Rheumatoid arthritis-related interstitial lung disease: associations, prognostic factors and physiological and radiological characteristics—a large multicentre UK study

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Abstract

Objectives. The prevalence of interstitial lung disease (ILD) in RA is ~5%. Previous work identified increasing age, active articular disease and articular damage as risk factors for RA-associated ILD (RA-ILD). The roles of high-resolution CT (HRCT) and lung function testing in defining the nature and extent of pulmonary involvement have recently been explored. This study is the first to examine predictive and prognostic factors for the development of RA-ILD and to report on the physiological and radiological characteristics of the condition from a large multicentre UK network.

Methods. We collected data from centres across the UK on patients with both RA and ILD (proved on HRCT) diagnosed over a 25-year period from 1987 to 2012 using a standard pro forma. Potential predictors of RA-ILD were analysed. Baseline lung function data were recorded and related to HRCT findings. We analysed HRCT for subtype and extent of lung involved and examined the relationship between these and both all-cause and pulmonary mortality. We compared our results with case controls matched for age and gender using computer-generated selection from the RA population from one contributing centre.

Results. A total of 230 patients were identified from across the UK with proven RA-ILD diagnosed over 25 years. Median age at diagnosis was 64 years and the male:female ratio was 1:1.09. Univariate analysis showed anti-CCP antibody titres to be the single most strongly associated predictor of RA-ILD. Male gender, age at onset, smoking and RF were all independently associated with RA-ILD on multivariate analysis. Vital capacity (VC) was preserved in limited disease but reduced in extensive disease, while gas transfer was reduced in both. Usual interstitial pneumonia (UIP) was the most common subtype on HRCT and both this and extensive disease were associated with increased all-cause mortality.

Conclusion. This is the largest study of RA-ILD in the UK. Anti-CCP antibodies were strongly associated with RA-ILD in both sexes. Smoking was strongly associated with ILD in males, which may explain the higher frequency of RA-ILD in men. The predominant HRCT pattern was UIP and most patients had limited disease at presentation. The presence of UIP and extensive disease are associated with increased mortality. Baseline gas transfer is a useful screening tool for ILD, while the preservation of VC at baseline might predict limited disease on HRCT.

Key words: rheumatoid arthritis, lung disease, risk factors, prognosis, pulmonary function, high-resolution computed tomography.
Introduction

Early studies identified a high post mortem incidence of interstitial lung disease (ILD) in RA and these were subsequently supported by high-resolution CT (HRCT), which confirmed that up to 25% of RA patients had radiological evidence of ILD [1, 2]. A recent large survey of the clinical features of RA in 15 countries across Europe reported ILD in 4.5% of nearly 10 000 patients [3]. ILD is the only complication of RA reported to be increasing in prevalence and it has been shown to account for ~6% of all RA deaths [4–6].

The Early Rheumatoid Arthritis Study (ERAS) group previously showed an association between RA-associated ILD (RA-ILD) and increased age, increased ESR and high HAQ scores in a group of 52 patients with the condition [7]. Other reported predictors for the development of RA-ILD include male gender [8, 9] and smoking [10–13]. An association between positive RF and ILD in RA is well established, and a similar link with antibodies to CCP has been reported [14–16]. Factors associated with ILD in RA have not been previously described in a large multicentre UK cohort.

The prognosis of RA-ILD has been reported to be poor in previous studies, with a mean survival of just 3 years from diagnosis of RA-ILD [4–6, 15]. However, the importance of HRCT of the lung in assessing the ILD subtype has now been established, and the pattern of ILD can now be determined by HRCT. This appears to be a major determinant of prognosis, with usual interstitial pneumonia (UIP) carrying the worst outlook and those with non-specific interstitial pneumonia (NSIP), cryptogenic organizing pneumonia (COP) and overlap syndromes (OS) faring better [17–19]. The predominance of UIP in RA may explain the overall impression of poor prognosis in previous work [20, 21]. Recent data also suggest that HRCT assessment of disease extent predicts survival in RA-ILD [22]. We have examined the subtype and extent of ILD by HRCT in a large multicentre cohort of RA-ILD patients to assess the effects of each on outcome and have related the extent of disease to baseline pulmonary function.

