Interstitial lung disease in rheumatoid arthritis: a review

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Introduction

Interstitial lung disease (ILD) is a progressive fibrotic disease of the lung parenchyma. It occurs in association with several rheumatic diseases including rheumatoid arthritis (RA). This review will focus on ILD occurring in the context of RA (RA-ILD) and will address several areas where new data have recently become available.

Early studies identified a high post-mortem incidence of RA-ILD and this was subsequently supported by high-resolution computed tomography (HRCT) which confirmed that up to 25% of RA patients had ILD.¹,² 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.³,⁴

Until the end of the last century patients with RA rarely complained of breathlessness resulting from ILD. Their mobility was usually limited by pain and dysfunction associated with articular manifestations of the disease. As earlier and more effective treatment for the articular manifestations of RA has become the norm, patients are less likely to be limited by joint disease, while respiratory involvement in the form of ILD has become increasingly recognised 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 20 years with most papers concluding that the mean survival from diagnosis is about 3 years.⁵-⁷ (Table 1, Figure 1). Conflicting results have been reported on whether RA patients with ILD fare differently to those without RA.⁸ However, there is now increasing evidence that patients with RA and other connective tissue disorders do have a better overall prognosis than those with idiopathic pulmonary fibrosis.⁹

- Rheumatoid arthritis interstitial lung disease (RA-ILD) is increasingly recognised and is clinically significant in up to 5% of patients with RA
- RA-ILD is strongly associated with male gender, a history of smoking and seropositivity. Although considered a complication of RA, lung disease may predate or develop at the same time as synovitis
- Full assessment of RA-ILD requires clinical awareness, chest examination, pulmonary function testing and high resolution computed tomography (HRCT) of the thorax, which will confirm the diagnosis and allow assessment of subtype and disease extent
- Treatment remains largely empiric in the absence of a therapeutic evidence base, but cyclophosphamide, mycophenolate and rituximab all offer promise
To answer questions on disease outcome and response to therapy, the British Rheumatoid Interstitial Lung (BRILL) network has been established. A key aim of the network is to collect follow-up data on several hundred patients with RA-ILD over the next few years.

Aetiology and pathogenesis
Predictors of the development of RA-ILD are reported to include male gender, smoking and the presence of other systemic features. Many older males with RA-ILD will exhibit significant comorbidity with vascular disease, recurrent infection and occasionally vasculitis. The ERAS (Early Rheumatoid Arthritis Study) group has previously published an association between RA-ILD and increasing age, disease activity (as evidenced by elevated erythrocyte sedimentation rate (ESR)) and disease severity (as indicated by high Health Assessment Questionnaire (HAQ) scores) in a group of 52 patients with the condition.4

An association between positive rheumatoid factor (RF) and RA-ILD is well established, and a similar link with antibodies to cyclic citrullinated peptides (CCP) has been proposed.24-26 Airway changes have been reported in early RA even in those who have never smoked, independent of seropositivity.27,28 Evidence that specific isotypes of RF may be associated with smoking emerged several years ago, and this was rapidly followed by the recognition that in vivo citrullination might occur in the lungs of smokers. Positive CCP antibodies in ILD may predate subsequent RA, especially in smokers.22,23 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 and promoting lung abnormalities very early in the rheumatoid process.24 Smoking might therefore trigger HLA-DR (shared epitope)-restricted immune reactions to autoantigens by increasing peptidylarginine deiminase 2 enzyme expression and citrullination in the lung.25

New data from the BRILL network support this theory. They confirm the presence of RF in 89% and anti-CCP antibodies in 94% of 230 RA-ILD patients with a median age of 64 years.29 Most patients (67%) were past or present smokers, and smoking was significantly more prevalent in men, who also accumulated more pack years than women. In both groups, mean tobacco consumption was greater than in RA controls without ILD. The network also investigated the temporal relationship between the onset of articular symptoms and lung problems. Although joint disease predated ILD in most, lung disease preceded RA in 10% and the conditions were synchronous in a further 5%. They concluded that RA-ILD often occurs at a relatively young age, in contrast to previous reports, and usually within the first decade of RA. They suggest that the association with smoking may account for the relatively higher frequency of RA-ILD in men, and could be mediated through B-cell activation as a result of smoking, evidenced by the production of anti-CCP antibodies.29

It appears likely that genetic predisposition may also be important, with several studies over the years reporting an increased frequency of polymorphisms at the HLA-B40 and B54 antigen sites in RA patients with ILD and cryptogenic organising pneumonia (COP).31,32 Patients with RA-ILD are less likely to be DR4 positive but more likely to possess specific alleles of α1 proteinase inhibitor.33

