EXTENDED REPORT

Predictors of progression of HRCT diagnosed fibrosing alveolitis in patients with rheumatoid arthritis

J K Dawson, H E Fewins, J Desmond, M P Lynch, D R Graham

Ann Rheum Dis 2002;**61**:517–521

See end of article for authors' affiliations

Correspondence to: Dr J K Dawson, Department of Rheumatology, St Helens Hospital, Marshalls Cross Road, St Helens, Merseyside WA9 3DA, UK; twodocs@doctors.org.uk

Accepted 11 December 2001

Background: Fibrosing alveolitis (FA) is the most serious pleuropulmonary extra-articular feature of rheumatoid arthritis (RA). Features that predict progression of FA in patients with RA have not yet been determined.
Objective: To identify clinical features that predict progressive FA in patients with RA.
Methods: An unselected cohort of 29 patients with RA and FA confirmed by high resolution computed tomography (HRCT) were studied prospectively for 24 months. Three monthly clinical assessment, four monthly pulmonary function tests, and yearly HRCT scanning was undertaken on these patients. Progressive FA was defined as >15% fall in carbon monoxide transfer factor (TLCO) with evidence of increasing FA on HRCT or death as a result of FA.
Results: During 24 months of follow up 10/29 (34%) patients had progressive FA. Progression on HRCT was seen as acute ground glass exacerbations or increasing reticular pattern lung involvement. Progressive FA was associated with the presence of bibasal crackles (p=0.041), TLCO (p=0.001), and extent (p=0.026) and distribution (p=0.031) of lung involvement on HRCT at initial presentation. When multiple logistic regression was used, only TLCO remained significant. Receiver operator curve analysis was employed to identify presenting TLCO of progressive FA. A TLCO <54% of the predicted value demonstrated 80% sensitivity and 93% specificity in predicting progressive FA.
Conclusions: A TLCO <54% of the predicted value is a highly specific predictor of disease progression.

Retrospective studies on the natural history of fibrosing alveolitis (FA) associated with rheumatoid arthritis (RA) show a varied clinical course. Some patients have a slowly progressive course that may last for a decade, whereas others have a fulminant course with death less than six months after the onset of pulmonary symptoms. Currently, published reports on prognosis are retrospective and tend to originate from tertiary referral centres, which is likely to contribute significant bias towards a worse outcome.

Turner-Warwick *et al* reported a series of patients with RA and lung disease and found no difference in mortality rate from that found in cryptogenic FA.[1] Hakala reported the course of 57 patients with RA admitted to hospital with interstitial lung fibrosis, and the median survival for the group was 3.5 years.[2]

Akira *et al* reported the clinical events occurring in 29 patients with RA who had lung disease diagnosed by chest high resolution computed tomography (HRCT) between 1986 and 1997.[3] Mean survival of those dying was three years (range four months to seven years), which is similar to pre-HRCT studies.

As yet no published study has correlated clinical features, pulmonary function tests, or HRCT appearances with progressive FA in patients with RA. Our aim was to observe an outpatient cohort of patients with RA and FA and assess them regularly with full pulmonary function tests and HRCT for two years in order to determine the natural history of FA associated with RA on HRCT and also identify clinical features of progressive FA.

METHODS

The study group comprised 29 patients attending St Helens and Knowsley Trust Hospitals rheumatology outpatient departments. These patients with FA were identified from a previous study,[4] when a cross section of 150 patients with RA underwent HRCT scanning, irrespective of the presence or absence of respiratory symptoms. This hospital is based in northwest England and its catchment population is from an industrialised area. The patients were diagnosed with definite RA as defined by the American Rheumatism Association 1987 criteria[5] and were diagnosed with FA based on HRCT diagnosis.

The research ethics committee of St Helens and Knowsley Hospitals approved the study.

