Interstitial lung disease in rheumatoid arthritis: an update on diagnosis and management

There has been increasing recognition of the importance of respiratory disease in patients with rheumatoid arthritis (RA) over the last 5 years. Interstitial lung disease (ILD) is the only complication of RA increasing in prevalence and accounts for approximately 6% of all RA deaths, with a mean survival of just 3 years following diagnosis in several historic series. Clinically significant ILD is present in approximately 3–5% of all RA patients, making RA-ILD a common and potentially fatal disorder. Although the presence of RA-ILD increasingly influences therapeutic decision-making, our understanding of its pathogenesis remains limited, as is the evidence base to guide therapeutic intervention. Recent data suggests that RA-ILD may relate to smoking and/or the presence of CCP antibodies. High-resolution computed tomography has allowed clarification of the type and extent of pulmonary involvement without recourse to lung biopsy in most cases. Moreover, the use of certain therapeutic agents may be contraindicated in patients with RA-ILD, while latest figures suggest that the prognosis of the condition has improved with the introduction of newer therapeutic agents.

KEYWORDS: interstitial lung disease ■ mortality ■ rheumatoid arthritis ■ survival

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Learning objectives

Upon completion of this activity, participants should be able to:

- Describe the mortality and morbidity associated with interstitial lung disease (ILD) in patients with rheumatoid arthritis (RA), based on a review
- Describe diagnostic evaluation of patients with RA-ILD, based on a review
- Describe treatment considerations for patients with RA-ILD, based on a review

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Natural history

A decade ago, patients with rheumatoid arthritis (RA) were usually rate limited by the pain and dysfunction associated with the articular manifestations of RA. Earlier studies had identified a high post-mortem incidence of interstitial lung disease (ILD) in RA and these were supported by high-resolution computed tomography (HRCT), which confirmed that up to 25% of RA patients had ILD [1,2]. As more effective treatment for the articular manifestations of RA has become available, patients are less likely to be limited by joint disease, while respiratory involvement in the form of ILD has become increasingly recognized as a major factor in determining morbidity and mortality in RA [3,4]. The prognosis of patients with RA-ILD has been the subject of several studies in the last decade with most papers concluding that the mean survival from diagnosis is approximately 3 years [3,5,6]. It is likely that this represents a predominance of usual interstitial pneumonia (UIP) in these series, as this carries a worse prognosis than the other subtypes as described in subsequent sections.

Conflicting results have been reported on whether RA patients with ILD fare differently to those with idiopathic ILD [7,8]. However, the value of these data has been limited by being small single center work or coming from a general practice database. ILD is the only complication of RA reported to be increasing in prevalence and it has been shown to account for around 6% of all RA deaths [9]. The pattern of ILD can be determined by HRCT, and appears to be a major determinant of prognosis, with UIP carrying the worst outlook [10–12]. Recent data suggests that HRCT assessment of disease extent also predicts survival in RA-ILD [13].

Epidemiology

An association between positive rheumatoid factor and ILD in RA is well established, and a similar link with antibodies to cyclic citrullinated peptides (CCP) is likely [14–16]. Positive CCP antibodies in ILD may predate the subsequent onset of RA, especially in smokers [17]. The possibility that CCP antibodies might therefore predict the later development of ILD in patients with RA merits consideration. This may be particularly true in active smokers as smoking promotes site-specific citrullination in the lungs leading to generation of CCP antibodies thus promoting lung abnormalities very early in the rheumatoid process [18]. The range of lung abnormalities during the development of early RA includes airways disease and might suggest the lung as a site of initiation of RA. Smoking is an obvious candidate catalyst for this process, but it is likely that other factors that generate local airway inflammation may prove important as airway changes have been reported in early RA, even in never smokers with and without CCP positivity [19,20].