Radiology and mortality
The prognosis of patients with RA-ILD has been the subject of several studies since 1993 and most papers reported a mean survival from diagnosis of 3 years.34-36 This was felt to be consistent with the predominance of usual interstitial pneumonia (UIP) in RA. However, unpublished data suggest survival may have improved over the last 10 years to around 4 years (Table 1, Figure 1). The pattern of ILD can be determined by HRCT, and appears to be one major determinant of prognosis with UIP carrying the worst outlook and those with non-specific interstitial pneumonia (NSIP), COP and overlap syndromes (OS) faring rather better.36-38 Recent data suggest HRCT assessment of disease extent also predicts survival, with extensive disease defined as >20% of lung affected on HRCT.

The patterns of different forms of RA-ILD have been well characterised on HRCT and correlate well with histological findings in UIP.36,37 The appearances of NSIP on HRCT may be more variable and less closely matched to histology.41,42 Table 2 demonstrates the subtypes of RA-ILD and their relative frequency in clinical practice. New data from the BRILL network

<table>
<thead>
<tr>
<th>Year of diagnosis of RA-ILD</th>
<th>% dying from RA-ILD</th>
<th>Median age at death (years)</th>
<th>Median survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1987-93</td>
<td>67%</td>
<td>63</td>
<td>33</td>
</tr>
<tr>
<td>1994-99</td>
<td>42%</td>
<td>68</td>
<td>36</td>
</tr>
<tr>
<td>2000-05</td>
<td>54%</td>
<td>72</td>
<td>50</td>
</tr>
<tr>
<td>2006-12</td>
<td>30%</td>
<td>76</td>
<td>48</td>
</tr>
</tbody>
</table>

TABLE 1. Changes in mortality rates in RA-ILD, median age at death, and median survival in those dying from RA-ILD, by year of onset of RA-ILD, as shown from data collected by the British Rheumatoid Interstitial Lung (BRILL) network.
has clarified the relationship between mortality and both subtype and extent of RA-ILD and demonstrated an all-cause mortality rate across the UK of just 20% over 14 years, half of deaths being directly due to ILD.\textsuperscript{43} UIP was the predominant subtype, accounting for 66% of cases, followed by NSIP (25% of cases), OS (6%) and COP (4%). Mortality did relate to subtype, with UIP showing a relative risk of all-cause mortality of 3.3 compared to NSIP. In addition, more patients had limited (56%) than extensive (44%) disease at presentation. Extensive disease was associated with a doubling of the relative risk of dying compared to limited disease. This large UK study affirms that RA-ILD subtype and extent are both important predictors of mortality, with UIP and extensive disease carrying significantly increased relative risks of both pulmonary and all-cause mortality.\textsuperscript{43}

### Pulmonary function tests

Pulmonary function tests (PFTs) are a very sensitive but relatively non-specific tool in the assessment of lung disease in RA-ILD. Several studies have previously confirmed abnormalities in both static lung volumes and gas transfer assessment in patients with RA-ILD.\textsuperscript{44-46} However, there has been little consistency across studies, largely as a result of poor population definitions and the lack of standardisation of disease subtypes in the historical literature. A recent study examined baseline vital capacity (VC) and gas transfer ($T_{LCO}$) at presentation with RA-ILD (both expressed as percentage predicted for age and gender).\textsuperscript{43} The authors calculated and compared values of VC and $T_{LCO}$ in those with extensive against those with limited disease. They found that VC was preserved in limited disease but significantly reduced to 70% among those with extensive disease. By contrast, $T_{LCO}$ was reduced in both limited (61%) and extensive (52%) disease. It therefore appears that lung volumes are relatively preserved in limited disease and may be more useful than gas transfer in predicting disease extent at baseline.

However, the main value of pulmonary function testing is in the assessment of the change over time. Patients with static disease will have stable test results, while those with progressive decline in lung volume or gas transfer are likely to have progressive disease. As pulmonary function testing is safer and more sensitive than repeat HRCT, we recommend that this is repeated 6–12-monthly in patients with established RA-ILD. Those with progressive decline are likely to

### TABLE 2. Relative frequency of the different histological subtypes of RA-ILD and their radiological pattern.

<table>
<thead>
<tr>
<th>Subtype</th>
<th>%</th>
<th>Pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>Usual interstitial pneumonia (UIP)</td>
<td>66%</td>
<td>Fibrosis and honeycombing</td>
</tr>
<tr>
<td>Non-specific interstitial pneumonia (NSIP)</td>
<td>24%</td>
<td>Variable levels of alveolitis</td>
</tr>
<tr>
<td>Cryptogenic organising pneumonia (COP)</td>
<td>4%</td>
<td>Multifocal peripheral consolidation</td>
</tr>
<tr>
<td>Overlap syndromes (OS)</td>
<td>6%</td>
<td>Mixed</td>
</tr>
</tbody>
</table>

require more aggressive therapy, particularly if they have UIP or extensive disease on HRCT.