Clinical assessment

A questionnaire was completed for each patient by JKD. This noted duration of RA, extra-articular complications, current and previous disease modifying drugs, corticosteroid use, early morning joint stiffness, and patient assessment of disease activity. Each patient filled in the Modified Stanford Health Assessment Questionnaire to assess functional impairment. Respiratory questions were asked about previous chest disease, cough, dyspnoea, sputum production, chest pain, weight loss, and risk factors for respiratory disease such as smoking, drugs, domestic pets, and occupation. Cigarette consumption was evaluated in pack years (one pack year—20/day for one year). Current smokers were those who had smoked during the previous six months: non-smokers had smoked fewer than 20 packets of cigarettes during their lifetime. A detailed clinical examination was performed. Table 1 shows the patients' details.

All patients had venous blood taken for full blood count, plasma viscosity, renal and liver function, C reactive protein, and plasma proteins. Immunological investigations included

Abbreviations: FA, fibrosing alveolitis; HRCT, high resolution computed tomography; ILD, interstitial lung disease; RA, rheumatoid arthritis; TLCO, carbon monoxide transfer factor

Table 1 Patient characteristics

Age (years)	
Range	56–70
Median	61
Sex	
Male	9
Female	20
Duration (years)	1–24
Mean	11
Rheumatoid nodules present	18
Cough	18
NYHA III dyspnoea	5
Cigarette pack years	
Range	0–80
Median	21
Bilateral basal crackles	15
Finger clubbing	5
HAQ	0–2.875
Median	1.875
FEV_1 (litres)	
Range	1.15–4.35
Median	2.19
FVC (litres)	
Range	1.23–5.67
Median	2.79
FVC (% of predicted)	
Range	52–123
Median	96
FEV_1/FVC	
Range	49–96
Median	78
TLCO (% of predicted)	
Range	25–99
Median	59
RV (% of predicted)	
Range	55–185
Median	95
CXR characteristic of FA	4
HRCT lung involvement (%)	
Range	0.12–95.42
Median	5.96

NYHA, New York Heart Association grading for dyspnoea; HAQ, modified Standford Health Assessment Questionnaire; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; TLCO, carbon monoxide transfer factor; RV, residual volume; CXR, chest radiograph; FA, fibrosing alveolitis; HRCT, high resolution computed tomography.

immunoglobulins, rheumatoid factor (latex agglutination, positive at 1/20 dilution), and antinuclear antibody. All patients underwent echocardiography, electrocardiography, chest radiography, HRCT, and full pulmonary function testing.

Pulmonary function testing

Lung function was measured by a standard protocol and included spirometry (Sensor Medics water spirometer, California, USA), lung volumes (Sensor Medics helium dilution analyser), and transfer factor measured by single breath diffusing capacity (Sensor Medics autolink breath system). The highest of three reproducible measurements was used, and expressed as the percentage predicted for age, height, and sex according to standardised tables.[6] One senior technician performed the measurements in the cardiorespiratory department at Whiston Hospital.

Pulmonary function tests were performed within four weeks of the HRCT scan. Full pulmonary function tests were carried out four monthly.

High resolution computed tomography

All the study group underwent chest HRCT scanning, which was performed on a Siemens Somatom hiQ scanner. Scanning time was 1.3 s. Supine and prone views were taken. Serial slices were taken 2 mm in width and 10 mm apart. All images were obtained at window levels appropriate for lung parenchyma settings (window width 1300 HU; window level 600 HU) and mediastinum (window width 350 HU: window level 40 HU). A chest radiograph was taken at the same time as the HRCT scan. The HRCT scans were interpreted and graded for FA by consultant radiologists JD and HEF, who were unaware of the clinical details. Each radiologist reviewed the scans independently of the other and a consensus opinion between JD and HEF was taken in the event of disagreement.

Interpretation of the HRCT scan

A ground glass pattern was defined as a patchy or diffuse increase in lung density that did not obscure pulmonary vasculature. A reticular pattern was defined as the presence of intersecting lines that formed anything from a fine network to frank honeycombing; this was defined as FA if the appearance was thought to be typical of usual interstitial pneumonia.[7] A κ score for the level of agreement between radiologists on the presence of FA was 0.741. Other lung disease present on HRCT was systematically noted.

The scans were analysed according to the type, distribution, and extent of FA as described by Wells *et al*.[8] HRCT was repeated yearly.

