

Interstitial Lung Disease in Patients with Rheumatoid Arthritis: Comparison with Cryptogenic Fibrosing Alveolitis over 5 Years

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ABSTRACT. *Objective.* There is little information on the natural history of patients with rheumatoid arthritis (RA) and associated interstitial lung disease (ILD). Cryptogenic fibrosing alveolitis (CFA) is known to have a poor longterm prognosis, and we compared the 2 conditions through a longitudinal prospective study. *Methods.* We previously compared baseline clinical, physiological, and radiological characteristics in 18 RA-ILD patients with 18 case controls with CFA. Clinical, physiological, and radiological assessment was repeated in all survivors at 5 years, and data on treatment and mortality were collected. *Results.* The median age in each group was 77 years and 10 patients in each group were male. More patients with RA-ILD survived to 5 years (8 RA-ILD vs 2 CFA; $p = 0.03$), and median survival was significantly longer for patients with RA-ILD (60 mo) compared to CFA (27 mo; $p < 0.05$). Death was due to respiratory failure in half the patients with CFA, but was more often due to other causes in patients with RA. Clubbing and reduced baseline gas transfer were predictors of poor prognosis, while normal technetium clearance enhanced survival in nonsmokers. *Conclusion.* Patients with RA-ILD did better than those with CFA, and died less often from respiratory failure. Patients with finger clubbing and/or low gas transfer declined more rapidly. (First Release June 1 2006; J Rheumatol 2006;33:1250-3)

Key Indexing Terms:

RHEUMATOID ARTHRITIS
FIBROSING ALVEOLITIS

PULMONARY FIBROSIS
5 YEAR SURVIVAL

The outcome of cryptogenic fibrosing alveolitis (CFA) is known to be poor, with median survival from diagnosis being 3 to 5 years^{1,2}. Prognostic markers are not well established and there is limited evidence to guide attempts at therapeutic intervention³. Interstitial lung disease (ILD) is clinically detected in under 5% of patients with rheumatoid arthritis (RA)⁴, although studies have shown a much higher prevalence of interstitial lung changes using high resolution computed tomography (HRCT)⁵. The natural history of ILD in RA has not been well studied, but conflicting opinions exist on whether the prognosis is better⁶ or worse⁷ than that of CFA.

We have previously described the baseline characteristics of a cohort of patients with RA-ILD and case controls drawn from a population of patients with CFA⁸. We have followed

these patients over a 5 year period to compare the clinical outcome in the 2 disorders. This report describes and compares the 5 year survival of each group and offers some evidence to aid the assessment of prognosis in individual patients.

MATERIALS AND METHODS

The detailed assessment of our RA population for detection of those with definite ILD has been reported⁸. These patients and their case controls with CFA underwent full pulmonary function testing, HRCT of the thorax, and technetium lung scanning⁹ at baseline using described techniques⁸. All HRCT scans were graded by the same radiologist (PL) blinded to knowledge of the patients' clinical status¹⁰.

During the 5 year followup period all drug therapy was recorded, as were developments of new clinical events in all patients. Death due to any cause, death from respiratory failure, and the development of lung cancer were specifically noted. Pulmonary function was reassessed annually. Five years after recruitment to the study all survivors were formally reassessed. They underwent repeat full pulmonary function tests and HRCT of the thorax using the same equipment and techniques as at baseline. A change of 10% or more in forced expiratory volume (FEV1), vital capacity, or gas transfer was considered significant, as was a change in grade on CT scanning.

Kaplan-Meier analysis of survival was used to compare outcome between the 2 groups. The chi-square test was used to calculate any significant differences between the clinical features of patients with CFA and those with RA-related ILD. Differences in pulmonary function and radiological measurements between the 2 groups were assessed using Student's unpaired t test.

RESULTS

Eighteen patients with RA with evidence of ILD had been identified and matched with case controls with CFA for age

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(median 77 yrs), sex (10 male), and duration of dyspnea (30 mo). Baseline pulmonary function was similar in both groups. On HRCT, ground-glass shadowing had been reported in 5 patients, 4 of whom had RA. Further baseline data were as reported⁸.

All-cause mortality was high, as expected, with only 10 patients in total still alive 5 years after initial assessment (Figure 1). The majority of survivors had RA-ILD (n = 8) rather than CFA (n = 2), a significant difference (p = 0.031). Further, median survival was significantly longer for RA patients (60 mo) than for those with CFA (27 mo; p = 0.042).