**Articular disease and the lung**

Data on articular disease activity and its correlation with indices of lung disease are sadly lacking in the literature to date. However, there is some recent evidence that disease activity scores in 28 joints (DAS28) may be lower in RA patients with severe ILD than in those without at presentation. This suggests that in patients with ILD the autoimmune process might preferentially be directing its attention to the lung, leading to relative sparing of the joints at least initially. However, after 5 years of follow-up there were no differences in DAS28 scores between survivors with and without ILD, although all-cause mortality was much greater in those with ILD. These data suggest that clinicians might wish to focus on treating lung disease rather than articular symptoms in those RA-ILD patients with low DAS28 scores as these patients may have higher mortality from their lung involvement.

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, these agents should be used with caution in patients with RA-ILD.

Methotrexate (MTX) has been associated with pneumonitis in patients with RA. Although it is difficult to predict which patients may develop MTX pneumonitis it is agreed that those with abnormal pulmonary function due to RA-ILD are at greater risk of death as a result of their reduced pulmonary reserve. 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%. MTX has not been shown to accelerate the progression of underlying RA-ILD but the increased risk of pneumonitis means that it may not always be the safest first-line disease-modifying anti-rheumatic drug (DMARD) in such patients.

Leflunomide has also been reported to cause pneumonitis, although this appears to occur much more frequently in Japanese and Korean patients, suggesting a genetic link with causality. The frequency with which pneumonitis complicates leflunomide therapy in Caucasians is <0.1 per 100 patient-years, but patients with a history of MTX pneumonitis are also at increased risk of pneumonitis with leflunomide.

There is some evidence that several anti-tumour necrosis factor (TNF) agents used in the treatment of RA may accelerate progression of ILD. There have been reports of patients with mild ILD started on etanercept, infliximab and adalimumab who have developed rapidly progressive and often fatal pulmonary fibrosis. It is unclear how many of these cases were due to the effect of MTX, which is usually co-prescribed, but 95% of cases occurred within 3 months of starting anti-TNF therapy with a mortality of 40%. Caution with use of this combination has recently been recommended in the treatment of patients with RA-ILD in America.

A recent report from the British Society for Rheumatology Biologics Register (BSRBR) has revealed that all-cause mortality was no greater in 299 patients with RA-ILD treated with anti-TNF therapy than in those 68 treated with DMARDs alone. However, death from RA-ILD was recorded in 21% of those on anti-TNF treatment compared with 7% who received DMARDs. The adjusted mortality rate ratio for death from ILD recorded 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. It has been suggested that patients with prior RA-ILD should receive anti-TNF treatment with caution.

**Evidence base for treatment of RA-ILD**

RA patients were historically more limited by joint disease and less attention was paid to treating pulmonary disease until recently. Oral steroids were used with limited benefit and fewer data, while azathioprine was often added in patients who appeared to respond. Although it was shown 20 years ago that azathioprine and steroids appeared to offer greater survival benefits in idiopathic pulmonary fibrosis (IPF) than steroids alone, this finding has been challenged by recent evidence from the PANTHER-IPF (Prednisone, Azathioprine, N-acetylcysteine: a study THat Evaluates Response in Idiopathic Pulmonary Fibrosis) study. The study was terminated prematurely as a result of finding excess mortality among the patients treated with azathioprine and prednisone. Much of this was due to pulmonary infection. This study is also re-evaluating the role of oral N-acetylcysteine which has been previously shown to reduce the rate of decline of pulmonary function in IPF. Trials of low-dose warfarin also initially appeared to show a significant improvement in survival but these data have been questioned as a result of the ACE-IPF (AntiCoagulant Effectiveness in Idiopathic Pulmonary Fibrosis) study which was also terminated prematurely because of excess mortality in those treated with warfarin.

Several other agents have been trialled as potential treatment for IPF, with negative or equivocal results to date: these include bosentan, interferon, pirfenidone and the anti-TNF agent etanercept. Imatinib is presently undergoing clinical trials. It remains uncertain whether the results of studies in patients with IPF can be directly extrapolated to those with RA-ILD and it
may be dangerous to assume that they can. Although recent NICE guidance (CG163) is totally negative about the role of immunosuppression in IPF,62 such therapeutic nihilism may not apply to patients with RA-ILD.