Predictors of the development of RA-ILD have been reported in a number of studies. They include male gender [21,22], smoking [23], long disease duration and the presence of other systemic features [24]. The strongest association lies with smoking, while the link with male gender is more tenuous. Many older males with RA-ILD will exhibit significant comorbidity with vascular disease, recurrent infection and occasionally vasculitis. However, finger clubbing is not a common feature and is seen much less than

in patients with pulmonary fibrosis who do not have RA, even at equivalent levels of pulmonary dysfunction and hypoxia [25]. The reason for this difference remains unexplained. In addition, it is likely that genetic predisposition may play an important part [26], with several studies over the years reporting an increased frequency of polymorphisms at the HLA-B40 and B-54 antigen sites in RA patients with ILD and cryptogenic organising pneumonia [27,28]. Patients with RA-ILD are less likely to be DR-4 positive [29] but more likely to possess the site encoding for the alpha-1 protease inhibitor [30].

Evaluation of ILD

Symptoms of ILD are usually those of increasing exertional breathlessness, often associated with a dry cough. Some patients complain of increasing fatigue and this becomes an invariable feature once hypoxia develops. Resting hypoxia is frequently associated with ankle edema due to secondary pulmonary hypertension [101]. Physical signs include bibasal lung crackles, initially fine and heard in late inspiration, progressing to louder coarser crepitations audible throughout inspiration as the disease process advances. No clearing with coughing occurs. Finger clubbing is relatively uncommon, occurring in under 20% of patients. Central cyanosis may accompany resting hypoxia.

Blood gases will assess the degree of hypoxia and disproportionately low oxygen saturations at rest may indicate the need to exclude other contributory factors, such as infection or pulmonary embolism. Hypercapnia is only seen as an end-stage phenomenon of advanced ILD. Raised lactate levels may accompany intercurrent infection. Plain chest radiography is often normal in the early stages of RA-ILD and may prove falsely reassuring. Established disease will usually be visible as reticular shadowing accompanied by increasingly nodular opacification of the lower lobes, usually in a broadly symmetric pattern. Lung cancer is an occasional complication of established ILD and is more likely in smokers [7]. An isolated nodule or coin lesion, or lobar collapse should raise this suspicion.

HRCT of the thorax provides much more definitive information and is required to make a confident diagnosis of ILD. It has three other important roles: first, it allows the type of ILD to be established; next it allows the extent of disease to be assessed; and finally it allows exclusion of other pathologies that might mimic ILD or coexist with it. Taking each in turn, the majority of patients with RA and ILD have UIP with a relatively poor prognosis [31]. Nonspecific interstitial pneumonia is found in approximately one-third of patients, while cryptogenic organizing pneumonia is seen in approximately 10% of patients [32]. This subgroup generally carries a more favorable prognosis and appears more responsive to therapy [33]. Overlapping features may be found in some patients. The extent of disease is categorized as limited if less than 20% of the lung parenchyma is affected and as extensive otherwise. This definition was initially shown to match with prognosis in scleroderma lung disease [34], and has recently been shown to also apply to RA-ILD [13]. Finally, HRCT will differentiate patients with bronchiectasis from those with ILD, a distinction that cannot be confidently made on clinical grounds or plain chest radiography alone. HRCT will also often demonstrate air trapping as a result of small airways disease, a feature that is increasingly recognized in RA [35–37].

Pulmonary function tests (PFTs) are sensitive but very nonspecific. They are largely unhelpful in making a diagnosis of ILD but sequential PFTs are invaluable in assessing the progress of the condition and its response to treatment. Baseline measurement of at least vital capacity and gas transfer corrected for lung volume is recommended, as these are the most consistent comparators. Repeat measurement at intervals of 6 months allows the rate of decline to be plotted and the effect of intervention to be assessed.

Treatment trials

For many decades therapeutic nihilism reigned supreme in the management of RA-ILD, largely as a result of the perception that it did not produce symptoms of relevance to the patient already disabled by their joint manifestations. Oral steroids were used sporadically but with limited benefit and no controlled data existed to guide intervention. Azathioprine was given to patients who appeared to improve with steroids to allow dose reduction, but without clinical trials to inform, the efficacy of this agent in stabilizing disease progression remained unclear. Although it was shown that azathioprine and steroids appeared to offer greater survival benefits than steroids alone in idiopathic pulmonary fibrosis 20 years ago [38], this is no longer felt to be the case in the light of more recent evidence from the as yet unpublished PANTHER study.

