CONCISE REPORT

Ten year follow up of pulmonary function in patients with primary Sjögren's syndrome

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Abstract

***Objectives*—To follow up a previous report on the lung function of patients with primary Sjögren's syndrome (SS), and describe the findings having followed up this cohort for a median duration of 10 years (range 8–12 years).**

***Methods*—30 patients fulfilling Fox's criteria for definite or probable primary SS were assessed within six months of diagnosis and after a median duration of four and then 10 years by a clinical examination, chest radiograph, and lung function studies (FEV_1, FVC, TLCO, and KCO).**

***Results*—At baseline, symptomatic dyspnoea was a common finding, reported by 13/30 patients, of whom two had evidence of fibrosing alveolitis on plain chest radiograph. Five patients had a carbon monoxide transfer factor (TLCO) more than two standardised residuals below the predicted value. After four years' follow up two further patients developed radiological fibrotic changes and there were significant reductions in TLCO ($p<0.02$) and transfer coefficient (KCO) ($p<0.02$) compared with the baseline measurements. At 10 years' follow up four patients had died and four were lost to follow up. One patient with fibrosing alveolitis had died from chest disease. There were no further cases of pulmonary fibrosis identified on plain chest radiograph. The lung function studies showed no further deterioration from the results found at year four with significant improvements in both TLCO ($p<0.001$) and KCO ($p<0.001$). Those patients who were anti-Ro antibody positive had significantly lower transfer factors than patients with primary SS without this serological marker ($p<0.02$).**

***Conclusion*—This long term follow up of lung disease in primary SS is reassuring, and suggests that most patients do not develop progressive lung disease. Pulmonary disease occurs predominantly in anti-Ro antibody positive patients and presents early in the course of the disease.**

(*Ann Rheum Dis* 2000;**59**:709–712)

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Accepted for publication
24 February 2000

Primary Sjögren's syndrome (SS) is an autoimmune condition characterised by lymphocytic infiltration of lachrymal and salivary glands. Patients who are anti-Ro antibody positive often develop more systemic manifestations,[1] with lung disease being commonly reported.[2 3] The most frequently described pulmonary abnormalities are interstitial lung disease and small airways disease. It has been suggested that the early detection of subtle pulmonary changes may precede the appearance of symptoms in primary SS by a number of years.[4] High resolution computed tomography is often abnormal in these patients, even in the absence of respiratory symptoms.[5] Few longitudinal studies have been undertaken and their results are conflicting. Linstow *et al* detected no significant change in the pulmonary function of 27 patients over seven years,[6] whereas we have previously reported a significant deterioration in lung function of 30 patients with primary SS over a follow up period of four years.[7] We have now followed up this cohort for 10 years and have examined serological variables which might predict poor outcome.

Patients and methods

Thirty patients were recruited from a specialist clinic and fulfilled objective criteria for "definite" or "probable" primary SS as proposed by Fox *et al*,[8] with no evidence of another autoimmune disease. All were white women with a median age at diagnosis of 54 years (range 36–76). A clinical examination for glandular and extraglandular manifestations was undertaken, including Schirmer's tests, rose bengal staining of the conjunctiva and minor salivary gland biopsy specimen. Subjective xerostomia supported by the absence of a salivary pool under the tongue was accepted as a criterion. Serological tests were performed for antinuclear antibodies (ANA), rheumatoid factor (RF), anti-Ro and anti-La antibodies. Symptoms and signs of possible pulmonary disease were recorded together with a smoking history. A chest radiograph and pulmonary function tests (forced expiratory volume in one second (FEV_1), vital capacity (VC), carbon monoxide transfer factor (TLCO), and transfer coefficient (KCO); results expressed as standardised residuals[9]) were performed within six months of referral. Patients were reassessed after a median duration of four and then 10 years, including a full clinical examination, chest radiograph, and pulmonary function tests.

Table 1 Clinical details of 30 patients each fulfilling diagnostic criteria for "definite" or "probable" primary Sjögren's syndrome (SS)[8]