Patients and methods

We collected data from multiple centres representing rural, urban and inner city populations across the UK using a standard pro forma (Fig. 1) on patients with both RA [23] and ILD (proved on HRCT) diagnosed over a 25-year period from 1987 to 2012. Hospitals represented included Burton Hospital; University Hospitals, Coventry and Warwickshire; Betsy Coed Hospital, North Wales; The Orthopaedic Hospital, Oswestry; Medway Maritime Hospital, Gillingham; Winchester Hospital; Grimsby Hospital; Sheffield Hospitals; Basingstoke Hospital; Chelmsford Hospital; Birmingham Hospitals; The City Hospital, St Albans; Wrightington Hospital; St Helens Hospitals and the Queen Elizabeth Hospital, Gateshead. We had two main objectives, which are both addressed in this article. The first was to identify factors associated with the development of RA-ILD and the second was to describe the radiological and physiological features of the disease in the hope of identifying useful prognostic indicators.

Cases were selected on the basis of symptoms and/or signs of ILD, confirmed on HRCT by a radiologist. Each participating unit collected data on all cases identified this way, acknowledging that this will provide an underestimate of the true prevalence of RA-ILD, as scanning was only performed on RA patients with clinical features of ILD. There was consistency in terms of the percentage of the RA population identified as having RA-ILD across contributing centres, with 2–3% showing clinical and radiological features of ILD. Lung function testing was not performed except in those patients with clinical features of ILD, so HRCT was never performed for reduced transfer factor of the lung for carbon monoxide (TLCO) in the absence of a clinical indication.

We studied the temporal relationship between the onset of both RA and ILD. We analysed factors including gender, age, age at onset, duration of both RA and ILD, etc.
smoking history and serology—both RF and CCP antibody status—to determine associations. We compared our results with a control group of 230 age- and gender-matched RA patients with neither clinical nor radiological evidence of ILD. These case controls were randomly selected by computer and all were drawn from one participating centre.

Data from five of these centres contained enough information to permit further analysis of baseline pulmonary function and HRCT findings over a period of 14 years from 1998 to 2012. Sequential data were available for all patients in this group, allowing all-cause and respiratory mortality to be assessed for these patients. HRCT results were analysed for both subtype (UIP, NSIP, COP or OS) and extent of lung involvement. We defined disease extent based on the percentage of lung involved as assessed by HRCT (>20% = extensive; <20% = limited) [22]. We also collected data on baseline vital capacity (VC) and TLCO, both expressed as a percentage predicted for age, height and gender. We examined the relationship between mortality and both subtype and extent of RA-ILD. We calculated the median baseline values of VC and TLCO and related these to disease extent on HRCT. Relative risk (RR) was calculated to compare the proportion of patients dying between groups defined by disease subtype and by extent, while non-parametric tests were used to calculate and compare group median values for factors associated with RA-ILD and for pulmonary function data.

Logistic regression analysis was undertaken using categorical dependent variable regression models (CDVMs). This was felt to be the most appropriate technique in view of the categorical nature of the dependent variable (presence of ILD or not) and for reducing bias and providing sensible ways of estimating parameters. The independent variables tested in the model were smoking, age at onset, gender, RF and anti-CCP (the latter two both separately and jointly in models). Continuous variables were compared by Mann–Whitney test and categorical values were compared by the chi-squared method using SPSS software (IBM, Armonk, NY, USA).

No external funding was obtained and the study was conducted by clinicians on their own time. Ethical approval was obtained from each participating centre and all patient data were anonymized.

**Results**

A total of 230 patients were identified with proven RA-ILD diagnosed over 25 years from six centres across the UK. In total, 110 patients (48%) were male, giving a male:female ratio of 1:1.09. Their median age at diagnosis of RA-ILD was 64 years (range 42–83). This did not differ significantly between males and females.

