testing for pulmonary and articular manifestations followed by multidisciplinary discussion can establish the diagnosis of RA-ILD.

Abbreviations: CT = computed tomography, DLCO = diffusing capacity for carbon monoxide, MRI = magnetic resonance imaging, US = ultrasound

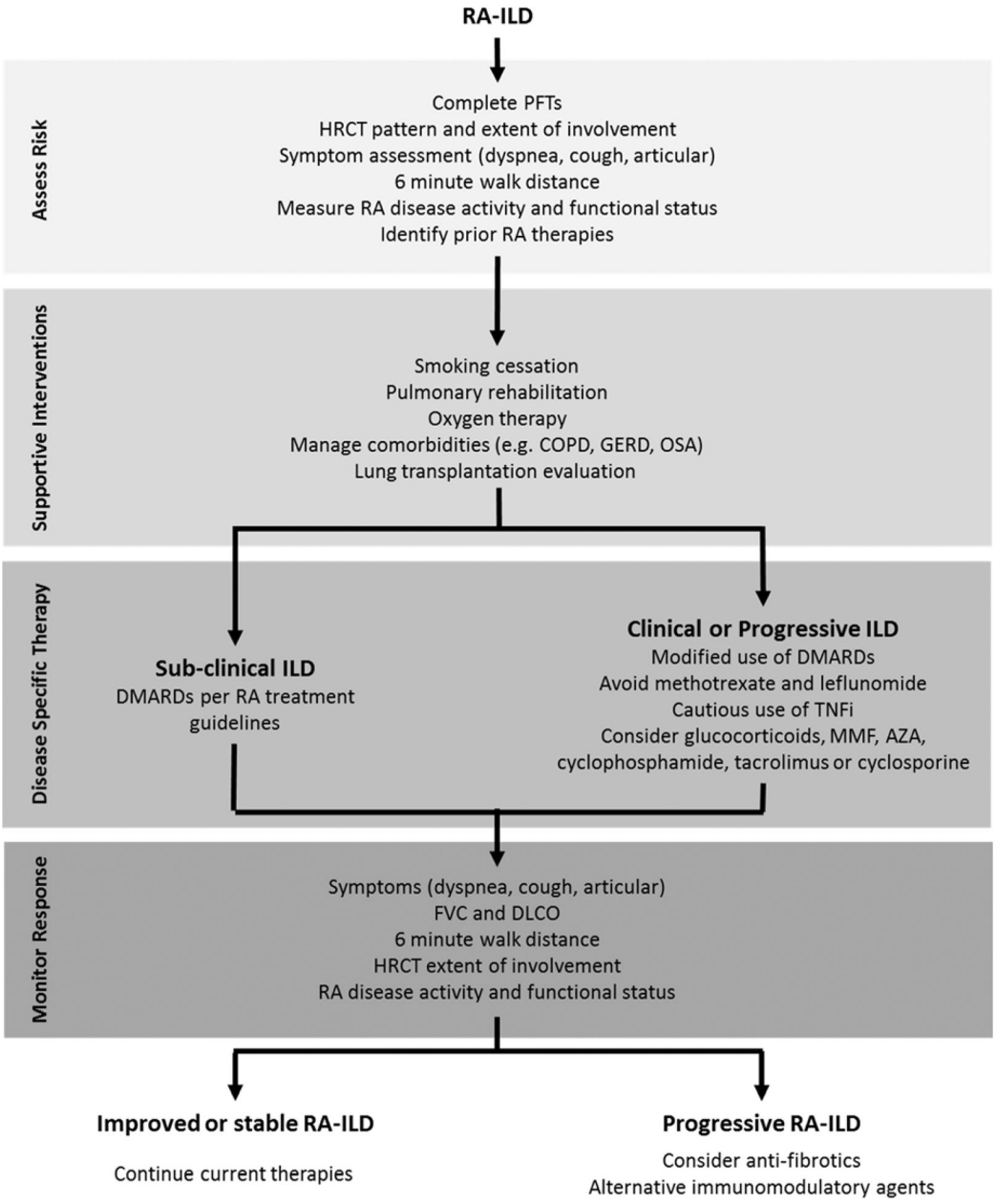

Figure 2. Approach to the management of rheumatoid arthritis-associated interstitial lung disease.

Management of rheumatoid arthritis-interstitial lung disease (RA-ILD) begins by assessing severity and risk for progression. All patients should receive non-pharmacologic therapies. Those with clinically significant RA-ILD may have their RA disease-modifying therapies adjusted and consideration given to other immunomodulatory therapies and glucocorticoids. If progression occurs despite these therapies, anti-fibrotics and alternative immunomodulatory therapies should be considered.

Abbreviations: AZA = azathioprine, COPD = chronic obstructive pulmonary disease, DLCO = diffusing capacity for carbon monoxide, DMARD = disease-modifying anti-rheumatic drug, FVC = forced vital capacity, GERD = gastroesophageal reflux disease, HRCT = high-

resolution computed tomography, MMF = mycophenolate mofetil, OSA = obstructive sleep apnea, PFT = pulmonary function tests, TNFi = tumor necrosis factor inhibitor