Rheumatoid Arthritis and Lung Disease: From Mechanisms to a Practical Approach

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Semin Respir Crit Care Med 2014;35:222–238.

Abstract

Rheumatoid arthritis (RA) is a common chronic systemic autoimmune disease characterized by joint inflammation and, in a proportion of patients, extra-articular manifestations (EAM). Lung disease, either as an EAM of the disease, related to the drug therapy for RA, or related to comorbid conditions, is the second commonest cause of mortality. All areas of the lung including the pleura, airways, parenchyma, and vasculature may be involved, with interstitial and pleural disease and infection being the most common problems. High-resolution computed tomography of the chest forms the basis of investigation and when combined with clinical information and measures of physiology, a multidisciplinary team can frequently establish the diagnosis without the need for an invasive biopsy procedure. The most frequent patterns of interstitial lung disease (ILD) are usual interstitial pneumonia (UIP) and nonspecific interstitial pneumonia (NSIP), with some evidence for the prognosis being better than for the idiopathic equivalents. Risk factors depend on the type of disease but for ILD (mainly UIP and NSIP) include smoking, male gender, human leukocyte antigen haplotype, rheumatoid factor, and anticitrullinated protein antibodies (ACPAs). Citrullination of proteins in the lung, frequently thought to be incited by smoking, and the subsequent development of ACPA appear to play an important role in the development of lung and possibly joint disease. The biologic and nonbiological disease modifying antirheumatic drugs (DMARDs) have had a substantial impact on morbidity and mortality from RA, and although there multiple reports of drug-related lung toxicity and possible exacerbation of underlying ILD, overall these reactions are rare and should only preclude the use of DMARDs in a minority of patients. Common scenarios facing pulmonologists and rheumatologists are addressed using the current best evidence; these include screening the new patient; monitoring and choosing RA treatment in the presence of subclinical disease; treating deteriorating ILD; and establishing a diagnosis in a patient with an acute respiratory presentation.

Keywords
- rheumatoid arthritis
- lung
- interstitial
- drug induced
- anticitrullinated protein antibodies
- biologic disease modifying antirheumatic drugs
- prognosis

Rheumatoid arthritis (RA), a systemic autoimmune process characterized by a chronic symmetrical erosive synovitis, is frequently progressive and results in significant disability, especially if treatment is delayed.[1] In addition to articular disease, multiple other organ systems may be involved, with extra-articular manifestations (EAM) in the heart and vascular system, lungs, skin, and eyes, contributing to the excess morbidity and mortality of patients with RA.[2,3] The lung and pleura are frequently involved and contribute to 10 to 20% of overall mortality.[2–7] The type of involvement is very varied and can precede the development of joint symptoms or diagnosis of RA.[7–9] With improvements in imaging of the

Issue Theme Pulmonary Complications of Connective Tissue Disease; Guest Editors, Danielle Antin-Ozerkis, MD, and Jeffrey Swigris, DO, MS

DOI http://dx.doi.org/10.1055/s-0034-1371542.
ISSN 1069-3424.

lung, we now have a better understanding of the amount, severity, and type of lung and pleural disease that occurs in patients with RA. Recent findings provide fascinating insights into the pathogenesis of lung disease and how it may relate to the development of RA. The role of antibodies to specific citrullinated proteins in the diagnosis of early RA, as markers of RA-associated interstitial lung disease (ILD) and in the pathogenesis of both lung and joint disease is intriguing and may offer new options for detection, monitoring, and therapy.[10] Second, despite the availability of highly sensitive tools such as the high-resolution computed tomography (HRCT), the questions of which pleuropulmonary abnormalities are important, how screening and monitoring should be performed, and whether treatment directed at the RA should be modified because of the presence of subclinical or clinically apparent lung abnormalities is not clear.[3,4,11,12] Outcome from the interplay between lung disease and the new biological disease modifying antirheumatic drugs (bDMARDs) used to treat joint disease is unclear[11,13,14] and hence the risk versus benefit of bDMARDs in an individual patient with pulmonary EAM is uncertain.[11] Systematic reviews, however, suggest concerns about pulmonary complications with the use of DMARDs in patients with RA may be overstated.[11] This review will outline the breadth of lung involvement in patients with RA, but focus on the commonest forms in terms of pathogenesis, treatment, and uncertainties as outlined earlier. Interstitial, pleural, airway, and vascular disease and infection are either the most common or the most difficult to manage lung problems in patients with RA. Drug-induced lung disease is of importance and may complicate the management of patients with RA.[15,16] On the basis of this review, we aim to provide a guide as to how to approach patients with possible lung involvement, whether as a rheumatologist managing someone presenting with predominately joint disease, or as a pulmonologist needing to determine the type, significance, and management of lung disease.

Overview of Lung Involvement in Rheumatoid Arthritis

Prevalence and Type of Lung Disease

Almost all components of the respiratory system have been shown to have the potential to be abnormal in patients with RA. These changes appear to be a result of the systemic inflammatory process in RA, as evidenced by the frequency, temporal relationship, pathogenesis, and pathology[2,3,16]; or arise as a result of the treatment used for RA[13,14,16–18]; or comorbidities that involve the lung.[19,20]

Abnormalities involve the following:

- Pleura[21,22]
- Airways—upper and lower, large and small airways[23]
- Parenchyma with ILD and nodules[3,4,13,16]
- Vasculature[24]
- Infection related to RA or immunosuppressive therapy[17]
- Drug-related lung disease secondary to treatment of RA, for example, with DMARDs[11,16,25,26]
- Comorbid medical conditions such as venous thromboembolism[27,28] and lung cancer.[19,29]

The specific conditions associated with RA are shown in ►**Table 1**, which summarizes their importance and impact on patients.

In general, patients with RA have an increased standardized mortality rate, which is higher in hospital cohorts when compared with inception cohorts and higher with increased age, male gender, presence of comorbidities, higher activity of joint disease, and presence of EAM of RA.[4–6] In an inception cohort of 1,429 people with symptoms of < 2 years, there were 459 deaths during 18 years of follow-up.[5] The greatest cause of early mortality was cardiovascular death (31%), but lung problems were the next biggest contributor (29%).[5] Lung problems with significant mortality include infection (12% overall deaths), ILD (4%), and lung cancer (7%).[5] Some forms of lung involvement, such as obliterative bronchiolitis, are rare but associated with a high mortality.[2,44] In terms of morbidity, significant contributors are infection, ILD, pleural disease, and drug-related reactions.[3,4]

It is difficult to confirm the exact prevalence of the different types of RA-associated respiratory disease but it can vary widely, with ILD, for example, ranging from 5 to 60% in various reports. Differences in prevalence are seen between autopsy, hospital, and community-based studies.[46–51] Studies contain heterogeneous populations with differences in proportions with early or late stage disease, severity of disease, treatment, the method used to detect pulmonary abnormalities, sensitivity of equipment, expertise of those interpreting the tests used, and how "abnormal" is defined. The prevalence is undoubtedly influenced by smoking rates, other diseases in the community, genetic, and environmental factors.[2,3,16] Most published studies have used multifaceted assessment, but some tests are consistently better at detecting abnormalities than others. In a study of 36 patients with new onset RA, abnormalities consistent with ILD were found in 58% of patients (physiology 22%, chest X-ray [CXR] 6%, HRCT 33%, bronchoalveolar lavage [BAL] 52%, 99mTc-DTPA [technetium-99m diethylenetriamine pentaacetic acid] radionuclide scan 15%).[46] Despite all these abnormalities, only 14% were felt to have clinically significant ILD. Similarly, a large number of patients with RA have pleural abnormalities on HRCT, but a minority of patients have clinically troublesome disease.[52] Tests may be complementary, reflecting different aspects of structure or function. As much disease is subclinical and progression varied,[6,9] the significance of many of these abnormalities in terms of future morbidity and mortality is not clear and in the absence of validated prognostic indicators, it is the complete clinical picture, with the combination of symptoms and structural and functional abnormalities in terms of both presence, severity, and change over time,[55] which helps determine the importance of any one finding and the need for intervention.

