Interstitial lung disease has a poor prognosis in rheumatoid arthritis: results from an inception cohort

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Abstract

Objectives. Pulmonary complications of RA are well described. Although some are benign, interstitial lung disease (ILD) has a poor prognosis. Few RA inception cohorts have reported the natural history of ILD related to RA (RA-ILD). We examine its incidence, outcome and prognostic indicators.

Methods. Extra-articular features and comorbidity have been recorded yearly in a well-established inception cohort of RA with a 20-year follow-up. Standard clinical, laboratory and radiological measures of RA were recorded at baseline and yearly. Details of deaths were provided by a national central register.

Results. Out of 1460 patients, 52 developed RA-ILD, half either at baseline or within 3 years of onset. The annualized incidence was 4.1/1000 (95% CI 3.0, 5.4) and the 15-year cumulative incidence 62.9/1000 (95% CI 43.0, 91.7). Incidence of RA-ILD was associated with older age, raised baseline ESR and HAQ. Evidence to implicate any drug effect (e.g. MTX) was lacking. Of these patients, 39 died, attributed to RA-ILD in 28. Median survival following diagnosis of RA-ILD was 3 years.

Conclusions. RA-ILD is an important and early feature of RA. It is related to disease activity and has a poor prognosis. Further studies are required to determine whether screening for pulmonary disease would identify these patients at an earlier stage.

Key words: Rheumatoid arthritis, Interstitial lung disease.

Introduction

Pulmonary conditions in RA are common and well recognized, as either extra-articular features, known associations or as co-existent pathology that may complicate the management of RA [1]. Interstitial lung disease (ILD) is a progressive fibrotic disease of the lung parenchyma that includes a broad spectrum of disorders that vary greatly in their clinical presentation, natural history, pathology, pathogenesis, prognosis and treatment. ILD is associated with a number of connective tissue disorders (CTD-ILD), and although studied extensively in SSC, is also well recognized in RA (RA-ILD). Little is known of its aetiology, although genetic [2, 3] and environmental [4, 5] factors both may play a part, and some DMARDs, such as MTX, have been implicated [6–9].

In 2002, the American Thoracic Society and European Respiratory Society redefined the nomenclature now used for acute and chronic diffuse parenchymal lung diseases. This classification combines the histopathological pattern seen on lung biopsy with clinical information [10]. ILD is a subgroup of very heterogeneous acute and chronic conditions, some of which can resolve spontaneously (e.g. sarcoidosis), but others are characterized by progressive fibrosis, including idiopathic pulmonary fibrosis (IPF), RA-ILD and CTD-ILD. Estimates of the population incidence of IPF vary from 3.62/100 000 in Southern Spain [11] to 31.5/100 000 and 26.1/100 000 in males and females in the USA, respectively [12, 13].

Different aspects of ILD in RA have been reported in case–control study [14], a retrospective study [15] and...
prospective studies [16–18] but few in inception cohorts [19]. Few have compared RA-ILD with IPF [20, 21]. The reported prevalence of RA-ILD varies from 19 to 44% [14, 17, 22]. The inconsistency of these estimates of IPF and RA-ILD may be partly due to differences in diagnostic criteria, methods of detection and reporting, and may underestimate the true incidence. RA-ILD is often asymptomatic, at least initially. Clinical detection has been reported to be <5% using plain radiology [23], but 20–30% with high-resolution CT (HRCT) [19].

The prognosis of ILD is poor. Survival after diagnosis of RA-ILD has been reported as a median of 3.5 years [26] and a mean of 3 years [27], and this has changed very little in the last 30 years [15]. Some reports indicate that 5-year survival is better for RA-ILD (44%) compared with IPF (11%) [28, 29].

In a prospective study of mortality in RA, we reported cardiovascular disease as the most common cause of death and this increased when compared with population figures. An unexpected finding was the number of deaths from RA-ILD (6%), and this was the only classical extra-articular manifestation of RA that was recorded on death certificates as the main or contributing cause of death [30]. This inception cohort, the Early Rheumatoid Arthritis Study (ERAS), also has longitudinal data on major comorbidities in RA followed for up to 23 years. We report on the natural (treated) history of RA-ILD in this cohort and explore possible drug effects and predictive factors.