Scoring of distribution of FA on initial HRCT scans

The mean extent of abnormal lung was calculated for two levels in the upper part of the lung (the mid-arch of the aorta, the carina) and separately for two levels in the lower part of the lung (the pulmonary venous confluence, 1 cm above the right dome of the diaphragm). The overall distribution of disease was expressed as the ratio of the extent of disease in the upper zone to the extent of disease in the lower zone. For each HRCT scan, the mean figure for the two observers was used,

Extent of FA on initial HRCT scans

HRCT scans were evaluated at five levels (the origin of the great vessels, the mid-arch of the aorta, the carina, the pulmonary venous confluence, and 1 cm above the right dome of the diaphragm) for extent of disease. At each level, the extent of abnormal lung was visually estimated to the nearest 5%. An estimate of overall lung involvement was obtained by applying a weighting factor to correct for differences in lung volumes at each HRCT level

The ratios of the lung volumes for the five levels are 0.129 for level 1, 0.190 for level 2, 0.222 for level 3, 0.228 for level 4, and 0.230 for level 5. The percentage of abnormal lung at each level was multiplied by the corresponding ratio; addition of the five adjusted figures gave an estimation of the overall percentage of abnormal lung. For each HRCT scan, the mean figure for the two observers was used.

Follow up assessments

Clinical

The patients were assessed clinically every three months by JKD. A standard questionnaire was completed on each occasion. The patients were monitored over two years. Pulmonary function tests were repeated four monthly by the same technician. Chest HRCT was repeated at baseline, one, and two years.

Definitions

Criteria used to define significant change in pulmonary function measurements were (*a*) improvement, a rise of more than 15% from baseline value of the carbon monoxide transfer factor (TLCO); (*b*) stability, no change or a change of ±15% from the baseline value of TLCO; and (*c*) deterioration, a decline of >15% from the baseline value of TLCO.[8]

Increasing FA on HRCT was based on HRCT scans examined in sequence. The pattern, extent, and distribution of abnormal HRCT findings were compared with findings in the same region on previous and subsequent HRCT scans.[3]

Table 2 Clinical details of the six patients treated for FA

	Range	Median
Duration of RA (years)	2–18	9
Cigarette pack years	0–35	13
HAQ	0–2.625	1.875
FEV_1 (litres)	1.15–2.76	1.73
FVC (litres)	1.23–3.41	2.00
FEV_1/FVC	75–98	87
TLCO (% of predicted)	24–47	30.5
RV (% of predicted)	48–99	72
VC (% of predicted)	48–85	69
% Lung involvement on HRCT	7.29–95.42	41.5

FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; TLCO, carbon monoxide transfer factor; RV, residual volume; VC, vital capacity; FA, fibrosing alveolitis; HRCT, high resolution computed tomography.

Table 3 Clinical features of the patients with progressive FA

	Progressive (10)	Stable (15)	χ^2
Men	4	3	0.38
Smokers	6	5	0.24
Receiving prednisolone	3	5	1
Rheumatoid nodules	6	8	1
NYHA III	3	2	0.36
Finger clubbing	3	1	0.27
Bibasal crackles	5	8	0.04
RF positive	9	13	1
Coexistent emphysematous bullae on HRCT	5	5	0.44
CXR characteristic of FA	1	2	0.54

NYHA, New York Heart Association grading for dyspnoea; RF, rheumatoid factor; CXR, chest radiograph; FA, fibrosing alveolitis.

Progression of FA was defined as significant deterioration in pulmonary function tests with increased FA demonstrated on HRCT scan, or death as a result of respiratory failure before investigations were repeated.

Statistical analysis

The Mann-Whitney U test was used to compare quantitative data. χ^2 with Yates's correction was used to compare frequencies. Student's *t* test was used to compare normally distributed quantitative data.

Potentially significant parameters were tested for possible interrelationship by multiple logistic regression analysis.