Risk Factors for Lung Disease

Understanding risk factors for pulmonary EAM in patients with RA has led to insights into pathogenesis and may provide

Table 1 Frequency and impact of EAM in the lung in patients with RA[a]

	Frequency	Impact if present
Pleural[21,22,30–34]		
Pleuritis	++	++
Effusion[a]	++	++
Pleural thickening	+++	+
Other—unexpandable lung, empyema, chyliform effusion,[b] pneumothorax,[b] hemothorax,[b] pyopneumothorax,[b] bronchopleural fistula[b]	+	+++
Airway[2,23,35–42]		
Upper—cricoarytenoid immobility with vocal cord abnormality, cord nodules, recurrent laryngeal, or vagus nerve vasculitis and cord paralysis	+	++
Lower		
Airflow obstruction	++	+
Obliterative bronchiolitis	+	+++
Bronchiectasis[43]	+	+
Parenchymal[3,4,8,9,12,13,44–48]		
Interstitial lung disease	+++	+ +++
Apical fibrosis and Caplan syndrome	+	+
Nodules	+++	+
Vascular[24,49–51]		
Pulmonary hypertension	+	+++
Vasculitis	+	+++
Musculoskeletal related[3,18]		
Chest wall immobility and respiratory failure	+	+
Infection[17,52–54]		
Related to RA	+	+
Related to treatment	++	++
Treatment related[13–17,25,26]		
Pneumonitis	++	+++
Pleuritis/effusion (methotrexate, infliximab, adalimumab)	+	+
Increased risk[19,27–29]		
Lung cancer	+	+++
Pulmonary thromboembolism	+	++

Abbreviations: EAM, extra-articular manifestation; RA, rheumatoid arthritis.
[a]+ (infrequent or unimportant) to +++ (frequent or important).
[b]May be associated with a ruptured nodule.

guidance for screening and surveillance. Although RA is more prevalent in females, in most but not all studies,[45] males more commonly developed ILD[44,56] and nodules.[57] The findings with respect to smoking are mixed with evidence that current or previous smoking is a risk factor for ILD[58] (odds ratio [OR] 3.8 for >25 pack years),[59] although some studies have reported no association.[60] It is important to note RA-ILD can occur in nonsmokers.[39] The severity and duration of joint disease is associated with the presence of both airflow obstruction and ILD,[51] and older age with ILD.[61] The shared epitope human leukocyte antigen (HLA)-DRB1 allele is associated with ILD[62] and in other studies, HLA-DRB1*1502 with ILD (relative risk [RR] ratio = 4.02; $p = 0.013$) but not airways disease (RR ratio = 0.15; $p = 0.08$).[61] Rheumatoid factor is associated with a low diffusing capacity for carbon monoxide (DLCO),[47,61] anticitrullinated protein antibodies (ACPAs) with ILD[63] and airways disease,[61] and antibodies against anticitrullinated Hsp90α/β with ILD.[64]

Anticitrullinated Peptide Antibodies and Pathogenesis of Rheumatoid Arthritis

The role of ACPAs in joint inflammation and EAMs of RA has been a focus of much research over the last decade.[10] Citrullination is a posttranslational modification of proteins by the enzymes peptidyl arginine deaminsase-1 and -2 (PAD-1 and -2), in which arginine is converted to citrulline, thereby changing the tertiary structure and charge of the protein, increasing its immunogenicity. Several diseases have been associated with abnormal citrullination of peptides, including psoriasis, multiple sclerosis, and idiopathic pulmonary fibrosis (IPF).[10,63] In RA, a range of synovial proteins, including vimentin, filaggrin, and fibronectin, can become citrullinated and incite an antibody response. Antibodies to citrullinated peptides are quite specific for RA and may play a role in the disease process. Furthermore, citrillunated peptides are found within the lungs of patients with RA, especially in smokers where citrullination is triggered in the context of smoking-induced inflammation.[62] This is one mechanism by which smoking is a risk factor for RA. The early commercial assay for ACPAs was an enzyme-linked immunosorbent assay which used various filaggrin epitopes. The second, improved assay uses cyclic epitopes that mimic true conformational epitopes, which were selected from libraries of citrullinated peptides. This widely available commercial kit (second-generation anticyclic citrullinated peptide2 assay [anti-CCP2]) has been shown to have a moderate sensitivity (approximately 65%) and high specificity (approximately 95%) for RA.[65]

ACPAs could contribute to synovial inflammation through the deposition of immune complexes and targeting of synovial antigens. With regard to the lungs and ACPAs, there are several interesting observations. First, a range of interstitial and airway abnormalities were documented in a group of patients with ACPAs in the absence of clinical or serological evidence of RA or other connective tissue disorders (CTD).[66] Over time, joint inflammation did develop in a small number of these patients, demonstrating that generation of ACPAs can precede the development of joint disease.[66] In patients diagnosed with RA by clinical and serological methods, ACPAs have been associated with a variety of lung abnormalities including a low DLCO,[47] ILD,[61,63,64,67] bronchial wall thickening,[47] airflow obstruction,[61] and nodules.[47,63] Mori et al found high levels of ACPAs associated with RA-related airways disease (RR, 3.8; $p < 0.005$) and less so with RA-ILD (RR, 2.7; $p < 0.07$).[61]

The strength of these associations may be influenced by the type of ACPA measured. In recent work looking at ACPAs identified in the serum using a "reverse immunophenotyping" approach, Harlow et al demonstrated that a specific ACPA, against citrullinated Hsp90 has a high specificity (> 95%) and moderate sensitivity (20–30%) for RA-ILD relative to RA without lung disease or IPF.[64] In another study of 177 patients with RA, ACPAs were measured with both the anti-CCP2 commercial kit and by using a range of specific ACPAs that had been identified in previous studies. They found that RA-ILD was associated with both higher levels and a greater number of specific ACPAs than RA without ILD.[67] It is possible that an association between specific ACPAs and lung disease is hidden when the broad range, rather than specific ACPAs, is studied.