Patients, materials and methods

A total of 1460 consecutive patients diagnosed with RA were recruited between 1986 and 1998 from nine centres representing all social strata in England. Entry criteria included ≥2 years of symptoms and no prior treatment with DMARDs. Baseline and yearly assessments included standard clinical, laboratory, functional and socio-economic details, as previously described [30]. These included ACR criteria, swollen and tender joint counts, HAQ, pain score measured using a visual analogue scale, ESR, RF and anti-nuclear antibody (ANA) titres, BMI and hand/feet radiographs. Since the study began in 1986, the original three-variable disease activity score (DAS) has been used, which is a composite of swollen and tender joint counts and ESR [31]. Clinicians recorded extra-articular and co-existent medical conditions yearly, causes of death if known and all inpatient episodes. Smoking data are incomplete because they were not collected initially, but were added from 1998 in view of its recognized importance. HLA-DRB1 genotyping was carried out in a subgroup of 954 patients as previously described to determine shared epitope (SE) status [32]. Socio-economic groupings were based on the census-based Carstairs deprivation quintiles [33].

RA-ILD case definition

Full and routine screening for pulmonary disease for all patients was not included in this study. Patients with pulmonary symptoms or clinical features were further investigated as part of standard clinical practice, which included plain radiology, pulmonary function tests and HRCT if RA-ILD was suspected. In 43 patients, the diagnosis of RA-ILD was based on clinical, chest X-ray and HRCT findings. Most of these patients also had lung function tests (details not known), but none had lung biopsy. In nine patients, the diagnosis was only suspected terminally and recorded at autopsy and/or on death certificates.

Death certificates

All ERAS patients are tracked by the National Health Service Central Register. Death certificates are provided and coded by the Office for National Statistics (ONS), using the International Classification Code (ICD-10). Only patients not registered with a general practitioner in the UK or who moved from the UK permanently would fail to be recorded under this system. Death certificates were not available for five patients who were known to have died. Certificate details were cross-referenced with both the ERAS database and medical records for pre-morbid conditions and hospital episodes as previously described [30]. Places of death were mainly hospitals (64% of total, 82% RA-ILD), the remainder in hospices, nursing homes or homes. Autopsies were performed in 22% (18% of RA-ILD deaths).

Treatment profiles

All centres followed the framework of UK guidelines for the management of RA. One thousand two hundred and twenty-three (84%) patients received at least one DMARD, started at a median of 2 months from presentation. Sequential monotherapy was the standard practice, the ‘step up’ combination therapy being reserved for more severe disease. Of the patients treated with DMARDs, 55% had more than one DMARD.

The most commonly used DMARDs were SSZ (70%) and MTX (42%). The remaining patients (16%) were managed with NSAIDs and/or low-dose steroids. Patients with RA-ILD received various combinations of steroids, AZA and cyclophosphamide, with variable clinical response. None of our patients received biologics during the follow-up time of this analysis.

Statistical analysis

Summary statistics demonstrate baseline clinical features. Annualized incidence and 15-year cumulative incidence were calculated per 1000 patient-years and per 1000 population, respectively, with 95% CIs. Cumulative incidence and survival following the diagnosis of RA-ILD was calculated using the Kaplan–Meier method. Univariate hazard ratios (HRs) were calculated using Cox proportional hazards regression. Variables with significance values of \( P < 0.1 \) were included in multivariate Cox proportional hazards regression models for the incidence of RA-ILD and survival from diagnosis of RA-ILD. Baseline
clinical features were used as predictors in the incidence models, whereas clinical features at the visit preceding RA-ILD diagnosis were used in the survival model. In addition, the predictive values of HAQ, VAS pain, ESR and DAS during the early course of the disease were also assessed by calculating the area under the curve (AUC) for the first 3 years. The AUC was divided by the number of available data values to ensure comparability with individuals with <3 years of follow-up.