Interobserver variability, before consensus agreement, was evaluated for the grading of CT appearance, the assessment of whether the extent of disease had changed at follow up scanning, and the categorisation of which CT pattern had changed in extent. Agreement between observers was expressed as a κ value. Values of κ 0.40–0.75 were taken to indicate fair to good agreement between observers.

Receiver operator curves were used to identify sensitivity and specificity of cut off points for investigations predicting progression.

RESULTS

Clinical events

Twenty nine patients had typical FA on chest HRCT. Three (10%) had a predominantly ground glass pattern, three (10%) had equal predominance of ground glass and reticular pattern, and 23 (79%) presented with a predominantly reticular pattern FA. Twelve (41%) patients had apical emphysematous bullae in addition to FA.

Over two years, 10 (34%) patients showed a significant deterioration in pulmonary function as a result of FA and four (14%) patients died in hospital of FA with respiratory failure. One patient developed lung carcinoma; she was also a cigarette smoker.

Two patients did not continue to attend for serial investigations, two patients died of causes not related to FA—one of ischaemic heart disease, and one of disseminated non-pulmonary malignancy.

HRCT

Two patterns of deterioration were seen, increasing reticular pattern involvement of the lung (five patients) and also sudden deterioration with occurrence of a new ground glass pattern disease (two patients). The mean increase in extent of FA was by 9.4%. Two patients with predominantly ground glass pattern FA had spontaneous improvement in lung involvement without specific treatment.

Treatment of FA

Six patients were treated after significant deterioration in their lung condition. In two patients this was after the two year study period had ended. Three patients were male with a mean (SD) age 61.5 (9.6) years, two had finger clubbing, three had coexistent emphysematous bullae on HRCT, and three had predominantly reticular pattern FA. Table 2 gives further details of their pulmonary condition at the onset of treatment. In one patient with an acute ground glass exacerbation and one with predominantly ground glass pattern FA a severe deterioration in their clinical condition occurred requiring admission to hospital. An initial response to high dose corticosteroids was seen in all three patients with predominantly ground glass pattern FA or ground glass exacerbations, but this was only maintained in two.

The treatment was tailored to the patient's condition and concomitant drugs; patients were treated with 30–40 mg of prednisolone, which was reduced to a maintenance dose of

Table 4 Clinical features of the patients with progressive FA—continuous variables

	Progressive (10)		Stable (15)		Mann-Whitney U test p Value
	Median	Range	Median	Range	
Age (years)	66	49–75	57	47–71	0.103*
Disease duration (years)	8.5	2–18	6	1–24	0.559
Cigarette pack years	20	0–35	20	0–40	0.978
FEV_1/FVC ratio	79.5	69–93	98	55–123	0.597
TLCO (% of predicted)	50	25–70	69	51–99	0.001
RV (% of predicted)	92.5	60–132	95	55–185	0.254
HRCT score for FA distribution	0.775	0–5	0.05	0–3	0.031
% Lung involvement on HRCT	9.975	1.24–95.42	2.860	0.12–69.86	0.026

*Students *t* test.
FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; TLCO, carbon monoxide transfer factor; RV, residual volume; FA, fibrosing alveolitis; HRCT, high resolution computed tomography.

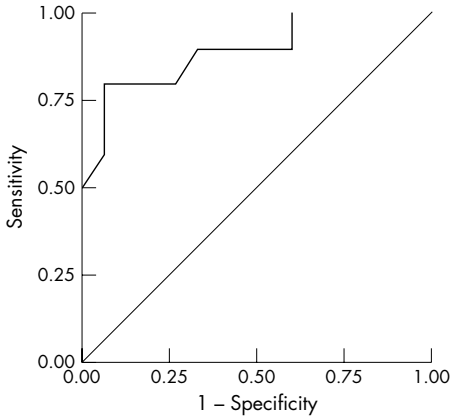

Figure 1 Receiver operator curve for carbon monoxide transfer factor.