The interaction between smoking, the lungs, and RA is intriguing. Smoking increases pulmonary PAD-2 and is also a recognized risk factor for airways disease and idiopathic and RA-related ILD. Citrullinated proteins are found in the BAL of smokers but not in nonsmokers.[62] ACPAs have been identified in the lungs of smokers, with elevated levels in the BAL and airways. Willis et al identified ACPAs in the sputum of a group of patients at risk for RA (based on family history) in the absence of seropositivity, which along with increased ACPA to total immunoglobulin (Ig) ratios in sputa, supports the lung being the site of autoantibody generation in the early development of RA.[68] It is possible immune responses to citrullinated proteins may occur and indeed start in the lung. Clearly, this is not the whole answer as RA-ILD can occur in nonsmokers.[69]

At this stage, apart from their use in the diagnosis of RA, these antibodies remain in the research domain. However, this work raise the possibility that specific antibodies may help predict ILD as an EAM in RA, as is seen in the antisynthetase syndrome where anti-Jo-1 is strongly predictive of ILD in the inflammatory myopathies.[10]

Interstitial Lung Disease in Rheumatoid Arthritis

Importance and Clinical Presentation

ILD is the most important pulmonary manifestation of rheumatoid disease, being the commonest pulmonary cause of death in RA and a significant contributor to morbidity.[5–7,70,71] An autopsy study of 81 patients with longstanding RA noted that 16% died of respiratory failure, while 34% had evidence of ILD.[70] In a large inception cohort in the United Kingdom followed for 18 years, excess mortality was seen for pulmonary disease overall (18%) and specifically ILD (4%).[6] Apart from the clinical consequences of ILD, the presence of either clinically overt or subclinical ILD may influence the choice of DMARDs although it should be noted that the majority of patients with RA are not troubled by lung disease.

The clinical presentation and disease spectrum of RA-ILD are generally similar to that of the idiopathic interstitial pneumonias (IIPs)[72] although differences have been noted in the pathology.[73] The classification of the idiopathic forms is regularly updated with progressive teasing apart of previously combined categories (cellular and fibrotic nonspecific interstitial pneumonia [NSIP]) and the addition of newly recognized IIP,[74,75] but all recommendations emphasize that the diagnosis is best made through multidisciplinary discussion (MDD) between pulmonologists, radiologists, and pathologists.[75,76] Castelino et al has emphasized the need for rheumatologists and pulmonologists to work together to enhance the accuracy of disease classification.[77] In a study of 50 patients referred with ILD, reclassification from idiopathic to CTD-associated ILD (CTD-ILD), or CTD-ILD to a different form of ILD occurred in a significant number (54%), with changes in therapy occurring in the majority of patients with CTD-ILD (84%). For those patients with

supposed idiopathic ILD, a number with predominately usual interstitial pneumonia (UIP) pattern, on review were reclassified as having an autoimmune featured-ILD, with manifestations of an undifferentiated CTD.[78] As ILD can predate the development of joint or serological manifestations,[7–9] supported by the finding that 21 of 603 patients in a population cohort had ILD diagnosed before the appearance of RA,[7] ongoing monitoring of presumed idiopathic ILD is warranted and ACPA measurement should form part of the screen for patients presenting with what appears to be idiopathic ILD.

For a patient with RA, an acute respiratory presentation may represent acute interstitial pneumonia (AIP), an exacerbation of ILD (with known or previously unknown preexisting disease), infection in an immunosuppressed host, a drug reaction, or a mixture of these. The differential diagnosis needs to remain broad, with a range of investigations covering the possibilities being included (see section "Approach to Patients with RA-ILD") and discussions should be held within a multidisciplinary team.[3] Diagnosis is based on clinical presentation, blood gases, and pulmonary function tests, if the latter can be performed, and HRCT scan, blood tests, sputum, possibly BAL, and very occasionally, a lung biopsy. Bronchoscopy and BAL are primarily useful in the exclusion of infection or diagnosis of other diffuse lung diseases (e.g., sarcoidosis, drug reaction). Nuclear imaging with gallium scans or DTPA scans do not have a useful role. With regard to a biopsy, transbronchial biopsies (TBBs) may be diagnostic with organizing pneumonia (OP) or confirm infection (fungal) but for most other possibilities are inadequate for diagnosis. Old HRCTs, including abdominal films, where upper slices may include the lung bases, are invaluable in determining if there is longstanding disease.

In the patient with RA presenting with chronic respiratory symptoms or the asymptomatic patient with RA, a range of interstitial patterns may be present. Modalities used to look for disease vary in sensitivity and frequently detect changes which may not be clinically significant. Of 36 patients with early rheumatoid disease, 33% had a DLCO $<$ 80% of predicted, but only 14% had symptoms.[44] It is the clinical picture with symptoms and crackles[79] and changes on HRCT, backed by a restrictive pattern on physiology, that are the key for confirming the type and significance of ILD, with the majority with significant disease showing abnormalities on all measures.

The common pathological and HRCT patterns of RA-associated ILD are shown in ►**Table 2**. These changes vary in terms of prevalence, prognosis, and histology but based on histological and HRCT-based studies, UIP and NSIP are the most common patterns found (44–56 and 33–44%, respectively), followed by mixed disease (0–12%).[80,81] OP and AIP are seen less commonly (0–11%),[82–84] and ymphocytic interstitial pneumonia (LIP) and desquamative interstitial pneumonia (DIP) are rare.[3,4,18,56,80,81,90] Most studies of prognosis are likely to include patients with a mix of UIP and NSIP, making recommendations for a specific pattern difficult. A poor prognosis is associated with more extensive fibrosis or worsening of the extent of disease on HRCT, although reliable techniques which minimize interobserver variation are still being developed[91–94] with the aim of better prediction of outcome. Goh et al have proposed a simple system classifying disease as extensive ($>$ 30% of lungs affected) or limited ($<$ 10% of lungs affected), with the significance in indeterminate category (10–30%) being determined by the forced vital capacity (FVC), with values $>$ 70% suggesting limited disease. A recent study showed traction bronchiectasis and honeycombing were related to mortality in CTD-ILD, and interobserver agreement was greatest for traction bronchiectasis.[95,96] The importance of asymptomatic changes will be discussed later.

Physiological abnormalities include a reduction in lung volumes, with total lung capacity (TLC) and FVC, a low DLCO, and oxygen desaturation during a 6-minute walk test

Table 2 Clinicopathological subtypes of RA-associated ILD[3,4,7,16,18,72,75,80–90]

	Prevalence[a]	Prognosis	Radiological pattern	Histological pattern
Usual interstitial pneumonia	+++	Poor	Subpleural, basal predominance, reticular abnormality, honeycombing with or without traction bronchiectasis, absence of inconsistent features	Subpleural and paraseptal interstitial fibrosis, fibroblastic foci, architectural distortion with honeycombing, temporal heterogeneity, patchy involvement
Nonspecific interstitial pneumonia	+++	Intermediate to good	Bilateral ground glass change may have traction bronchiectasis and bronchiolectasis	Ground glass opacification (cellular) through to interstitial fibrosis (fibrotic) without honeycombing, uniform process
Organizing pneumonia	++	Good	Patchy peripheral consolidation, subpleural and peribronchial, often migratory	Intraluminal organization in alveolar ducts, occasionally alveoli and bronchioles with preservation of background lung tissues; variable interstitial inflammation
Acute interstitial pneumonia/DAD	+	Poor	Patchy ground glass changes with basal consolidation, rapid progression	Acute DAD with edema and hyaline membranes.