Articular disease predated ILD in 191 patients (83%), lung disease in 22 (10%) and the conditions were synchronous in 17 (7%). The median duration of RA at the time of diagnosis of ILD was 9 years (range 0–31). The median age at diagnosis of RA was 56 years (range 23–76).

A total of 154 patients (67%) were past (121) or present (33) smokers with a median of 26 pack-years (range 5–88). Smoking was significantly more frequent among males (75%) than females (60%) ($P = 0.02$), and the odds ratio for ever smoking between males and females was 1.95 (1.11–3.43) ($P = 0.02$). The median number of pack-years was greater in males (35) than females (20) ($P = 0.01$). Smoking was less prevalent among RA controls (60%) and median pack-year consumption was lower at 21 (5–60) ($P = 0.03$).

Among patients with RA-ILD, RF and anti-CCP antibodies were positive in 89% and 94%, respectively. By comparison, RF and anti-CCP antibodies were present in 58% ($P = 0.01$) and 55% ($P = 0.006$) of RA controls, respectively. Titres of CCP antibodies were significantly higher in patients with RA-ILD. Detailed results are shown in Table 1.

Multivariate logistic regression with CDVM including both RF and anti-CCP showed them both to be significant predictors of ILD ($P < 0.008$ and $P < 0.003$, respectively). Interestingly, this combined model led to the significance of other variables (age at onset, gender and smoking) becoming less evident. However, data on anti-CCP status were unavailable in 60 cases and when all anti-CCP data were excluded, modelling RF titre alone

| TABLE 1 Factors associated with ILD in patients with RA |
|-----------------|-----------------|-----------------|
|                | RA-ILD patients | Control RA patients | $P$-value |
| Patients, n    | 230             | 230             |             |
| Smoking, %     |                 |                 |             |
| Males ever     | 75              | 60              | 0.02        |
| Females ever   | 60              | 59              | 0.92        |
| Total male pack-years, median (range) | 15 (15–120) | 21 (5–60) | 0.01 |
| Total female pack-years, median (range) | 20 (10–80) | 20 (5–75) | 0.96 |
| Serology       |                 |                 |             |
| RF, %          | 89              | 58              | 0.01        |
| CCP antibody, %| 94              | 55              | 0.006       |
| CCP antibody titres, median (range) | 180 (8–340) | 78 (8–340) | 0.02 |

ILD: interstitial lung disease.
maintained the significance of each of the other variables. These data are shown in Table 2.

A subgroup of 159 patients had sufficient data to analyse mortality and its relationship to investigations over a 14-year period. A total of 32 deaths (20%) occurred in this group over 14 years, of which 15 (47%) were directly due to ILD.

Subtype analysis showed that UIP was predominant (65%), with smaller numbers of NSIP (24%), OS (6%) and COP (5%). Mortality related to subtype, with patients with a U/P/O pattern having a RR of death from any cause of 3.9 (1.26–12.3) compared with those with a pattern of NSIP/COP. Disease extent on HRCT was also important. More patients had limited (57%) than extensive (43%) disease at presentation, but extensive disease was associated with a RR of death from any cause during follow-up of 2.17 compared with limited disease. These data are shown in Table 3. Although there was some association between disease subtype (UIP and OS combined) and extent (extensive), this did not quite achieve statistical significance ($P = 0.054$).

A history of smoking was significantly associated with subtype (UIP > NSIP) but not with disease extent. Mortality figures were not corrected for the excess smokers among those with UIP.

Baseline median VC was preserved at 101% (54–145%) in limited disease but decreased to 70% (44–117%) in those with extensive disease ($P = 0.001$). Baseline gas transfer was reduced in both limited and extensive disease at 61% (33–106%) and 52% (22–109%), respectively ($P = 0.07$). Detailed results on radiographic and physiological findings are shown in Table 3.