Although a clinical study showed no benefit of cyclophosphamide in IPF,63 this agent has recently been shown to have a modest benefit in scleroderma ILD64 and is now mainly used in extensive UIP in RA, albeit with limited efficacy data.65

Mycophenolate has recently been shown to be effective in the treatment of scleroderma lung disease,66-69 with a recent study reporting improvement in PFTs in 6, and stability in 5, of 14 patients followed for a year.70 Similar benefit has been reported in patients with RA-ILD.71 This agent appears to combine reasonable efficacy with relatively low toxicity, but the published evidence-base for its use in RA-ILD remains extremely limited.

Rituximab (RTX) is an anti-B-cell CD20 monoclonal 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 RTX,72-74 Some reporting bias may exist, so the data on the efficacy of RTX in specific disease settings must be interpreted with a degree of caution. However, RTX has been reported in the treatment of ILD complicating scleroderma, SLE and the antisynthetase syndromes in a total of 33 patients, with 1 death, 13 exhibiting stability and improvement recorded in 19 individuals.75-80

The demonstration of CD20 B-cell infiltrates in patients with RA-ILD has lent support to the concept of using RTX in this condition.81 The authors of a recent open-label pilot study of RTX in a small number of RA patients with a mean duration of 3 years of ILD reported no strong evidence for clinical efficacy of this treatment for RA-ILD. However their data showed improvement or stability in HRCT and PFTs in the majority of patients over 48 weeks, albeit with 2 deaths.82 A larger series of 48 patients with RA-ILD from the UK has reported RTX to be well tolerated with 1 death noted over 2.5 years follow-up, although the effects of treatment on HRCT and PFTs were not reported in detail.83 Two further deaths have been reported within a year of treatment with RTX in three other series totalling 80 patients with RA-ILD.84-86 Putting all the studies together demonstrates a total 1-year mortality of under 5% in RA-ILD patients treated with RTX to date. These mortality data remain significantly greater than expected in RA patients without ILD. In addition concern regarding the potential pulmonary toxicity of RTX has also been voiced. A total of 45 possible RTX-induced lung disease cases with 8 deaths87 have been identified, largely from the haematological literature, from over 100,000 patients treated with high-dose RTX over more than a decade. The implications of this experience for the treatment of patients with RA have recently been reviewed.88

Although no comparative trials evaluating survival in RA-ILD have been published since the advent of newer therapeutic agents, 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 RA-ILD may play a part in the observed increase in life expectancy from the onset of pulmonary symptoms.

**Whom to treat and how**

There is a dearth of objective evidence to support treatment of RA-ILD at present. Patients with RA-ILD appear to fall into three broad categories, and this distinction is important when deciding whom and how to treat (Figure 2).

1. **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. The use of MTX in this group does not appear to be specifically contra-indicated.

2. **Patients with gradually increasing symptoms of dyspnoea in the presence of proven RA-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 HRCT at diagnosis with RA-ILD. Such patients justify treatment for their pulmonary disease, in addition to single or combined DMARD therapy for articular features. Mycophenolate (2 g daily), with or without N-acetylcysteine (600 mg tds), has been advocated but awaits formal evaluation in RA-ILD. A trial to compare mycophenolate with azathioprine in the treatment of this subgroup of patients with RA-ILD would be of considerable interest.

3. **The third group comprises those RA patients with rapidly progressive ILD.** These patients are at risk of imminent respiratory failure and many will have extensive UIP on HRCT. Six cycles of intravenous cyclophosphamide (15 mg/kg) with methylprednisone (10 mg/kg) at 3–4 weekly intervals has proved effective but has never been formally studied in RA-ILD. Clinical experience suggests those patients who improve with this regime might then be maintained with mycophenolate.
The presence of ILD may also influence the choice of DMARD and biologic therapy in RA. The use of MTX in combination with anti-TNF agents should probably be avoided in the presence of ILD. In those patients whose DAS28 score justifies biologic therapy (>5.1 in the UK), RTX 1 g given intravenously on two occasions a fortnight apart might prove a safer option. It would seem highly desirable to test this in a clinical trial setting.

The future

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 has been proposed as a prognostic marker in scleroderma ILD. Patients with levels of >1500 at presentation had significantly increased mortality during follow-up. Although this has yet to be tested in RA-ILD, patients with elevated acute phase markers may fare less well.

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 above have not been successful. In order to answer questions on disease outcome and response to therapy, the BRILL network has been established to assess several hundred patients with RA-ILD over the next few years. Data from the BRILL network should then facilitate development of the drug studies needed to provide the solid evidence base that our patients with RA-ILD deserve and require.

References


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