Abbreviations: DAD, diffuse alveolar damage; ILD, interstitial lung disease; RA, rheumatoid arthritis.
[a]Prevalence + (rarest) to +++ (commonest).

(6MWT).[3,4,15,55] Both DLCO and desaturation with walking can be influenced by the coexistence of emphysema or pulmonary hypertension.[55] A low DLCO is the measure best associated with the extent of disease in ILDs and a poorer prognosis in RA-ILD and FVC alone is not useful for predicting prognosis in ILD. Dawson et al found that a low DLCO was an indicator of a poor prognosis, with 80% of patients whose disease progressed having a DLCO less than 54%, and 93% of patients whose disease did not progress had a DLCO greater than 54% (i.e., 80% sensitivity and 93% specificity).[45] Desaturation $< 88\%$ is associated with a worse prognosis in ILD and is useful for guiding need for oxygen therapy or referral for transplantation. In terms of monitoring disease, comprehensive tests rather than FVC should be measured to increase the accuracy.[55] A significant fall would be accepted as a decrease in DLCO by 15% and FVC by 10% from baseline values. If abnormalities are present, initial monitoring should be 3 to 6 monthly, then yearly if stable.[55]

The importance of investigations, in particular the HRCT and physiological assessment, is in determining the type of lung disease, the severity, and the change over time. It is extremely important to determine what type of underlying ILD is present in the IIPs because of differing prognoses and treatment,[95] but the importance of determining the subtype of ILD in RA is less clear. As in the IIPs, when the radiological picture is not classical, the diagnosis can be inaccurate when compared with histology.[74,96,97] One report in RA noted a UIP-like picture on HRCT but NSIP on histology, but this is uncommon.[98]

Outcomes in RA-ILD

Bongartz et al found in a longitudinal study that the 10, 20, and 30 years cumulative incidence of definite and probable ILD in patients with RA was 3.5, 6.3, and 7.7%, respectively, with a lifetime risk of 10%, suggesting disease can develop or progress late in the disease process.[7] Dawson et al noted 34% of patients with RA-ILD progressed[45] and Kim et al noted those with a definite UIP pattern on HRCT had a worse prognosis.[90] Hakala showed hospitalization was not common among patients with RA-ILD (one case per 3,500 patient-years), but those hospitalized for ILD had a median survival of only 3.5 years.[98] Solomon et al retrospectively reviewed 48 patients with RA-ILD proven on biopsy, 31% of them having UIP. Age and fibrosis predicted a poor outcome.[99]

In a retrospective review of 84 patients with RA-UIP who were monitored for 33 months, Song et al found respiratory abnormalities remained stable over that period in 50%, progressed in 30%, deteriorated with an acute exacerbation in 17%, and improved in 6%. A high TLC predicted stability.[97] Importantly, the stable group remained stable for a median of 45 months. Tsuchiya et al used HRCT and where available, pathology to retrospectively review outcome in 144 patients with RA-ILD, according to pathological patterns.[100] As expected the poorest prognosis was in those with diffuse alveolar damage (20.0% 5-year survival), followed by UIP (36.6%), OP (60.0%), bronchiectasis (87.1%), and bronchiolitis (88.9%), with the best prognosis in the patients with NSIP (93.8%). Importantly, diagnosis of NSIP was based on HRCT findings of predominant bibasilar ground-glass attenuation with limited reticulation and absent honeycombing.

Studies on the outcomes in RA-related UIP, NSIP, or unclassifiable patterns compared with the idiopathic forms, although not sufficiently powered to provide robust conclusions, suggest a better prognosis with RA than in IIP, including with a range of immunosuppressive therapies.[94,96,99–101] In one case–control study comparing 18 patients with RA-ILD versus 18 patients with IPF, the median survival was greater for patients with RA-ILD (60 vs. 27 months).[85] In a study of 86 patients with RA-ILD and 872 with IPF, survival was similar between the two groups.[87] Song et al reported a retrospective study where the prognosis of RA-UIP was significantly better than IPF, after matching for age, sex, smoking, and baseline lung function, with a median survival of 53 versus 41 months, respectively ($p = 0.015$).[97] Although the evidence is mixed, it does suggest that a substantial number of patients with RA-ILD have abnormalities that do not progress and a better outcome with RA-ILD than IPF.[100–103] These findings hold when the subgroup of RA-UIP is compared with IPF. Studies also show much heterogeneity in progression among patients, irrespective of the pathological picture.[80–94]

In view of the variability in outcomes, combined with significant comorbidities in patients with RA, unlike in the IIPs, a surgical lung biopsy is usually not sought. As will be discussed, a more pragmatic approach to diagnosis is tending to be taken and prognosis and need for treatment is guided more by the extent of disease on HRCT, severity of physiology impairment, and rate of progression determined during a period of observation, than histology.[103] This approach may change with information from better longitudinal studies regarding the clinical course and response to treatment with the different histological subtypes.

Treatment of RA-ILD

With regard to treatment, the evidence is of low quality or absent. Nondrug treatment to be considered includes education, psychological support, and exercise rehabilitation, the latter used in IPF, but in patients with RA is likely to be limited by joint disease. There are no randomized controlled trials for drug treatment of RA-ILD. The limited data come from series or case reports, or small trials, the most recent with rituximab, which was inconclusive.

In general, the approach to treatment is based on evidence from the IIPs, where OP is usually very responsive to glucocorticoids and treatment would be given, NSIP somewhat responsive, and treatment given especially if features suggested a nonfibrotic type, and UIP is poorly responsive and drug treatment would be avoided unless given as part of a clinical trial. In the retrospective study of Song et al, 41% of patients with RA-UIP were treated due to poor initial lung function or progression of the disease. Treatment was with high-dose corticosteroids combined with azathioprine, cyclophosphamide, or cyclosporine and median follow-up of 33 months.[97] Of the patients, 50% improved or had stable lung function and there was no difference in outcome between the treated and untreated groups, despite worse starting lung function in the treated group. Predictors of poor outcome

were age, low FVC, and a decrease in DLCO over time. This study was not prospective, randomized, or controlled but would suggest either the outlook with treatment is better in RA-UIP than IPF, or the clinical diagnosis of RA-UIP is not accurate and the group probably includes patients with RA-NSIP, shown to have a better prognosis and response to treatment.