### Discussion

The natural history of ILD in RA appears to be different from that seen in idiopathic UIP [24]. This is the largest study of factors associated with RA-ILD in the UK. It demonstrates that there is an almost equal prevalence of RA-ILD across genders, contrasting with the female predominance seen in RA itself. The condition often occurs within the first decade of onset of RA. We found that the duration of RA alone is not an independent factor associated with ILD. However, smoking is known to be associated with the development of RA-ILD. As tobacco consumption is both more prevalent and higher in males, it may contribute to the increased frequency of RA-ILD in men, although our data do not show that smoking is a risk factor for RA-ILD in women.

Our results show that the presence of RF and anti-CCP antibodies are both strongly associated with the development of RA-ILD, and titres of anti-CCP are very elevated in many patients with the condition. Positive anti-CCP antibodies may predate articular disease, especially in smokers [25–27], and this is consistent with our findings that a significant minority of patients with RA-ILD developed articular disease at or after the time that respiratory symptoms occurred. Lung abnormalities may develop before articular symptoms occur [28], and airway changes have also been reported in early RA [29, 30]. As anti-CCP antibodies can be detected before articular disease is evident clinically or radiologically [31], tobacco smoking might precipitate site-specific citrullination in the lungs, leading to the generation of anti-CCP antibodies in early RA [32]. This may alter enzyme expression in the lungs and trigger an abnormal response in genetically susceptible individuals [33–35].

Characteristics of HRCT in RA are now well defined [36] and UIP usually closely correlates with histological findings [37]. Reticular changes and honeycombing in the subpleural sections of the lower lobes are characteristic of UIP, although patients can occasionally turn out to have some features of NSIP on biopsy. Radiological features of NSIP often include ground glass shadowing with features of alveolar inflammation, which are also well described [38, 39]. The use of HRCT in defining the subtype and extent of disease is now well established, although it remains as yet an imperfect science.

The present study confirms that the predominant pattern of ILD in RA is UIP, which accounts for almost two-thirds of patients. The pattern of UIP is independently associated with a poorer prognosis and an increase in all-cause mortality. Our data demonstrate that disease extent is also an important predictor of outcome. The majority of patients with RA-ILD have limited disease at presentation, but those patients with extensive disease had twice the risk of dying during follow-up.

Pulmonary function tests are sensitive but non-specific. We found that neither lung volume nor gas transfer was able to predict the subtype on HRCT. Gas transfer was
significantly reduced at baseline in both limited and extensive disease and is a highly sensitive screening test for the presence of ILD. In contrast, baseline VC was usually preserved in limited disease and a reduction in baseline values might predict extensive disease on HRCT. Our data suggest that preserved lung function at the time of presentation is associated with a better outcome. Follow-up of these patients with regular spirometry and gas transfer remains an essential aspect of monitoring disease progression in all patients with ILD.

This study does have some limitations. The selection of the case controls from one participating centre depleted of patients with proven RA-ILD might alter estimates of smoking and seropositivity from within that population. However, <3% of RA patients were excluded on that basis and this is highly unlikely to have accounted for the substantial differences recorded. Ideally RA controls might have been drafted from a source outside the study, although this approach might have introduced the potential for population bias. It is also possible that the increased risk of death associated with UIP might have been due to smoking, as mortality was not corrected for smoking status in this study. Finally, the absence of a complete data set for anti-CCP status might have diluted the predictive effect of this for the presence of ILD, although this was highly significant even with incomplete data.

Our findings offer both an insight into the possible pathogenesis of RA-ILD, and some practical points for clinicians. We suggest that a detailed smoking history be obtained and titres of anti-CCP antibody recorded in all patients with RA. In those where ILD is suspected, baseline spirometry, gas transfer and HRCT should be performed. The reporting radiologist should be requested to determine both the subtype and extent of ILD where the diagnosis is confirmed. The mortality data from this study have identified that therapeutic efforts should be focussed on patients with extensive UIP on HRCT. Changes in the therapeutic approach to the treatment of RA patients with ILD may alter the profile and outcome of this disease.