10 mg daily, or equivalent, once a satisfactory response was seen. Azathioprine was instituted in combination with prednisolone wherever possible. The pattern of FA on HRCT at the start of treatment did not seem to predict response to conventional treatment, with one of three patients with predominantly ground glass FA and one of three patients with reticular pattern FA dying of their lung disease. The four surviving patients had been stable with treatment for 18 months at the time of submission of this paper. Unfortunately, the number of patients who were treated for their lung disease was small and meaningful statistical analysis cannot be undertaken. Treatment was also given at different stages of the disease process, which further limits our ability to draw firm conclusions from the data available.

Predicting progressive FA

Ten patients had significant deterioration in their FA over two years' follow up. These patients were compared with 15 patients with stable lung disease who continued to the end of the study. Tables 3 and 4 give a comparison of their clinical features. Clinical features associated with the progression of FA were the presence of bibasal crackles ($p=0.04$), a reduced TLCO ($p<0.001$), extent of FA on HRCT ($p=0.026$), and distribution of involvement of FA on HRCT ($p=0.031$). On forward conditional logistic regression only TLCO remained significant ($p=0.024$, estimated odds ratio 0.85, 95% confidence interval 0.74 to 0.98). The level of TLCO was investigated with receiver operator curves to identify clinical predictors of progressive FA (fig 1). It was found that a 54% percentage of predicted TLCO cut off gave 80% sensitivity and 93% specificity.

DISCUSSION

This is the largest prospective HRCT based study of FA in patients with RA to date. With this study we have been able to assess the natural history of FA and to determine over the short term what proportion of patients have rapidly progressive FA and how many have a more benign course. The FA was mainly reticular pattern (80%) and coexistent emphysema was present in 41%. We found in this unselected cohort of patients with RA and FA that over a two year period pulmonary function deteriorated significantly in 10/29 (34%) patients, including four (14%) patients who died of respiratory failure. HRCT has shown that progression can occur with increased reticular pattern or ground glass exacerbations. Predominantly ground glass pattern FA involvement can spontaneously improve. When the presenting clinical features were examined, progressive FA was associated with the presence of bibasal crackles, TLCO, and extent and distribution of lung involvement on HRCT at initial presentation. However, TLCO is the most reliable independent predictor of progression. With a TLCO <54% we found in this group, with 93% specificity, that significant progression of their lung disease occurred. Measured TLCO will vary between centres, but it might be reasonably assumed that with a 5% standard deviation[9] a trial of treatment with corticosteroids should be considered when the TLCO is consistently between 50% and 60% of the predicted value.

It is possible to question whether lung biopsy should have been undertaken on these patients, but now that it has been prospectively shown that HRCT correlates with lung biopsy in 90% of cases in diagnosing FA this would seem to be unnecessary when considering a diagnosis of FA.[10] HRCT has been shown to be equal to, if not better than, lung biopsy in predicting survival in idiopathic pulmonary fibrosis.[11] It is the extent of fibrosis present that determines outcome in FA, which is where HRCT gives a particularly accurate, global assessment.[7 8] However, the exact nature of the ground glass pattern interstitial lung disease (ILD) cannot be known with certainty with HRCT. This might be due to fine fibrosis or cellular infiltration as found in desquamative interstitial pneumonia, non-specific interstitial pneumonia and, to a lesser extent, in usual interstitial pneumonia. Certainly, those patients with the remitting ground glass pattern ILD are likely to have had non-specific or desquamative interstitial pneumonia cellular infiltrations. The extended classification of lung histology now described in cryptogenic FA[7] needs to be evaluated in RA associated FA.

The presence of emphysema complicates the study, but there is increasing evidence that smoking is associated with RA.[12–14] Recently, Rajasekaran *et al* found that active smoking is higher in patients with RA related ILD than those with cryptogenic FA[15]; it is therefore not surprising that emphysema and FA occur in RA associated FA. In our patients, HRCT showed apical emphysematous bullae that did not interfere with the diagnosis or grading of the scans for FA. In anticipation of emphysema and smoking producing a progressive fall in TLCO that might be falsely attributed to FA, evidence of HRCT progression of FA was included in the definition of progression. We also included the presence or absence of bullae in the multiple logistic regression analysis, and this was not associated with progression at two years. We suggest that if a more sensitive scale for the HRCT assessment of emphysema were developed it might be possible to improve prediction of progression in patients with RA and FA even further.