Approach to Patients with RA-ILD

How does this translate into practical advice for the clinician? An approach taken by Ryerson et al with unclassifiable ILDs was to categorize disease by behavior, taking into account independent predictors of survival with low DLCO and high radiological fibrosis score from the HRCT.[103] To quote Cottin, in an editorial linked to the article of Ryerson et al,[104] the classification as "self-limited, reversible, stable, or progressive and irreversible (with and without the potential for long-term stabilisation with therapy) may help to adapt treatment goals and the monitoring strategy." The approach is used in recent guidelines on IIPs and can be usefully applied to RA-ILD with heterogeneous outcomes, infrequent pathological confirmation, and little data to guide treatment other than on clinical behavior.[72] An adaptation of the approach for RA-ILD, incorporating drug-induced lung problems, is shown in ►**Table 3**. Using this as a guide, the treatment for drug reactions and RA-OP is relatively clear. For the many forms of RA-ILD, we would recommend the following be considered, in deciding whether or not to treat with drugs:

- MDD to confirm the diagnosis and review severity of ILD based on extent of fibrosis on HRCT and DLCO ($< 54\%$).
- Unless severe symptomatic disease, monitor comprehensive lung function (spirometry, lung volumes, DLCO, and 6MWT) for 3 to 6 months if initial measurements are abnormal.
- Consider potential impact (positive or negative) of drugs required for joint disease (DMARDs) and monitor lung function during therapy.[105]
- Consider treatment if extensive disease (extent of fibrosis on HRCT $> 30\%$, DLCO $< 54\%$, desaturation with exercise), deteriorating (decrease from baseline in FVC by 10% or DLCO by 15%) or very symptomatic.
- Review age and comorbidities (obesity, osteoporosis, cardiovascular disease, infection risk, diabetes, coexisting lung disease such as chronic obstructive pulmonary disease [COPD]).
- Determine patient's informed wish.

Treatment may be considered, irrespective of whether the pattern of ILD is UIP or NSIP, if disease is clinically significant (symptoms, severity of abnormalities), progressive and if the patient is younger, has minimal comorbidities, and is keen for treatment.

There are no randomized controlled trials for the treatment of RA-ILD. There are reports of the benefits of prednisolone/azathioprine, prednisolone/cyclophosphamide, cyclophosphamide, azathioprine, hydroxychloroquine, d-penicillamine, and cyclosporine,[3,4,18,94,97,106–108] but there are no data as yet on N-acetyl cysteine or pirfenidone, although a study of the former is underway. Outcome was poorer when methotrexate (MTX) was part of therapy. In acute severe disease, pulsed intravenous methylprednisolone is recommended. There are reports of bDMARDs resulting in an improvement in ILD; however, as discussed later, reports have also documented rapid, occasionally fatal progression of lung disease and the development of new ILD.

Table 3 RA-associated interstitial pneumonias: classification according to disease behavior, adapted from Travis et al,[72] classification for the idiopathic interstitial pneumonias[a]

Clinical behavior	Treatment and treatment goal	Monitoring strategy
Potentially reversible with risk of irreversible disease (e.g., cases of drug-related lung disease in RA)	Remove cause, treat to obtain a response to reverse changes	Short-term (3–6 mo) observation to confirm disease regression, or occasionally need for palliation
Reversible disease with risk of progression (e.g., RA-cellular NSIP and some RA-fibrotic NSIP, RA-OP)	Treat to initially achieve response and then rationalize longer term therapy	Short-term observation to confirm treatment response. Long-term observation to ensure that gains are preserved
Stable with residual disease (e.g., some RA-fibrotic NSIP, some RA-UIP)	No treatment if stable, aiming to maintain status	Long-term observation to assess disease course
Progressive, irreversible disease with potential for stabilization (e.g., some RA-fibrotic NSIP, some RA-UIP)	Consider treatment trial to stabilize	Long-term observation to assess disease course
Progressive, irreversible disease despite therapy (e.g., RA-DAD, most RA-UIP, some RA-fibrotic NSIP)	In absence of contraindications, consider treatment trial in selected patients to slow progression	Short (DAD) or long-term observation to assess disease course, and need for transplant or effective palliation

Abbreviations: DAD, diffuse alveolar damage; NSIP, nonspecific interstitial pneumonia; OP, organizing pneumonia; RA, rheumatoid arthritis; UIP, usual interstitial pneumonia.

[a]Based on a diagnosis established by a multidisciplinary team and with disease behavior classification reviewed with longitudinal measurement.

If a patient fails to respond or deteriorates, different immunosuppression could be considered but if the patient is young, early referral for lung transplantation is required and for others, following extensive discussion with the patient and family, active palliation may be instituted.[109–111] Lung transplantation is often not possible because of age, immobility, osteoporosis, and EAM. Palliative measures include oxygen, titrated to reduce the exercise-induced hypoxia, treatment for cough, reflux, and breathlessness.[109–111]

Subclinical RA-ILD and Progression

Subclinical disease is frequent and the best way to approach a patient with abnormalities but no symptoms is unclear.[8,9,59] In practical terms, subclinical disease is when HRCT shows interstitial changes, but symptoms and other tests do not support clinically important disease. The importance of subclinical disease is that early disease can progress and there is hope that deterioration can be prevented. RA patients who were older at the time of disease onset, male and who had more severe RA, were on MTX[59] or continued to smoke were at highest risk of progression.[6] Although these studies demonstrate progression, the majority of patients do not have problems so how aggressively patients should be monitored, with investigations such as HRCT which carry some risk with radiation, is not clear. Doyle et al have outlined an algorithm for those with idiopathic disease, but also those seen to be at higher risk, as in the setting of familial ILD and CTD-related ILD.[12] This investigating all patients with RA as they are "at risk" would result in a large number of investigations. To minimize unnecessary tests, a threshold for instigating further investigations needs to be considered. Cottin and Cordier have argued crackles may be a useful screen, which should lead to a CXR, and comprehensive lung function, as spirometry (FVC) alone may underestimate abnormalities.[55,79] A history of smoking should lead to investigation with a CXR and spirometry (looking for airflow obstruction) in the first instance. When DMARDs, such as MTX, should be avoided in patients with subclinical ILD will be discussed in the next section.

Drug-Induced Lung Disease in Rheumatoid Arthritis

Developments in drug therapy, with earlier use of conventional nonbiologic DMARDS and bDMARDs, often in combination or with a rules-based treat-to-target strategy, has had a profound impact on the morbidity and mortality of RA.[1,12–14] Infrequently, DMARDs have been associated with drug-related pulmonary disease with significant mortality, which needs to be considered when choosing treatment.[112,113] The most common problems are infection (discussed elsewhere),[16,17] diffuse interstitial processes,[16] and less commonly, airway disease or the development of nodules.[114] The risk of pneumonitis, in particular, in the presence of pre-existing lung disease, may be overemphasized, especially in the context of the benefits of DMARDs.

Differentiating between a drug reaction, underlying RA-associated lung disease, infection, or another problem can be difficult so a careful history and clinical assessment is important.[12] The Web site, www.pneumotox.com[113] provides a comprehensive collection of the published literature relating to adverse drug effects involving the lungs. ►**Table 4** summarizes the drugs, their reactions, and predisposing factors. However, with new drugs entering the market on a regular basis, up to date information on adverse reactions should be obtained if there is any concern.