Although a clinical trial has shown no significant benefit of cyclophosphamide in idiopathic pulmonary fibrosis [39], this agent has recently been shown to have a modest benefit in scleroderma ILD [40] and is now used in RA-ILD,

albeit with limited efficacy data [41]. Other authorities have advocated the use of cyclosporine or hydroxychloroquine in the treatment of RA-ILD, with very limited supporting evidence.

The British Thoracic Society, among others, conducted trials of two new therapeutic approaches in ILD patients over the last decade, although these did not focus specifically on patients with RA. *N*-acetylcysteine (NAC) in the dose of 600 mg three-times daily was shown to be effective in reducing the rate of decline of pulmonary function in idiopathic pulmonary fibrosis [42]. This led to the addition of NAC to prednisone and azathioprine as standard triple therapy for idiopathic pulmonary fibrosis (IPF). However, the recent PANTHER study, which compared triple treatment against NAC alone, with a placebo group, has terminated the triple therapy arm prematurely as of October 2011 because of increased mortality from a variety of causes, with approximately half of respiratory origin. The NAC single therapy arm has continued and results are expected later in 2012.

Trials of low-dose warfarin initially appeared to show a significant improvement in survival [43] associated with a reduction in D-dimer levels [44]. Anticoagulants were felt to reduce pulmonary thromboembolism, a common terminal event in advanced ILD. These data have also been questioned as a result of the ACE-IPF study, which also terminated prematurely as a result of excess mortality seen in those treated with warfarin over the control group. Routine use of warfarin is no longer recommended.

Several other agents have been trialled as potential treatment for IPF with negative or equivocal results to date: these include bosentan, interferon, perfenidone and the anti-TNF agent etanercept. Imatinib is presently undergoing clinical trials. It remains uncertain as to whether the results of studies in patients with IPF can be directly extrapolated to those with RA-ILD.

Mycophenolate has recently been shown to be effective in the treatment of ILD in scleroderma [45–48], with a recent study reporting improvement in PFTs in six and stability in five of 14 patients followed for a year [49]. Similar benefit has been reported in patients with RA-ILD [50]. This agent appears to combine reasonable efficacy with relatively low toxicity, but the evidence base for its use in RA-ILD remains limited at present. The agents used in the treatment of RA-ILD, both previously and presently, are shown in Table 1.

Rituximab is an anti-CD20 antibody with the potential to modify the immune response. Promising results in the treatment of several pulmonary complications of systemic lupus erythematosus (SLE) have been reported with rituximab, including lupus pneumonitis [51], shrinking lung syndrome [52,53] and pulmonary hemorrhage complicating ILD [51]. An open-label pilot study of rituximab in patients with ILD complicating antisynthetase syndromes also showed a good response [54]. Some publications relate to single cases where reporting bias may exist, so the data on the efficacy of rituximab in specific disease settings must be interpreted with a degree of caution. In total, however, rituximab has been reported in the treatment of ILD complicating scleroderma, systemic lupus erythematosus and the antisynthetase syndromes in a total of 33 patients with one death, 13 exhibiting stability and improvement recorded in 19 individuals [55–59].

The demonstration of CD20 B-cell infiltrates in patients with RA-ILD has lent support to the concept of using rituximab in this clinical setting [60]. The authors of a recent open-label pilot study of rituximab in a small number of RA patients with a mean duration of 3 years of ILD reported that "we did not find a signal for clinical efficacy of this treatment for RA-ILD". However, their data did show improvement or stability in HRCT and PFTs in the majority of patients over 48 weeks, although two deaths were recorded [61]. A larger series of 48 patients with RA-ILD from the UK has reported that rituximab to be well tolerated with one death noted over 2.5 years follow-up, although the effect of treatment on HRCT and PFTs were

Table 1. Comparison of traditional versus newer therapeutic agents in the management of rheumatoid arthritis–interstitial lung disease.