Results

Demography

Table 1 summarizes the baseline characteristics of the whole cohort \((n = 1460)\). Total time at risk was 12,586 person-years; median follow-up was 10 years with a maximum of 23 years, during which time RA-ILD was diagnosed clinically and with HRCT in 43 patients (2.9%), and in a further 9 (0.6%) terminally or at autopsy. DMARDs were used in 86% (>1 in 65%) in RA-ILD and in 84% (>1 in 51%) in the remainder. Type of DMARD and the median time to first DMARD were the same for both groups (SSZ 74%, 2 months). Five hundred and eighty-six (41.5%) and 24 (50%) received MTX at a median of 49 and 35 months from baseline, respectively. In 13 patients, MTX was started before diagnosis of RA-ILD, but in only 1 patient was MTX thought to be possibly related.

Incidence

RA-ILD was diagnosed in 52 patients. It was already present at the baseline assessment in 12 of them and developed in a further 12 within 3 years of follow-up, indicating an early feature in this cohort. The annualized incidence rate was 4.1/1000 (95% CI 3.0, 5.4). Figure 1 displays the cumulative incidence of RA-ILD, which at 15 years is 62.9/1000 (95% CI 43.0, 91.7).

Table 1

<table>
<thead>
<tr>
<th></th>
<th>Total ((n = 1460))</th>
<th>RA-ILD ((n = 52))</th>
<th>No RA-ILD ((n = 1408))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>491 (33.6)</td>
<td>22 (42.3)</td>
<td>469 (33.3)</td>
</tr>
<tr>
<td>Female</td>
<td>969 (66.4)</td>
<td>30 (57.7)</td>
<td>939 (66.7)</td>
</tr>
<tr>
<td>RF(^a)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>543 (37.5)</td>
<td>18 (34.6)</td>
<td>525 (37.3)</td>
</tr>
<tr>
<td>Positive</td>
<td>376 (26.0)</td>
<td>13 (25.0)</td>
<td>363 (26.8)</td>
</tr>
<tr>
<td>Positive (high)</td>
<td>528 (36.5)</td>
<td>21 (40.4)</td>
<td>507 (36.0)</td>
</tr>
<tr>
<td>X-rays of hands and feet(^b)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No erosions</td>
<td>1050 (74.3)</td>
<td>38 (76.0)</td>
<td>1012 (74.2)</td>
</tr>
<tr>
<td>Erosions</td>
<td>364 (25.7)</td>
<td>12 (24.0)</td>
<td>352 (25.8)</td>
</tr>
<tr>
<td>Smoking(^a)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>536 (59.1)</td>
<td>20 (51.3)</td>
<td>516 (59.5)</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>174 (19.2)</td>
<td>8 (20.5)</td>
<td>166 (19.1)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>197 (21.7)</td>
<td>11 (28.2)</td>
<td>186 (21.4)</td>
</tr>
<tr>
<td>HLA-DRB1 SE(^a)</td>
<td></td>
<td></td>
<td></td>
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<td>None</td>
<td>283 (29.7)</td>
<td>8 (23.5)</td>
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<td>One copy</td>
<td>447 (46.8)</td>
<td>20 (58.9)</td>
<td>427 (46.4)</td>
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<tr>
<td>Two copies</td>
<td>224 (23.5)</td>
<td>6 (17.6)</td>
<td>218 (23.7)</td>
</tr>
<tr>
<td>Age at onset, years</td>
<td>57 (45, 66)</td>
<td>65 (58, 71)</td>
<td>56 (45, 66)</td>
</tr>
<tr>
<td>Symptom duration(^b)</td>
<td>6 (4, 11)</td>
<td>7 (5, 11)</td>
<td>6 (4, 11)</td>
</tr>
<tr>
<td>Pain VAS</td>
<td>45 (23, 63)</td>
<td>50 (35, 70)</td>
<td>43 (23, 63)</td>
</tr>
<tr>
<td>ESR, mm/h</td>
<td>38 (19, 62)</td>
<td>50 (30, 77)</td>
<td>37 (18, 66)</td>
</tr>
<tr>
<td>HAQ</td>
<td>1.0 (0.5, 1.8)</td>
<td>1.4 (0.8, 2.0)</td>
<td>1.0 (0.5, 1.8)</td>
</tr>
<tr>
<td>DAS</td>
<td>4.1 (3.0, 5.3)</td>
<td>3.9 (3.4, 5.7)</td>
<td>4.1 (3.0, 5.3)</td>
</tr>
</tbody>
</table>