Nonbiologic DMARDs

MTX remains the most commonly used DMARD in patients with RA and is recommended as first-line therapy. The most common noninfectious pulmonary complication is AIP, with uncommon reports of interstitial fibrosis, nodules, asthma, and air trapping.[16,119–125] Importantly, MTX has been associated with progression of preclinical interstitial disease,[63] raising the issue of screening and avoidance of MTX in certain patients. However, this is a rare occurrence and with the high prevalence of minor abnormalities and the significant benefit of MTX, a decision as to whether to avoid the drug or not should be based on both the severity of the joint disease and underlying lung disease. Acute pneumonitis may be an idiosyncratic reaction, as it does not always recur on rechallenge with MTX. Pneumonitis can occur with low doses (< 20 mg per week), usually within 2 years but can begin early after commencement and on changing from oral to parenteral,[120] or in one case, a month after it was discontinued. In patients with RA, the overall likelihood of developing acute pneumonitis during MTX therapy is 0.3 to 11.6%.[127] A multicenter, case–control study of 29 patients and 82 controls[122] found older age (OR, 5.1), diabetes mellitus (OR, 35.6), hypoalbuminemia (OR, 19.5), pre-existing pleural or lung involvement with RA (OR, 7.1), and smoking and use of other DMARDs, in particular penicillamine (OR, 5.6) which is rarely used now, were risk factors for MTX-induced pneumonitis. In general, patients respond to MTX withdrawal and the prognosis is usually good, although the reaction can be fatal in some cases. Uncontrolled studies suggest glucocorticoids may be important in severely ill patients. Cautious rechallenge is an option if the drug is essential for management.[16] Concern over the long-term effects of MTX upon lung function have not been supported by studies and although a mild reduction in spirometry has been reported, it is not clinically important.[12,125]

Leflunomide blocks pyrimidine synthesis in activated lymphocytes and has been associated with ILD and nodule formation, with a RR of ILD of 1.9 compared with other DMARDs,[126–128] although the risk was insignificant if there was no prior diagnosis of ILD or MTX use. Similar findings were reported in a large observational study with 1.2% of patients treated with leflunomide developing new or worsening ILD. As with MTX, safe prescribing requires assessment of risk factors with severity of pre-existing lung disease being the most important factor[128] as well as smoking, low body weight, and use of a loading dose.

Table 4 Reported adverse pulmonary reactions to drugs used to treat RA

Drug group	Adverse reaction	Risk factors for adverse reaction
Anti-inflammatory drugs		
NSAID (high-dose) anti-inflammatory[114,115]	Eosinophilic pneumonia (naproxen)	n/a
Corticosteroids[116–118]	Infection	• Dose related • Pre-existing severe lung disease • Biologic DMARD
Nonbiologic DMARD		
MTX[119–125]	Pneumonitis	• Abnormal lungs (DLCO $<$ 70% increased risk by 10%) • Smoking, low albumin, previous use of DMARD
Leflunomide[112,126–128]	Pneumonitis—ALI/DAD Nodulosis	• Pre-existing ILD • Previous MTX—OR, 8.17; 95% CI, 4.63–14.4 • Japanese origin
Sulphasalazine, gold, penicillamine[16,129]	Pneumonitis—OP and NSIP	
Biologic DMARD[134,135]		
TNF blockade[130–139] • Etanercept (soluble p75 TNFα receptor fusion protein) • Infliximab (dimeric anti-TNFα) • Adalimumab (anti-TNFα monoclonal antibody) • Golimumab • Certolizumab	Infection including TB (pneumonia 0.8%) Pneumonitis—ALI/UIP/NSIP (0.6%) Noninfectious granulomatous disease New lung nodules	• Previous lung disease • Low body weight • Older age • Previous MTX pneumonitis • CXR and Mantoux or QuantiFERON Gold before therapy
Anakinra (IL-1 blocker)[140,141]	Infection	No reports of pneumonitis
Rituximab (anti-B cell monoclonal antibody)[141–146]	Rare—rapidly progressive, OP	
Abatacept (a selective costimulation modulator which prevents T cell CD28 binding)[141]	Pneumonitis	
Tocilizumab (humanized anti-IL-6 receptor mAb)	Rare exacerbation of pre-existing ILD	

Abbreviations: ALI, acute lung injury; CI, confidence interval; CXR, chest X-ray; DAD, diffuse alveolar damage; IL, interleukin; NSIP, nonspecific interstitial pneumonia; OP, organizing pneumonia; OR, odds ratio; TNFα, tumor necrosis factor alpha; UIP, usual interstitial pneumonia.

Biologic DMARDs

Biological DMARDs are used second line after MTX and work in a variety of ways.[13,14,16,24,130,131] They have been shown to improve symptoms, joint disease, and possibly lung disease in patients with RA; however, pulmonary toxicity with a high mortality has also been described.[14–16] Overall, however, the rate of adverse reactions is low. A variety of lung toxicities are shown in ►**Table 4**.

Useful information comes from the many biologic registers around the world.[130–132] The British Society for Rheumatology Biologics Register (BSRBR) prospectively collects data on all patients in the United Kingdom receiving bDMARDs ($>$ 8,000 patients).[140] The OR for mortality was 4.4 times higher (95% confidence interval [CI], 1.8–10.7) for those patients with RA and pre-existing pulmonary disease who were treated with bDMARDs compared with those without pulmonary disease,[140] although some case reports show an improvement in ILD with bDMARDs.[105] Overall, the risk is low at around 1% although the mortality with a reaction appears to be high at 35.5%.[11] Despite case reports, it is not clear if combination therapy, such as with MTX and leflunomide, significantly increases the risk of an adverse reaction with bDMARDs.[11]

Use of DMARDs in the Presence of Subclinical or Clinically Apparent Lung Disease in RA

The overall risk of pneumonitis from MTX, leflunomide, or tumor necrosis factor (TNF) inhibitors has been estimated from a systematic literature review, at around 1%.[11] The fatality rate from the reaction is reported to be 13% with MTX, 18% with leflunomide, and 35.5% with TNF inhibitors. In recognizing the significant impact, these drugs have had on

joint disease and overall morbidity and mortality,[1] the oft recommended avoidance of these drugs in the setting of any pulmonary abnormality seems inappropriate. Important considerations are pulmonary reserve and other comorbidities, and whether the patient would tolerate the development of pneumonitis.[11] With significant abnormalities with symptoms, signs (crackles), and abnormal HRCT and physiology, the drugs should be avoided or used with caution, but most other patients are likely to tolerate therapy without pulmonary consequences. Patients should understand the small risk and be educated to seek early review with the development of any new pulmonary symptoms. If DMARDs are used in patients with lung disease, regular monitoring with comprehensive lung function, initially at 3 to 6, then 12-month intervals if stable, is recommended.[55] Repeat HRCT should be used if deterioration in lung function is noted.

Infection in Rheumatoid Arthritis

The reported prevalence of infection in patients with RA varies substantially among studies and although it is not clear if there is an increase in mild infections in patients with RA, several studies confirm an increase in severe infections with probably worse outcomes.[137,139,141] Most of these studies have not reported on infection by site,[142] but pulmonary infection, in particular bacterial pneumonia, is the commonest form of severe infection.[146,147] Other forms of pulmonary infection include bronchitis, exacerbations of bronchiectasis, empyema, or infected nodules. Predisposing factors for severe infection include host defense abnormalities related to RA (e.g., premature aging of the immune system), more active disease, comorbidities (e.g., underlying lung disease, smoking, diabetes, kidney disease),[53,54] and RA-related drug therapy.[147–150] It is estimated that corticosteroids increase the risk of serious infection fourfold.[118] Nonbiologic DMARDs such as MTX and low-dose azathioprine have not been shown to consistently increase the risk of infection,[5–54] but may delay recovery from an infection, and although there is no clear evidence, some recommend the drug should be stopped during the episode of severe infection.