Traditional approach	Idiopathic pulmonary fibrosis	Newer agents
Oral steroids	*N*-acetylcysteine	Mycophenolate
Azathioprine	Bosentan	Rituximab
Oral cyclophosphamide	Perfenidone	Intravenous cyclophosphamide
Cyclosporin	Imatinib	*N*-acetylcysteine

not reported in detail [62]. Two further deaths have been reported within a year of treatment with rituximab in three other series totaling 80 patients with RA-ILD [63–65]. This equates to a total 1-year mortality of under 5% in RA-ILD patients treated with rituximab to date.

However, these mortality data are still significantly greater than expected in RA patients without ILD. In addition, it is important to note that concern regarding the potential pulmonary toxicity of rituximab has also been voiced. In patients treated with rituximab for lymphoma and with no evidence of lung disease at baseline, 16 cases of pneumonitis possibly due to rituximab were reported, with six resultant deaths by 2007 [66]. These figures were updated recently with a total of 45 possible rituximab-induced lung disease cases and a total of eight deaths [67]. These figures were accrued from over 100,000 patients treated with high-dose rituximab over more than a decade.

Although no comparative trials evaluating survival in RA-ILD have been published since the advent of these newer therapeutic agents, our experience suggests that the outlook for patients with RA-ILD may be improving since their introduction, although other factors, such as the earlier identification of ILD, may play a part in the observed increase in life expectancy from the onset of pulmonary symptoms. It appears possible that this improvement in outlook is largely confined to those patients without UIP whose prognosis remains poorer. Figure 1 shows mortality data for patients with RA-ILD for the decades either side of the year 2000.

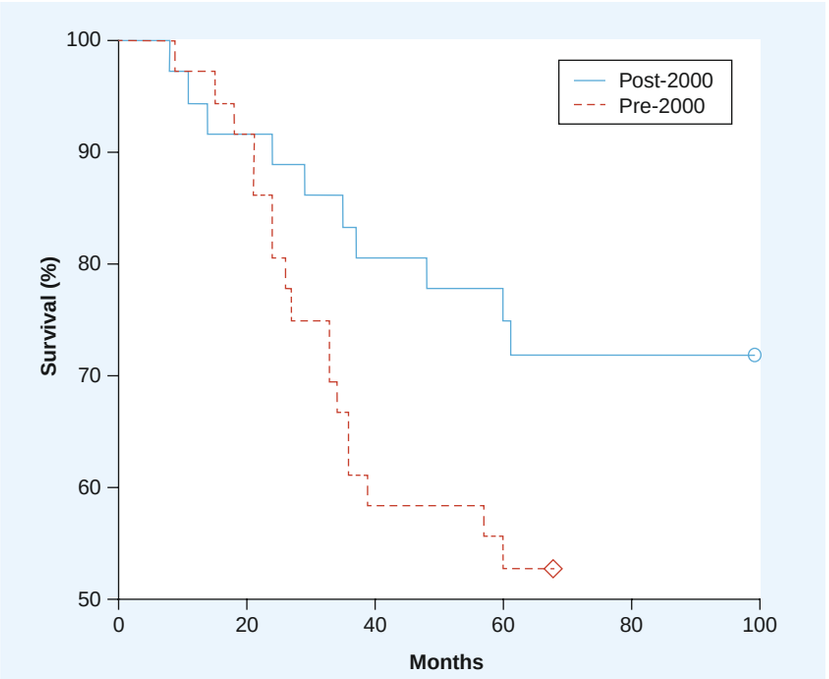

Figure 1. Comparing survival trends in rheumatoid arthritis–interstitial lung disease over the decades either side of 2000 suggesting an improvement in outcome over time.

Adverse effects of antirheumatic drugs on the lung

The treatment of RA patients is complicated by the potential for several drugs of proven articular efficacy to be associated with accelerated respiratory failure in the presence of ILD. Although there is limited evidence at present, we suggest these agents may be used with caution in patients with RA-ILD.