Akira *et al* specifically reported the course of CT diagnosed lung disease in patients with RA.[3] They described the clinical events occurring in 29 patients with RA who had lung disease diagnosed by chest HRCT between 1986 and 1997. Nineteen patients had features in keeping with FA, of whom 10 patients died of respiratory failure, and one died of small cell lung carcinoma. Mean survival of those dying was three years (range four months to seven years). This study was not able to correlate CT and lung histology with clinical features or pulmonary function tests and did not attempt to find predictors of the course of HRCT diagnosed FA in patients with RA. Progression of disease on HRCT showed a similar pattern to that found in our patients. They had a higher percentage of patients with rapid deterioration with the appearance of multifocal areas of ground glass attenuation (38%), and unfortunately all these patients died. Thirty one per cent of their patients showed extension of honeycombing from peripheral to central parts of the lung on HRCT. The difference in frequency of deterioration probably reflects the retrospective nature of the study of Akira *et al*.

Remy-Jardin *et al* included follow up CT data on four patients.[16] HRCT was repeated owing to clinical deterioration, rather than at regular intervals. One patient had progression in the extent of honeycombing from the peripheral to central portions of both lungs. In three patients CT showed rapid changes in lung abnormalities, with extension of honeycombing centrally and concurrent replacement of ground glass

attenuation by honeycombed lung. This occurred within four months in two patients and six months in the other patient. Again all three patients with this rapid deterioration died.

Fujii *et al* repeated HRCT at one year in 28 patients with RA in whom ILD had been diagnosed at the first examination.[17] Similar results to those of our study were found, with 57% of patients having no change in HRCT findings; however, progression was seen in nine patients. In three patients the HRCT appearance improved, all these patients had ground glass pattern ILD. Interestingly, like our patients they had not been treated with corticosteroids between HRCT assessments and so it seems the cellular component of the disease can spontaneously regress without specific treatment.

For idiopathic pulmonary fibrosis (or cryptogenic FA), predictors of progression have been studied more extensively. It is important to study predictors of progression of lung disease and not to confuse this with response to treatment and survival, as current treatment options are often unsatisfactory.[18] The extent of HRCT lung involvement,[19] which has been shown to correlate with the pulmonary function parameters, forced vital capacity and TLCO,[20] has also been shown to be associated with progressive disease in idiopathic pulmonary fibrosis. Currently, several different scoring systems are available for assessing the type, extent, and distribution of FA on HRCT. We did not find the Wells systems of classification to be independently better than TLCO in predicting progression of FA, in our patient group.

Although the initial number of patients with RA associated FA in our study was reasonably large, the number with progression at two years was low and so we would suggest further studies should recruit larger numbers of patients, incorporate each type of pattern of FA, and use all the different HRCT scoring systems. As mentioned previously, a formal score for coexistent emphysema may also improve the accuracy of the HRCT assessment.

Now that we have identified a readily available predictor of progression in FA associated with RA, a standardised approach to monitoring patients and initiation of treatment can be taken in clinical practice and in controlled treatment trials.

ACKNOWLEDGEMENTS

We thank the staff at Whiston Hospital cardiorespiratory department, in particular Karen Eyres. We also thank Sheena Hennell for providing helpful suggestions and comments on the paper. Financial support for the research was provided by the British Lung Foundation.

Authors' affiliations

J K Dawson, M P Lynch, Department of Rheumatology, St Helens and Knowsley Trust Hospitals, Liverpool, UK
H E Fewins, Department of Radiology, Cardiothoracic Centre, Liverpool, UK
J Desmond, Department of Radiology, St Helens and Knowsley Trust Hospitals
D R Graham Department of Respiratory Medicine, St Helens and Knowsley Trust Hospitals