Data presented as \(n\) (%) or median (inter-quartile range). \(^a\)Missing data: RF = 13 (0.9), X-rays = 46 (3.2), Smoking = 553 (37.9), HLA = 506 (34.7). \(^b\)Duration of symptoms in months from onset of RA to baseline visit.
Features at baseline and predictive factors

Crude HRs indicated older age ($P < 0.001$), increased baseline ESR ($P = 0.001$) and increased baseline HAQ ($P = 0.045$) as significantly associated with an increased risk of development of RA-ILD (Table 2). Sex, socio-economic status, smoking, HLA-DRB1 SE, baseline RF and ANA titres, DAS, VAS pain, nodules and X-ray erosions were not associated with an increased incidence ($P > 0.05$). Neither was the prior use of MTX. Age, baseline ESR and HAQ were entered into a multivariate Cox Proportional Hazards Regression model.

Only age and baseline ESR were significantly associated with increased risk of RA-ILD. The adjusted risk estimates relate to a 10-year difference in age and are associated with a 64% increase in the likelihood of a rheumatoid patient developing ILD over a shorter period, and a 10-unit increase in baseline ESR associated with an 11% increase. Considering the 3-year AUCs for HAQ, VAS pain, and DAS, the crude HRs were all significant (HAQ: HR = 2.65, 95% CI 1.17, 5.99; VAS pain: HR = 1.02, 95% CI 1.00, 1.04; ESR: HR = 1.04, 95% CI 1.02, 1.05 and DAS: HR = 1.27, 95% CI 1.00, 1.61). However, when included in a multivariate model, along with age, the only estimate for ESR remained significant (HR = 1.03, 95% CI 1.01, 1.04).

Outcome of RA-ILD

(i) Survival: of the 52 patients, 39 with RA-ILD died, relating to 7% of all deaths within the cohort. Cause of death was attributed to RA-ILD in 28 (primary in 21, secondary in 7), and in the remainder death certificates recorded bronchopneumonia (in 4), ischaemic heart disease (in 3), heart failure (in 2), pulmonary embolus (in 2), cerebrovascular disease (in 2) and miscellaneous (in 5). Chronic obstructive pulmonary disease (COPD) was a contributory cause in five patients and one patient had features of both RA and scleroderma. None developed or died of lung cancer or other malignancies except one patient who was successfully treated for Hodgkin’s lymphoma. Co-existent pulmonary conditions in life included COPD (six patients) and bronchiectasis (one patient). RA-ILD was not recorded on death certificates in 11 who had the diagnosis based on clearly documented clinical and HRCT findings in medical records. In nine patients, the diagnosis of RA-ILD was only made terminally or at autopsy, and in five of these, survival from diagnosis of RA was <12 months.

Figure 2 shows the all-cause mortality survival function for the 43 patients where diagnosis of RA-ILD was not made terminally or at autopsy. Median survival time was 3 years, with a 5-year survival of 38.8% (95% CI 23.3, 54.1).

(ii) Crude HRs revealed that only VAS pain at visit before diagnosis of RA-ILD was significantly related to survival ($P = 0.048$). However, older age at diagnosis ($P = 0.065$).