Methotrexate & leflunomide

The first-line disease-modifying antirheumatic drug (DMARD) in RA is methotrexate (MTX). Historically, this has been associated with 'MTX pneumonitis', an adverse respiratory event previously thought to be an acute drug hypersensitivity reaction. The absence of a universally agreed definition of MTX pneumonitis to differentiate between causes of respiratory failure has complicated work in this area and we are currently unable to predict with confidence who will get MTX pneumonitis. It is agreed that patients with baseline abnormalities in pulmonary function due to ILD are at greater risk as such patients have reduced pulmonary reserve and are likely to fare worse [68]. Patients are most likely to develop pneumonitis within the first 6 months of MTX therapy and prognosis tends to be worse in this group with a case fatality rate of 20% [69]. Overall, the incidence of MTX pneumonitis appears to have fallen in the last decade from approximately one case in every 100 patient years to approximately 0.5 cases [70]. MTX has not been shown to accelerate the progression of underlying ILD in RA but the increased risk of pneumonitis means that it may not always be the safest first-line DMARD in such patients. We have previously recommended the strategy of performing baseline pulmonary function testing in RA patients in whom MTX is considered in order to screen for the presence of underlying lung disease [71]. Patients who subsequently develop dyspnea while taking MTX, which is not uncommon, may therefore have a baseline to compare to subsequent results. Such an approach may help to avoid unnecessary cessation of MTX therapy in those with stable pulmonary function.

Leflunomide has also been reported to cause pneumonitis, although this appears to occur

much more frequently in Japanese and Korean patients [72], suggesting a genetic link with causality. The frequency with which pneumonitis complicates leflunomide therapy in Caucasians is less than 0.1 in every 100 patient years, but patients with a history of MTX pneumonitis are also at increased risk of pneumonitis with leflunomide.

Anti-TNF drugs

There is some evidence that several anti-TNF agents used in the treatment of RA may accelerate progression of ILD. There have been a number of reports of patients with mild ILD at baseline commenced on etanercept [73], infliximab [74] and adalimumab [75] who have developed rapidly progressive and often fatal pulmonary fibrosis. It is unclear as to how many of these cases were due to the effect of MTX, which is usually coprescribed, but 95% of cases occurred within 3 months of starting anti-TNF therapy with a mortality of 40%. A recent report from the British Society for Rheumatology's Biological Register has revealed that all-cause mortality was no greater in 299 patients with RA-ILD treated with anti-TNF therapy, compared with those 68 treated with DMARDs alone. However, death from ILD was recorded in 21% of those on anti-TNF treatment as compared with 7% who received DMARDs. The adjusted mortality rate ratio for death from ILD on the death certificate was 2.63 for those treated with anti-TNF therapy, although a number of factors could have introduced bias in both directions [76]. It has been suggested that patients with prior RA-ILD should receive anti-TNF treatment with caution and a strategy to actively exclude such patients from anti-TNF therapy has been considered [71,77].