Cohort studies from registries show an increased risk of infection with bDMARDs[53,54,135,151] with suggestions TNFα inhibitors increase risk twofold. However, results from the German bDMARD registry RABBIT of TNFα inhibitors use have shown, over 3 years of observation, that the risk of severe infection fell from 4.8 to 2.2/100 patient-years.[147] This, in part, relates to the drop out of high-risk patients, but is likely to also relate to the bDMARD with improvement in RA with therapy resulting in better mobility and less need for corticosteroids.[147] In terms of disease control and reduction in corticosteroid use, the use of bDMARDS outweigh the risk of infection with these drugs.[53,150] With respect to corticosteroids in RA, it is estimated a dose of 5 mg/d is associated with a RR for severe infection of 1.4 (95% CI, 1.2, 1.6), for 5 to 10 mg/day a RR of 1.9 (95% CI, 1.7, 2.2), and for 10 to 20 mg/day a RR of 3.0 (95% CI, 1.9, 4.7),[23,54,119,120] so minimizing the dose should be a priority.

It is important to be aware of the possible infectious agents when caring for an individual unwell with respiratory symptoms. Many infections reflect the organisms endemic to a geographical area. From cohorts and case series treated with corticosteroids and DMARDS, both common organisms such as pneumococcus, and opportunistic infections such as *Pneumocystis jiroveci* pneumonia (PJP), cryptococcal pneumonia, invasive pulmonary aspergillosis and disseminated histoplasmosis, other fungal species, Nocardia, Listeria, and viral pneumonia caused by parainfluenza and cytomegalovirus and tuberculosis have been reported.[149–157] Kameda from Japan showed, in a study of patients on bDMARDs presenting with acute onset ILD thought to be drug related, 13/26 had definite and 11/26 had probable *P. jiroveci*,[152] with good outcomes with treatment.

The development of tuberculosis, with both mycobacterium tuberculosis (MTB) and nontuberculous mycobacteria (non-TBM) has been associated with bDMARDs. From the British Biologics Register, the development of MTB was greatest in those treated infliximab and adalimumab, and lowest with etanercept.[140] The majority of the disease was extrapulmonary (62%) with a significant number presenting with disseminated disease. Appropriate screening (history, CXR, and Interferon Gold/Mantoux) before the start of treatment has had a significant impact on the development of active TB during therapy.[58] The development of non-TBM, most commonly due to *Mycobacterium avium*, probably relates to preexisting disease, with a range of CT abnormalities being evident before treatment commenced, from small nodular lesions, bronchial abnormalities, and bronchiectasis to alveolar abnormalities.[152] Outcome for non-TBM with treatment was favorable and it has been suggested the bDMARD could be continued during treatment for the non-TBM with successful outcome for both RA and the non-TBM.[154,155] Monitoring for at least 6 months after anti-TNF therapy is stopped is required.[153,157]

Attempts have been made to estimate the size of the contribution each of these factors, such as severity of RA, comorbidities, and RA therapy, to infection risk,[117,118,147–150] and to provide a guide when considering RA treatment options in any individual. For example, in patients with comorbidities such as COPD and older age, and a dose of glucocorticoids which cannot be reduced despite other therapy, the risk of bDMARDs probably outweighs the benefit. The most important measure to reduce risk appears to be minimizing the dose of corticosteroids in all patients, and selective use of other immunosuppressive drugs. Other general measures which are important are vaccination with pneumococcus and influenza vaccines,[53] which appear to reduce morbidity and mortality.[146,150] The responses to pneumococcal vaccination is not significantly diminished by bDMARDs. Prophylaxis against PJP during treatment for RA is not routine but could be considered when high-dose corticosteroids ($\geq$20 mg of prednisone daily for 1 month or longer) are required, especially when combined with a TNFα inhibitor or another immunosuppressive drug. When rituximab is considered, low IgG levels increase risk of infection and so levels should be measured.[153,157]

Bronchiectasis

An association between diffuse bronchiectasis and RA (RA-BB) has been noted, but for many, the disease is not troublesome.[43] As with other forms of lung disease, the HRCT is a sensitive way of detecting airway abnormalities. In a study of 26 patients with extensive bronchiectasis, the delta F508 mutation of the transmembrane conductance regulator gene (*CFTR*) was seen in 15.4%, significantly higher ($p < 0.05$) when compared with patients with RA but no bronchiectasis (0%) or the general population (2.8%).[158] In a family study, the CFTR mutation cosegregated with RA-DB (sib transmission disequilibrium test $= 10.82$, $p = 0.005$), indicating that a mutation unrelated to RA is linked to EAMs of RA.[159] Treatment of symptomatic disease does not differ from bronchiectasis unrelated to RA but significant disease and ongoing infection would be a contraindication to the use of bDMARDs.

Changes in Extra-articular Lung Disease over Time and with New Therapies

There have been significant changes in the management of RA over the past 25 years and as a result the development of disabling joint disease is much less common.[1] A shift has occurred from simple symptom management, to anti-inflammatories such as corticosteroids, to the consistent and early use of DMARDs, such as MTX, and bDMARDs, alone or in combination.[11,15] The aim with early treatment is to reduce the inflammation and structural joint damage, and this has resulted in improvement in long-term outcomes, with significantly reduced mortality and morbidity.[13,160–163] As the EAMs of RA are related to the activity, severity, and duration of the joint disease, one would predict early treatment of joint disease, with better drugs, may reduce the incidence or severity of EAM. This predicted improvement, however, could be masked by adverse effects of the DMARDs.

Earlier longitudinal cohort studies did not show any change over time in the prevalence of severe EAM or vasculitis (up to 1995).[161] Recently, however, several studies have shown a reduction in amyloidosis and vasculitis but not nodules or ILD. Glace et al followed 10 patients on the French AutoImmunity and Rituximab/Rheumatoid Arthritis registry, who had lung nodules found at recruitment. A significant reduction in nodule size was seen after treatment.[162] However, the major focus is on ILD. As noted, there are numerous case reports or case series of the development of a variety of forms of ILD in patients with RA treated with MTX and with biological modifiers, but also reports showing substantial improvement in pre-existing lung disease with MTX and bDMARDs. In a group of 122 patients with RA, with and without lung disease before treatment, Perez-Alvarez et al found worsening or new ILD of various histological types developing after commencement of anti-TNFα agents.[163] As noted, both new and worsening of pre-existing ILD after anti-TNF therapy carried a high mortality.[11] Conversely, a study in 1993 of 59 patients with RA who had no pulmonary symptoms showed 18% who were taking DMARDs (MTX, chloroquine, gold, penicillamine) had abnormal histology on TBB but 42% who were not on DMARDs had abnormal histology.[164]

Large studies from registries,[12] including from the BSRBR, with patients with known RA-ILD on DMARDS and bDMARDs, found after adjustment for age, sex, and other potential confounders, the adjusted mortality rate ratio was 0.81 (95% CI, 0.38–1.73) for the bDMARD cohort compared with the DMARD cohort. RA-ILD, however, was a more common cause of death in the TNFα blockers cohort.[165] Two large cohorts from Japan involving over 10,000 patients found a low prevalence of ILD and good outcomes when treated with etanercept and infliximab combined with MTX.[11] As noted previously, although there is a range of potential biases, the recent systematic literature review would support the safety of these agents, showing pulmonary toxicity was rare.