**TABLE 2** Crude and adjusted HRs and 95% CI for incidence of RA-ILD and mortality following diagnosis of RA-ILD

<table>
<thead>
<tr>
<th>Variable</th>
<th>Incidence ($n = 1460$)</th>
<th>Survival ($n = 43$)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>aHR (95% CI)</td>
</tr>
<tr>
<td>Age at onset</td>
<td>1.06 (1.03, 1.08)</td>
<td>1.05 (1.03, 1.08)</td>
</tr>
<tr>
<td>Male</td>
<td>1.55 (0.89, 2.68)</td>
<td>1.49 (0.71, 3.16)</td>
</tr>
<tr>
<td>Low SES</td>
<td>0.75 (0.41, 1.40)</td>
<td>1.08 (0.64, 1.84)</td>
</tr>
<tr>
<td>Smoker</td>
<td>1.21 (0.83, 1.76)</td>
<td>0.59 (0.21, 1.59)</td>
</tr>
<tr>
<td>HLA1</td>
<td>1.26 (0.57, 2.79)</td>
<td>1.05 (0.97, 1.07)</td>
</tr>
<tr>
<td>HAQ</td>
<td>1.39 (1.07, 1.81)</td>
<td>1.01 (1.00, 1.02)</td>
</tr>
<tr>
<td>Pain VAS</td>
<td>1.22 (0.94, 1.59)</td>
<td>1.02 (1.00, 1.02)</td>
</tr>
<tr>
<td>DAS</td>
<td>1.11 (0.79, 1.53)</td>
<td>1.02 (1.00, 1.02)</td>
</tr>
<tr>
<td>ESR</td>
<td>1.04 (0.97, 1.12)</td>
<td>1.04 (1.00, 1.02)</td>
</tr>
<tr>
<td>RF positive</td>
<td>1.18 (0.60, 2.30)</td>
<td>1.76 (0.87, 3.54)</td>
</tr>
<tr>
<td>Nodules</td>
<td>1.14 (0.97, 1.31)</td>
<td>2.18 (0.97, 4.91)</td>
</tr>
<tr>
<td>Erosions</td>
<td>1.76 (0.87, 3.54)</td>
<td>1.96 (0.66, 5.85)</td>
</tr>
</tbody>
</table>

Variables with $P < 0.1$ included in multivariate model. SES: socio-economic status.
socio-economic status (P = 0.054) and increased ESR at visit before RA-ILD diagnosis (P = 0.084) were borderline significant and were included in the multivariate analysis. Sex, RF and ANA titres, DAS, smoking, HLA-DRB1 SE and MTX use were not related to worse survival. A Cox proportional hazards regression model (Table 2) indicated that only older age was predictive of death. The effect relates to an ~53% increase for each decade older that a person is at the diagnosis of RA-ILD. Risk of death was almost double in patients with low socio-economic status, although this was not statistically significant.

**Discussion**

The present study identified 52 patients with RA-ILD, relating to an annualized incidence rate of 4.1/1000 and a 15-year cumulative incidence of 62.9/1000. The annualized incidence of RA-ILD was reported as 2.6/1000 by Wolfe et al. [34], although these figures are not directly comparable because they were based on hospitalization for ILD. RA-ILD was an early feature of RA in our study, 25% already diagnosed at presentation. Median survival after diagnosis of RA-ILD was only 3 years, a figure that appears to have changed little in studies published over the last 30 years [15, 26–29]. Adverse prognostic factors were older age and measurements of disease severity.

RA-ILD was the third most common condition in a retrospective study of extra-articular RA (46-year cumulative incidence 6.8%) [35]. Most of the other studies have reported only prevalence, figures that vary considerably according to disease definition and diagnostic methods. Gabby et al. [19] calculated the prevalence from a study of 36 early-onset RA patients according to chest X-ray (6%), DTPA scan (15%), pulmonary function tests (22%), HRCT (33%), bronchoalveolar lavage (52%) and technetium scan (15%). The revision of nomenclature and diagnostic criteria for ILD published recently may make comparisons between studies difficult [10].

Prognosis following diagnosis of RA-ILD was comparable with previous research. The natural history of RA-ILD has been reported in a 2-year prospective study in 29 patients, of which 10 deteriorated (six deaths, four from respiratory failure), 15 remained stable and 4 were lost to follow-up [18]. Akira et al. [27] reported a mean survival of 3 years (range 4 months to 7 years) in 29 patients followed up for 3–108 months with CT-diagnosed lung disease. Similar to our findings, survival was related to patient’s age at the time of diagnosis and to disease severity. Furthermore, Hakala [26] reported similar figures in 57 patients hospitalized for diffuse interstitial fibrosis where median survival was 3.5 years after diagnosis, with a 39% 5-year survival rate.

Dawson et al. [22] reported the natural history of the disease in their prospective study of 150 RA patients who were attendees rheumatology outpatient departments. In contrast to the findings of the present study, prevalence of RA-ILD by HRCT was 19% and mainly reticular in 80% and co-existent emphysema was found in 41%. Thirty-four per cent had significant deterioration over a 2-year period and 14% died of respiratory failure. This study screened patients with HRCT, a more sensitive method than conventional chest X-ray. ERAS patients were not routinely screened for RA-ILD, and only had chest X-rays performed if indicated clinically or before MTX therapy. As a result, our incidence estimates may be downwardly biased and may have excluded patients with milder RA-ILD.