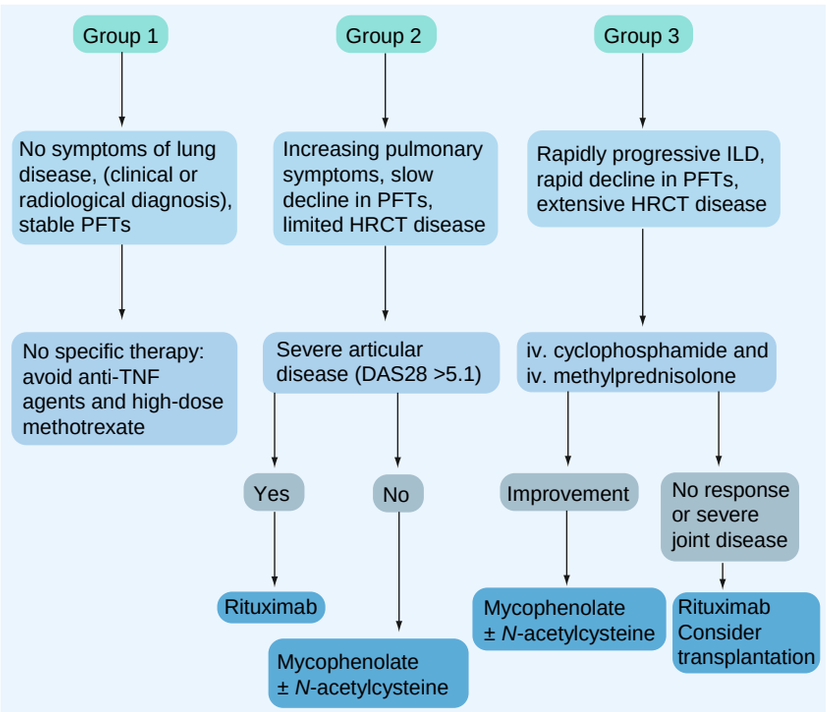

Figure 2. Proposed therapeutic approach to patients with rheumatoid arthritis–interstitial lung disease.
DAS: Disease Activity Score; HRCT: High-resolution computed tomography; ILD: Interstitial lung disease; iv.: Intravenous; PFT: Pulmonary function test.

Lung biopsy

Although the use of HRCT has reduced the need for lung biopsy, there are still circumstances where histological information may be useful. Open lung biopsy is generally avoided in patients with RA because of the increased complication rate, so transbronchial biopsy or video assisted thoracoscopic biopsy is preferred. This should be considered in patients where HRCT has been unable to offer a clear cut diagnosis, especially if the possibility of malignancy or chronic infection cannot otherwise be excluded. This is particularly important in younger patients with rapidly progressive disease or systemic features, such as weight loss or fever. The use of immunosuppressive agents without excluding malignancy or infection can have devastating consequences.

Whom to treat & how: expert opinion

There is a dearth of objective evidence to support treatment of RA-ILD at present. This section summarizes our present clinical approach. Patients with RA-ILD fall into three broad categories, and this distinction is important when deciding who and how to treat. The first group are those with no symptoms of lung disease in whom the discovery of ILD has been incidental and based on clinical or radiological examination, confirmed by HRCT. If these patients remain asymptomatic and have no evidence of progression with time as evidenced by stable PFTs, then no specific therapy for their lung disease appears necessary. Nonetheless, the presence of ILD in such patients may influence the choice of antirheumatic therapy for the reasons already outlined. MTX should be used with caution in Caucasian patients, while leflunomide should be avoided in patients of Japanese/Korean origin. Their use in combination with anti-TNF agents may be best avoided in the presence of ILD. In those patients whose DAS28 score justifies biologic therapy (>5.1 in the UK), rituximab 1 g

given intravenously on two occasions a fortnight apart might prove a safer option.

Patients with gradually increasing symptoms of dyspnea in the presence of proven ILD require a more targeted approach. Many of these will have evidence of steady deterioration in their pulmonary function and/or radiological appearances, although most will exhibit limited disease on baseline HRCT. Such patients justify treatment for their pulmonary disease, in addition to single or combined DMARD therapy for articular features. Many clinicians still prescribe prednisone in the dose of 20 mg daily and taper this depending on clinical response. We advise the use of mycophenolate at the dose of 1–2 g daily, with the option to add NAC at the dose of 600 mg thrice daily. Again, those patients meeting criteria for biologic treatment may benefit from rituximab. In such patients the addition of mycophenolate and NAC may be unnecessary.

The third group comprises those RA patients with rapidly progessive ILD. These patients are at risk of imminent respiratory failure and most will have extensive disease on HRCT with a marked reduction in gas transfer. We recommend the use of intravenous cyclophosphamide at 15 mg/kg with methylprednisone at 10 mg/kg on six occasions 4 weeks apart. Coprescription of mesna coincident with the infusions reduces the risk of cystitis and cotrimoxazole 960 mg thrice weekly is valuable prophylaxis against atypical pneumonia. At present we only use warfarin in patients with proven pulmonary embolism. The majority of patients improve or stabilize with this regime, and can then be treated with mycophenolate from 6 months. In those who continue to deteriorate, the prognosis is poor and lung transplantation should be considered if the patient is suitable. Rituximab is indicated in those whose articular disease activity justifies biologic therapy. These recommendations are summarized in Figure 2.