The majority of patients died from respiratory causes, as expected. However, there were differences between the 2 groups, as shown in Table 1. Patients with CFA died from their disease progressing to respiratory failure more often than those with RA-related ILD (44% vs 11%, respectively; p = 0.028). Patients with RA had a higher death rate from lung cancer than those with CFA (28% vs 17%), although this was not statistically significant. However, finger clubbing at baseline was significantly associated with later lung cancer (p = 0.038). Clubbing was present in 5 patients with RA-ILD, of whom 4 later died of lung cancer. Age and symptom duration predicted death during followup, but sex and rheumatoid factor status did not.

Transfer factor at baseline did predict survival, with the

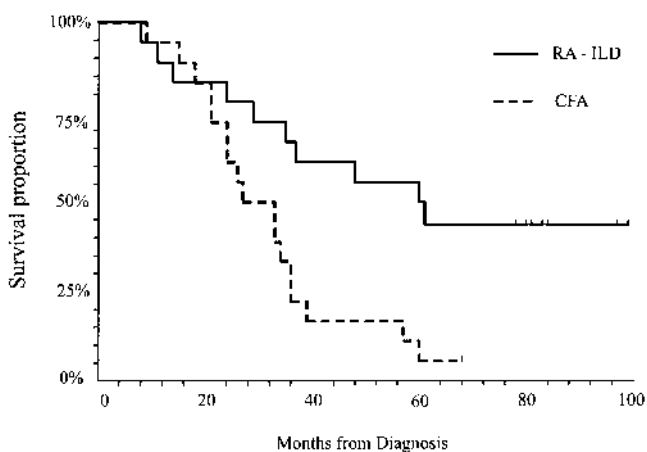


Figure 1. A Kaplan-Meier plot to compare outcome in patients with RA-ILD to those with cryptogenic fibrosing alveolitis (CFA).

Table 1. Causes of death in patients with CFA and RA-ILD over a 5 year period.

Cause of Death	RA, n (%)	CFA, n (%)
Respiratory failure	2 (11)	8 (44)
Lung cancer	5 (28)	3 (17)
Vascular	2 (11)	4 (22)
Tamponade	1 (5)	0
Septicemia	0	1 (5)
Total	10 (55)	16 (88)

mean baseline value in survivors being 57.5% of the predicted value, compared to 47.1% in those dying (p < 0.01). Lung volumes at baseline were not significantly predictive of outcome. HRCT was useful at baseline, in that ground-glass shadowing did predict those patients likely to survive (80%). The prognostic value of technetium lung scans was more difficult to assess: a half-life under 30 minutes represents abnormally fast clearance and, although more RA patients had accelerated technetium clearance times than CFA patients (11 vs 8), this was not significant. In addition, there was no correlation of clearance times with survival for individuals, probably due to the confounding effects of smoking.

At 5 years, pulmonary function had improved by > 10% in 4 patients, stabilized in one, and deteriorated by > 10% in 3 patients with RA, while deteriorating in both surviving patients with CFA (Table 2). Median percentage of predicted values for FEV1 and vital capacity fell slightly, while gas transfer rose in survivors with RA. Radiological changes on HRCT mirrored physiological trends at followup, with significant improvement in 2 patients with RA and stabilization in 4 more. Two patients in each group demonstrated deterioration.

Immunosuppressive drug therapy was used in 14 patients, and consisted of azathioprine, with or without prior cyclophosphamide, which was always given with steroids. Steroids alone were given to a further 7 patients. Selection of patients for immunosuppression was based on the presence of ground-glass opacification (n = 3) or markedly accelerated technetium clearance (n = 11). Use of immunosuppression itself did not necessarily correlate with survival, with 5 patients taking cytotoxics and 4 taking steroids alone surviving to followup. Slightly more patients with RA were treated with immunosuppressive agents (n = 8) or steroids (n = 5) than were CFA patients (6 and 2, respectively). Table 3 shows indications for treatment, together with outcome, in both groups of patients. Five of the 8 deaths from lung cancer occurred in patients treated with immunosuppressives.

DISCUSSION

This study is the first to prospectively address the history of ILD in patients with RA, and to compare the outcome with matched controls with CFA. We observed that the outcome of ILD associated with RA is generally better than that in patients with CFA. The Kaplan-Meier graph shows a significant survival advantage for RA patients and a greater probability of stabilization of disease. However, our findings emphasize the poor prognosis generally associated with ILD, especially in an elderly population. The only other study comparing the 2 diseases found no difference between them in survival⁷. However, it was a retrospective survey in primary care and relied entirely on the accuracy of the general practitioners' database. There was no means of ascertaining baseline function in the 2 groups, which were unlikely to have been comparable.

There were no significant differences between the groups

Table 2. Baseline and followup pulmonary function.