How to balance the risk of adverse lung reactions, including from infection and the possible benefit in terms of "treating" underlying lung disease will require more data from longitudinal studies, but as recommended, a sensible approach is to assess the risk factors for adverse effects (smoking, significant pre-existing lung disease, older age, comorbidities such as diabetes mellitus, need for high-dose corticosteroids) and closely monitor patients, through educating patients to seek help early with symptoms and monitoring of lung function. Longer and larger studies of the use of biologic DMARDs in a range of stages of RAILD and in combination with a variety of risk factors will better guide our ability to accurately predict risk.

Summary: A Practical Clinical Approach to Patients

The importance of lung disease in patients with RA has been recognized for some time, and the extent highlighted by improvements in the sensitivity and accuracy of investigations such as the HRCT. Numerous case reports raise concerns about drug toxicity with the DMARDs in patient with no lung disease, subclinical or clinically important lung disease. However, reactions are rare and overall, there does not appear to be worse outcomes. ►**Table 5** outlines an approach for either pulmonologists or rheumatologists for the commonest clinical scenarios they will see, namely, a new patient presenting with RA; a patient with RA and subclinical pulmonary abnormalities; a patient with known RA with pulmonary symptoms and interstitial abnormalities referred for assessment by pulmonologist; and finally, a patient with known RA treated with nonbiologic or biologic DMARDs. More data are required to allow us to accurately predict the risk of worsening RA-related lung problems or adverse lung reactions to therapy. In considering infection in the setting of RA, progress has been made in modeling risk and estimating the impact of being on corticosteroids at varying levels, additional DMARDs in the presence of other comorbidities and underlying lung disease (including ILD and COPD). With more data, we should be able to take a similar approach with estimating the risk of the development or worsening of ILD in the setting of treatment for RA. Until that time, the need for effective RA

Table 5 Approach to patients with RA and possible pulmonary EAM

Scenario 1: Patient with new onset RA presenting to a rheumatologist
In patient with new onset RA, it is important to determine the type and severity of lung involvement as part of the EAM, or presence of other lung disease, which may impact choice of RA treatment. A recommended approach would be to assess • Symptoms (breathlessness, cough, chest pain), smoking status, occupational, or other exposures • Signs (crackles) • Ensure receives yearly influenza vaccination and 5 yearly pneumococcal vaccination[153,166] • If considering biologic DMARD, obtain history of TB exposure, and perform CXR and Mantoux or QuantiFERON Gold[153,166] If normal and nonsmoker • Nil apart from ongoing monitoring of symptoms and signs If normal but significant smoking history (previous or current) • Smoking cessation • Spirometry • CXR • Monitor if abnormalities If significant abnormalities • Smoking cessation • Comprehensive lung function (spirometry, lung volumes, diffusion capacity) and 6MWT • CXR and HRCT • Consider review by a pulmonologist • Monitor 3–6 monthly (comprehensive pulmonary function tests), then yearly if stable • If evidence of latent TB and/or TB exposure, consider TB prophylaxis if using biologic DMARD
Scenario 2: Patient with known RA with subclinical or clinically apparent interstitial pulmonary abnormalities (rheumatologist or pulmonologist)
Consider • Initial assessment to include clinical assessment, comprehensive lung function and 6MWT, CXR and HRCT, autoantibodies, ACPA • Consider multidisciplinary review to establish ◦ Pattern and severity of lung disease ◦ Treatment options for RA • Ensure receives yearly influenza vaccination and 5 yearly pneumococcal vaccination • If considering biologic DMARDs, obtain history of TB exposure and perform Mantoux or QuantiFERON Gold[153,166] • Monitor symptoms, comprehensive lung function, 6MWT initially 3–6 monthly, 12 monthly if stable • HRCT if decline in lung function. • Avoid MTX if clinically significant lung disease and comorbid factors • If biologic DMARD, close monitoring[166] of symptoms and 3–6 monthly lung function, and if evidence of latent TB and/or TB exposure, consider TB prophylaxis. Avoid if severe chronic lung infection
Scenario 3: Patient with known RA with pulmonary symptoms and interstitial abnormalities referred for assessment by pulmonologist
Consider the possible diagnoses • New onset ILD associated with RA • Known or unknown pre-existing ILD with ◦ Worsening/exacerbation of disease ◦ Superimposed infection or other problem (e.g., pulmonary embolism, heart failure) ◦ Superimposed drug reaction • Drug reaction • Other problem (pulmonary embolism, heart failure) Approach to assessment • History looking for timing of start of symptoms or decline, examination for crackles • Look for pre-existing disease with old X-rays, including abdominal or spinal CTs, which may include basal lung fields • Sputum for culture, blood tests exploring infection and RA • HRCT, lung function, oxygenation, 6MWT • Consider bronchoscopy, washings (infection, drug reaction) • Multidisciplinary review of type and extent of disease • Consider surgical lung biopsy if unusual or if felt it would change management (rarely required) If deteriorating • Multidisciplinary discussion to confirm the diagnosis and review severity of ILD based on extent of fibrosis on HRCT and DLCO ($< 54\%$) • Unless severe symptomatic disease, monitor comprehensive lung function (spirometry, lung volumes, DLCO, and 6MWT) for 3–6 mo if initial measurements are abnormal • Consider potential impact (positive or negative) of drugs required for joint disease (DMARDs) and monitor lung function during therapy • Consider treatment if extensive disease (extent of fibrosis on HRCT $> 30\%$, DLCO $< 54\%$, desaturation with exercise), deteriorating (decrease from baseline in FVC by 10% or DLCO by 15%) or very symptomatic

• Review age and comorbidities (obesity, osteoporosis, cardiovascular disease, infection risk, diabetes, coexisting lung disease such as COPD) • Determine patient's informed wish
Scenario 4. Patient with known RA treated with nonbiologic or biologic DMARD
• Educate patient to seek advice early with any new unexplained symptom • Monitor for new symptoms or signs (crackles) 3–6 monthly initially • If subclinical interstitial disease, monitor lung function • Ensure receives yearly influenza vaccination and 5 yearly pneumococcal vaccination[166] • If evidence of latent TB and/or TB exposure, monitor for TB for at least 6 mo after discontinuing anti-TNF therapy[166]

Abbreviations: ACPA, anticitrullinated protein antibody; CT, computed tomography; CXR, chest X-ray; DLCO, low diffusing capacity for carbon monoxide; DMARD, disease modifying antirheumatic drug; EAM, extra-articular manifestation; FVC, forced vital capacity; HRCT, high-resolution computed tomography; ILD, interstitial lung disease; MTX, methotrexate; RA, rheumatoid arthritis; 6MWT, 6-minute walk test; TNF, tumor necrosis factor.

therapy should drive treatment decisions and therapy avoided only in those patients with severe or worsening lung disease. The rest can be monitored closely during therapy and have a good outcome.

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