From previous reports, RA-ILD appears to be more common in the setting of older age, disease severity, high RF, subcutaneous nodules and male sex [18, 23, 26]. In our study, the only early features with predictive value were age, ESR and HAQ. The older age of onset (mean 64 years) was similar to other studies [26]. Most studies report higher RF titres in extra-articular RA, including pulmonary features, but there is little information on RF and severity of extra-articular manifestation. We have previously reported that RA patients carrying particular HLA-DRB1 SE genotypes are at increased risk of mortality from cardiovascular disease and malignancy, but not for RA-ILD [32]. The present study adds further evidence that the HLA-DRB1 SE genotype is not related to RA-ILD.

Saag et al. [36] tried to determine the important clinical predictors of radiographic and physiological abnormalities indicative of RA-ILD by analysing an unselected cohort of 336 patients with RA-ILD. Pack-years of cigarette smoking remained a significant predictor of low diffusion capacity, low flow volume capacity and interstitial abnormalities on chest radiograph. There is some evidence that presentation of ILD may be affected by smoking and increases the rate of declining pulmonary function. Smoking is related to various pathological and histological abnormalities in the lungs, but only a few studies have reported on smoking and ILD. Rajasekaran et al. [21] found that smoking rates were higher in patients with ILD-RA compared with IPF, but pulmonary function and gas transfer tests showed no significant differences between the groups.

In our study, past or current smoking was not related to the development of RA-ILD, nor was it related to survival in those who developed RA-ILD. However, since smoking information was not collected for over one-third of the ERAS cohort, the analysis, especially of RA-ILD survival, may have suffered from low statistical power.

Whether MTX predisposes to RA-ILD and/or is related to its progression is controversial, and data from controlled studies are limited. Most studies since have not demonstrated a definite association between MTX and RA-ILD. However, it is well recognized that MTX can induce acute pneumonitis [37]. A more recent study found no association between MTX therapy and progression of chronic pulmonary fibrosis [34, 38], and no correlations have been observed between pulmonary conditions in RA and MTX dosage [6]. Although our study was not designed to answer these issues, we found no supporting evidence for an adverse relationship between MTX and RA-ILD. MTX use was lower in ERAS than current practice, but was typical of the 1980s and 1990s in the UK. None of our patients received biologics.
during the follow-up time of this analysis, and hence we were unable to assess any association.

Major strengths of this inception cohort are the length of follow-up in a large number of patients, details of onset and types of major comorbidities, and causes of death in all patients who died. These factors may account for some of the differences seen with other studies. Limitations of the study include lack of detailed information on severity of co-existent conditions, including RA-ILD, for which the only outcome measurement was survival. The true baseline prevalence and cumulative incidence figures may be underestimated because the routine screening for pulmonary conditions was neither a part of the study nor normal clinical practice. Mild RA-ILD with a good prognosis may have escaped detection. Since the incidence rate was low, the analysis of survival following diagnosis of RA-ILD was underpowered. Only further studies will detect whether improved survival occurs as a result of earlier detection with HRCT, now more widely used, and earlier more intensive therapy to suppress RA-ILD.

In summary, our study has shown that RA-ILD is an important comorbidity in early RA and has a poor prognosis. Since this is related to measurement of disease activity, it raises two issues. First, whether screening for pulmonary disease in RA would be practical and productive. It is likely that rheumatologists could identify and diagnose these patients at an early stage before the overt pulmonary symptoms that would prompt referral to a chest physician. Secondly, the option of more intensive interventional approaches [39]. This is currently important given the safety concerns of biologic therapies and pulmonary disease that have been recently reported [40–42]. RA joint disease itself should be suppressed actively as part of current good practice. Only further studies can examine whether the more effective therapeutic agents we have at present for suppressing disease activity in RA (e.g. biologics) will affect the occurrence and outcome of RA-ILD.

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References

Interstitial lung disease has a poor prognosis in RA