Future development

The use of prognostic markers to identify which patients are likely to develop progressive ILD has attracted interest of late. The use of serum ferritin as a prognostic marker in scleroderma ILD has been recently proposed [78]. Patients with levels of over 1500 µg/l at baseline had significantly increased mortality during follow-up. Although this has yet to be tested in RA-ILD, patients with elevated acute phase markers do appear to fare less well. Serological markers also offer promise in this regard. The titers of CCP antibodies in patients with RA-ILD are significantly elevated compared with control RA patients without ILD [79] and ongoing work is designed to assess whether those with the highest titers carry the worst outlook. Other more specific antibodies, such as vimentin, may also be of prognostic value here.

It is a source of continued surprise that the evidence base supporting the management of a serious complication of a common disease is still so underdeveloped. Attempts to fund comparative studies of the therapeutic agents described in the previous section have met with the rejoinder that they are premature. In order to obtain some comparative data on outcomes associated with different treatment regimes, we have proposed a UK national database to assess outcome in 500 RA-ILD patients over the next 3 years. Information from this should then facilitate development of the drug studies required to provide the solid evidence base that our patients with RA-ILD deserve and require.

Executive summary

Natural history

- Interstitial lung disease (ILD) has become well recognized as an important cause of mortality and morbidity in rheumatoid arthritis (RA).

Epidemiology

- A number of factors are thought to increase the probability of developing RA-ILD, including gender, smoking and disease duration.

Evaluation of ILD

- Clinical and physiological assessment of patients with RA-ILD must be combined with high-resolution computed tomography for full evaluation of pulmonary involvement.

Treatment trials

- There are very few treatment trials specific to RA-ILD, but the limited evidence points to potential benefit from a number of newer agents.

Adverse effects of antirheumatic drugs on the lung

- Several agents used in the treatment of RA can induce or exacerbate existing ILD, and clinicians should be alert to possible deterioration.

Whom to treat & how: expert opinion

- Treatment needs to take account of the individual patient's extent of disease, rate of progression and comorbid conditions.

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Medscape EDUCATION Interstitial lung disease in rheumatoid arthritis: an update on diagnosis and management

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Activity evaluation: where 1 is strongly disagree and 5 is strongly agree.

	1	2	3	4	5
The activity supported the learning objectives.					
The material was organized clearly for learning to occur.					
The content learned from this activity will impact my practice.					
The activity was presented objectively and free of commercial bias.					

1. Based on the review by Dr. Malik and colleagues, which of the following statements about the mortality and morbidity associated with rheumatoid arthritis and interstitial lung disease (RA-ILD) is **most likely** correct?

- ☐ **A** Post-mortem and high resolution computed tomography (HRCT) studies have shown that about 10% of RA patients have ILD
- ☐ **B** As treatment for joint involvement in RA improves, ILD is becoming increasingly recognized as a major factor in determining morbidity and mortality in RA
- ☐ **C** Mean survival from diagnosis of ILD in patients with RA is about 6 years
- ☐ **D** HRCT does not help determine the prognosis of patients with RA-ILD

2. Your patient is a 63-year-old male smoker with a 20-year history of RA who has recently developed increasing shortness of breath on exertion and dry cough. Based on the review by Dr. Malik and colleagues, which of the following statements about workup for suspected ILD is **most likely** correct?

- ☐ **A** Finger clubbing is required for diagnosis
- ☐ **B** Plain chest x-ray is always abnormal
- ☐ **C** Thoracic HRCT is required to make a confident diagnosis of ILD
- ☐ **D** Pulmonary function tests (PFTs) are highly specific for the diagnosis of ILD

3. The patient described in question 2 undergoes HRCT of the thorax and is diagnosed with ILD. Based on the review by Dr. Malik and colleagues, which of the following statements about treatment would **most likely** be correct?

- ☐ **A** Oral corticosteroids have been well studied and proven highly effective in RA-ILD
- ☐ **B** Azathioprine has been well studied and proven highly effective in RA-ILD
- ☐ **C** Limited or very limited evidence supports the use of cyclophosphamide, cyclosporine, or hydroxychloroquine
- ☐ **D** N-acetylcysteine (NAC) has no role in the treatment of RA-ILD