	CFA	RA-ILD	p
Baseline, no.	18	18	
FEV1, median (range)			
Absolute (l)	1.65 (0.50–2.95)	1.78 (0.97–2.43)	NS
% predicted	75 (33–109)	74 (113)	NS
VC, median (range)			
Absolute (l)	2.20 (0.70–3.80)	2.1 (1.30–3.10)	NS
% predicted	67 (47–99)	72 (40–107)	NS
TLCO, median (range)			
% predicted	53 (17–78)	47 (40–107)	NS
Followup, no.	2	8	
FEV1, median (range)			
Absolute (l)	(0.55–1.20)	1.90 (1.32–2.09)	
% predicted	(36–72)	66 (55–177)	
VC, median (range)			
Absolute (l)	(0.65–1.35)	2.20 (1.78–2.74)	
% predicted	(40–65)	64 (51–150)	
TLCO, median (range)			
% predicted	31–33	53 (24–91)	

FEV: forced expiratory volume, VC: vital capacity, TLCO: total lung capacity, NS: nonsignificant.

in clinical features, except for the greater prevalence of finger clubbing among the patients with CFA⁸, and this appeared to be a predictor of poor prognosis. The etiology of finger clubbing has long been debated¹¹, but it is recognized to carry an adverse prognosis in lung cancer, and appeared to be a strong marker of later lung cancer in our patients with RA.

Limitations of our study include the relatively small numbers and the high age of the index population, which may not be truly representative of the population. Careful case control maximized the information obtained, and physiological lung function at baseline was similar in both groups, with baseline gas transfer proving to be a useful measure of survival. We did not match the groups for respiratory symptoms at baseline⁸, as the mobility of patients with RA was likely to be lower than those with CFA, making interpretation difficult. HRCT was also useful, but revealed ground-glass shadowing in only a small minority of patients. However, these individuals had a better prognosis, confirming observations reported in scleroderma¹².

The rate of technetium clearance from the lung has been a useful prognostic predictor in this and other causes of pulmonary fibrosis^{13,14}, and has been studied in RA, with negative results¹⁵. A recent report indicated that it might prove to be of value in nonsmokers with RA¹⁶, and our work supports this, although its role is limited by the high prevalence of smoking in patients with RA.

Lung function remained reasonable in the surviving patients with RA, with an increase in median absolute values, and these individuals may carry a reasonable longterm prognosis. Those patients with poor lung function at baseline generally did not survive to followup. This is especially true of those with CFA, where only 2 patients survived to 5 years.

Differences in survival may relate to histological subtype.

Although we did not perform lung biopsy, recent investigation in patients with RA has shown that male smokers are more likely to have usual interstitial pneumonia (UIP) histologically, and generally did worse than those with nonspecific interstitial pneumonia (NSIP)¹⁷.

Lung cancer was a common complication in our patients and a frequent cause of death, especially in patients with RA. This has not been reported previously in the context of ILD-associated RA. Smoking is common in RA and was prevalent in our patients. However, another possible contribution may have been the immunosuppressive therapy that the majority of patients dying from cancer had received. RA-associated ILD has also been treated with monoclonal antibodies against tumor necrosis factor- α with benefit¹⁸. However, clinical concerns have been expressed about this approach, and adverse outcomes in patients with RA-ILD have recently been reported¹⁹.

Although this was a small study, our results indicate that established pulmonary fibrosis has a poor prognosis overall, although patients with RA do better than those with CFA. Patients with alveolitis may have a better outlook, while those with a low gas transfer and/or finger clubbing generally do less well.

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Table 3. Relationship between baseline radiological findings, treatment, and outcome.

	HRCT Findings	Technetium Clearance	Therapy	Outcome
Patients with RA				
1	G	A	P and I	S
2	F	A	P	S
3	F	A	P and I	D
4	F	N	None	S
5	G	A	P and I	D
6	F	N	None	D
7	F	A	P	S
8	F	N	P	S
9	F	N	None	D
10	F	A	P and I	S
11	F	A	P	S
12	G	A	P and I	D
13	F	A	P and I	D
14	F	N	None	D
15	F	A	P and I	D
16	G	N	P	D
17	F	A	P and I	S
18	F	N	None	D
Patients with CFA				
1	F	N	None	D
2	F	A	P and I	D
3	F	A	P and I	S
4	F	N	None	D
5	F	N	None	D
6	F	A	P and I	D
7	F	N	None	D
8	F	N	None	D
9	F	A	P and I	D
10	F	N	None	D
11	F	N	None	D
12	F	A	P and I	D
13	G	A	P	D
14	F	A	P	D
15	F	A	P and I	S
16	F	N	None	D
17	F	N	None	D
18	F	N	None	D

G: ground-glass appearance, F: fibrosis, A: accelerated, N: normal, P: prednisone, I: immunosuppressives, S: survivor, D: died.

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