REFERENCES

1 **Turner-Warwick M**, Burrows B, Johnson A. Cryptogenic fibrosing alveolitis: clinical features and their influence on survival. Thorax 1980;35:171–80.
2 **Hakala M**. Poor prognosis in patients with rheumatoid arthritis hospitalised for interstitial lung fibrosis. Chest 1988;93:114–18.
3 **Akira M**, Sakatani M, Hara H. Thin-section CT findings in rheumatoid arthritis-associated lung disease: CT patterns and their courses. J Comput Assist Tomogr 1999;23:941–8.
4 **Dawson JK**, Fewins HE, Desmond J, Lynch MP, Graham DR. Fibrosing alveolitis in patients with rheumatoid arthritis as assessed by high resolution computed tomography, chest radiography, and pulmonary function tests. Thorax 2001;56:622–7.
5 **Arnett FCS**, Edworthy M, Bloch DA, McShane DJ, Fries JF, Cooper NS, *et al*.. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315–24.
6 **Quanjer PH**. Standardized lung function testing. 1983 Report of the working party standardization on lung function testing. European community for Coal and Steel. Bull Europ Physiopath Respir 1983;19(suppl 15):1–82.
7 **Katzenstein A-LA**, Myers JL. Idiopathic pulmonary fibrosis. Clinical relevance of pathological classification. Am J Respir Crit Care Med 1998;157:1301–15.
8 **Wells AU**, Rubens MB, du Bois RM, Hansell DM. Serial CT in fibrosing alveolitis: prognostic significance of the initial pattern. AJR Am J Roentgenol 1993;161:1159–65.
9 **Laszlo G**. *Testing the mechanics of breathing. Pulmonary function a guide for clinicians.* Cambridge: Cambridge University Press, 1994.
10 **Raghu G**, Mageto YN, Lockhart D, Schmidt RA, Wood DE, Godwin JD. The accuracy of the clinical diagnosis of new-onset idiopathic pulmonary fibrosis and other interstitial lung disease: a prospective study. Chest 1999;116:1168–74.
11 **Gay SE**, Kazerooni EA, Toews GB, Lynch JP, III, Gross BH, Cascade PN, *et al*. Idiopathic pulmonary fibrosis: predicting response to therapy and survival. Am J Respir Crit Care Med 1998;157:1063–72.
12 **Karlson EW**, Lee IM, Cook NR, Manson JE, Buring JE, Hennekens CH. A retrospective cohort study of cigarette smoking and risk of rheumatoid arthritis in female health professionals. Arthritis Rheum 1999;42:910–17.
13 **Hutchinson D**, Shepstone L, Moots R, Lear JT, Lynch MP. Heavy cigarette smoking is strongly associated with rheumatoid arthritis (RA), particularly in patients without a family history of RA. Ann Rheum Dis 2001;60:223–7.
14 **Silman AJ**, Newman J, MacGregor AJ. Cigarette smoking increases the risk of rheumatoid arthritis. Results from a nationwide study of disease-discordant twins. Arthritis Rheum 1996;39:732–5.
15 **Rajasekaran BA**, Shovlin D, Lord P, Kelly CA. Interstitial lung disease in patients with rheumatoid arthritis: a comparison with cryptogenic fibrosing alveolitis. Rheumatology (Oxford) 2001;40:1022–5.
16 **Remy-Jardin M**, Remy J, Cortet B, Mauri F, Delcambre B. Lung changes in rheumatoid arthritis: CT findings. Radiology 1994;193:375–82.
17 **Fujii M**, Adachi S, Shimizu T, Hirota S, Sako M, Kono M. Interstitial lung disease in rheumatoid arthritis: assessment with high-resolution computed tomography. J Thorac Imaging 1993;8:54–62.
18 **Ryu JH**, Colby TV, Hartman TE. Idiopathic pulmonary fibrosis: current concepts. Mayo Clin Proc 1998;73:1085–101.
19 **Zompatori M**, Fasano L, Battista G, Cavina M, Bertaccini P. Course of idiopathic pulmonary fibrosis of the Wells grade III at presentation. Study using high-resolution computerized tomography. Radiol Med (Torino) 1997;94:611–17.
20 **Xaubet A**, Agusti C, Luburich P, Roca J, Monton C, Ayuso MC, *et al*. Pulmonary function tests and CT scan in the management of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 1998;158:431–6.