Our network, which includes rheumatologists and chest physicians, plans to investigate the implications of these findings with regard to therapeutic intervention in RA-ILD—a topic that has recently been reviewed [40]. It has been shown that rheumatological input to the assessment of ILD may alter subsequent diagnosis and management [41]. Data relating outcome to disease activity and the wide range of therapies to which patients have been exposed are presently being collated and analysed. It is our hope that this will lead to a more robust evidence base to guide future clinical care of this common condition that carries a high mortality [42].

Rheumatology key messages

- Men with RA, a history of smoking and strong seropositivity are at greatest risk for interstitial lung disease.
- High-resolution CT of the lung should be reported to include subtype and extent of interstitial lung disease.

**Table 3** Results of baseline investigations in patients with RA-ILD and effect on survival investigation

<table>
<thead>
<tr>
<th>Pulmonary function</th>
<th>Limited disease</th>
<th>Extensive disease</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vital capacity, % predicted (range)</td>
<td>101 (54–145)</td>
<td>70 (44–117)</td>
<td>0.001</td>
</tr>
<tr>
<td>Gas transfer, % predicted (range)</td>
<td>61 (33–106)</td>
<td>52 (22–109)</td>
<td>0.07</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>High-resolution CT</th>
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</thead>
<tbody>
<tr>
<td>Subtype</td>
<td>UIP</td>
<td>NSIP</td>
<td>OS</td>
</tr>
<tr>
<td>Number (%)</td>
<td>103 (65)</td>
<td>39 (24)</td>
<td>10 (6)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>RR of death during follow-up in patients with UIP/OS compared with those with NSIP/COP</th>
<th>RR</th>
<th>Z statistic</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death (all-cause), RR (range)</td>
<td>3.9 (1.26–12.3)</td>
<td>2.36</td>
<td>0.018</td>
</tr>
<tr>
<td>Death from ILD, RR (range)</td>
<td>5.7 (0.77–42.1)</td>
<td>1.71</td>
<td>0.088</td>
</tr>
<tr>
<td>Extent (Limited (&lt;20% of lung involved))</td>
<td>Extensive (&gt;20% of lung involved)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number (%)</td>
<td>90 (57)</td>
<td>69 (43)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>RR of death during follow-up in patients with extensive compared with limited lung disease</th>
<th>RR</th>
<th>Z statistic</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death (all cause), RR (range)</td>
<td>2.17 (1.14–4.13)</td>
<td>2.37</td>
<td>0.018</td>
</tr>
<tr>
<td>Death from ILD, RR (range)</td>
<td>1.50 (0.57–3.91)</td>
<td>0.81</td>
<td>0.412</td>
</tr>
</tbody>
</table>

Acknowledgements

We acknowledge the help and support of all the clinicians who have contributed data to the ERAS cohort over the years and who agreed to allow access to the amalgamated database for the purpose of this study. They include the following: Dr Josh Dixey, Dr Peter Williams, Dr Nigel Cox, Dr David James, Dr John Winfield, Dr Peter Prouse, Dr Paul Davies and Professor Paul Emery. We also acknowledge the help and support of the statistical support team from ERAS, who kindly analysed the data from this study using logistic regression analyses.

Disclosure statement: N.S. has received money from Pfizer, Servier and Menarini as part of their speakers’ bureaus and travel grants from Pfizer. All other authors have declared no conflicts of interest.

References


10 Linn-Rasker SP, van der Helm-van Mil AHM, van Gaalen FA et al. Smoking is a risk factor for anti-CCP antibodies only in RA patients that carry HLA-DRB1 shared epitope alleles. Ann Rheum Dis 2005;52:3058-62.


22 Sathi N, Urwin T, Desmond S, Dawson J. Patients with limited rheumatoid arthritis-related interstitial lung disease have a better prognosis than those with extensive disease. Rheumatology 2011;50:620.