	Age diag.	Year diag.	Duration symptoms	Schirmer's R	Schirmer's L	RB stain	Lip biopsy	Ro	La	Xero-stomia	Dyspnoea (0)	Dyspnoea (4)	Dyspnoea (10)	Cigs./day (0)	Cigs./day (4)	Cigs./day (10)	TLCO (SR) (0)	TLCO (SR) (4)	TLCO (SR) (10)	KCO (SR) (0)	KCO (SR) (4)	KCO (SR) (10)	CXR (0)	CXR (4)	CXR (10)
1	50	1988	5	2	0	+	+	−	−	+	−	−	−	15	−	−	−1.05	−1.95	−0.74	0	−0.2	−0.38	N	N	N
2*	48	1987	10	3	5	+	+	+	−	+	+	+	+	−	−	−	−2.3	−2.5	−1.2	−1.1	−1.45	−1.59	PT	FA	FA
3	57	1988	4	5	7	+	−	−	−	+	−	−	−	−	−	−	−0.3	−0.1	0.49	0.4	−0.2	0.38	N	N	N
4*	40	1986	2	25	20	−	+	+	+	+	+	+	+	−	−	−	−2.1	−2.7	−0.7	−1	−1.1	−1.31	FA	FA	FA
5†	43	1987	2	6	7	ND	−	−	−	+	−	−		−	−		−0.4	−1.5		−0.55	−0.6		N	N	
6	38	1987	3	3	4	ND	−	−	−	+	−	−	−	−	−	−	−0.5	−0.7	0.68	0.55	0.35	1.55	N	N	N
7	55	1987	3	2	0	ND	−	−	−	+	−	+	+	20	20	20	0.9	0.95	1.23	−0.1	−0.45	0.59	N	N	N
8*	63	1987	1	8	4	+	+	−	−	+	+	+		−	−		−3.15	−4.1		−2.05	−1.55		FA	FA	
9*	75	1987	15	4	5	+	+	+	−	+	+	+		−	−		−2.05	−3.1		−0.9	−0.9		N	N	
10	46	1987	1	0	0	+	+	−	−	+	−	+	+	−	−	−	0.5	0.1	0.94	0.4	0	1.45	N	N	N
11	65	1986	10	0	0	+	+	+	−	+	−	−	−	−	−	−	0.2	0.4	0.61	−0.1	−0.2	0.14	N	N	N
12	76	1987	4	1	2	ND	−	−	−	+	+	+		−	−		0.3	−1		−0.5	−0.65		N	N	
13	61	1987	10	0	0	+	−	+	−	+	−	−	+	−	−	−	1.2	0.8	0.56	0.2	−0.4	1.17	N	N	N
14	69	1987	4	12	15	+	+	−	−	+	+	+	+	−	−	−	1.2	0.95	1.52	0.65	0.4	1.41	N	N	CM
15	39	1987	4	0	0	+	+	−	−	+	+	+	+	−	−	−	0.15	0	0.18	−0.05	−0.1	0.62	N	N	N
16*	54	1986	10	2	4	+	+	+	−	+	+	+	+	−	−	−	−1.8	−1.95	−1.7	−1	−1.1	−2.41	N	FA	FA
17	61	1988	1	7	5	−	−	−	−	+	−	−	−	−	−	−	1.6	1.05	1.24	0	−0.1	0.31	N	N	N
18	54	1988	6	0	0	+	+	−	−	+	−	+	+	−	−	−	−1.2	−1.5	0.09	−0.05	−0.3	0.41	N	N	N
19	54	1987	1	0	0	+	+	+	−	+	−	+	+	15	10	10	−0.7	−1	−0.15	−0.1	−0.6	−0.52	N	N	COPD
20	73	1987	3	3	2	+	+	−	−	+	+	+		15	−		−1.2	−1.3		−0.7	−0.95		N	N	
21†	51	1987	3	2	10	ND	−	−	−	+	−	−		−	−		−0.5	−0.2		−0.55	−0.9		N	N	
22	36	1989	1	0	0	ND	+	−	−	+	+	+	+	−	−	−	−1.8	−1.8	−0.06	0	−0.5	0.41	N	N	N
23†	73	1987	5	10	20	+	−	−	−	+	+	+		−	−		0.5	0.2		−0.35	−0.85		N	N	
24*	48	1987	2	0	0	+	+	+	+	+	+	+	+	−	−	−	−2.1	−2.3	−0.52	−0.35	−0.55	−0.38	N	N	N
25	68	1986	6	0	5	ND	+	+	+	+	−	−	+	−	−	−	−1.5	−0.8	0.29	−0.2	−0.4	0.45	N	N	N
26†	72	1987	1	5	3	ND	ND	−	−	+	+	+		−	−		−0.2	−0.8		−0.55	−0.9		N	N	
27	50	1987	2	0	0	ND	+	−	−	+	−	−	+	20	20	20	0.6	0.5	0.44	0.2	−0.3	1.1	N	N	N
28	38	1985	2	0	0	+	+	+	+	+	−	−	+	−	−	−	−0.4	−0.9	0.02	−0.2	−0.4	0.66	N	N	N
29	66	1987	4	4	4	+	−	−	−	+	−	−	+	−	−	−	0.1	−0.5	0.61	0.25	0	2.38	N	N	N
30	51	1988	1	0	12	ND	−	−	−	+	−	−	−	−	−	−	−1.4	−1.5	−0.18	0.2	−0.5	0.31	N	N	N

Duration symptoms = time between first symptoms of SS and diagnosis; RB stain = rose bengal staining; Lip biopsy = focus score >1; Ro = anti-Ro antibody; La = anti-La antibody; Xerostomia = absence of salivary pool under the tongue; (0) (4) (10) = years follow up; Cigs./day = number of cigarettes smoked a day; TLCO = carbon monoxide transfer factor; KCO = transfer coefficient; (SR) = standardised residuals (ref 9),;ND = not done,;CXR = chest radiograph; PT = pleural thickening; FA = fibrosing alveolitis; CM = cardiomegaly; COPD = consistent with chronic obstructive pulmonary disease; N = normal.

*Patients treated with oral prednisolone (20 mg daily for one month followed by tapering reduction).

†Patients lost to follow up at 10 years. Causes of death (by death certificate) were bronchopneumonia secondary to fibrosing alveolitis (age 67, patient 8), transitional cell carcinoma bladder (age 85, patient 12), cerebrovascular accident (age 77, patient 20 and age 81, patient 9).

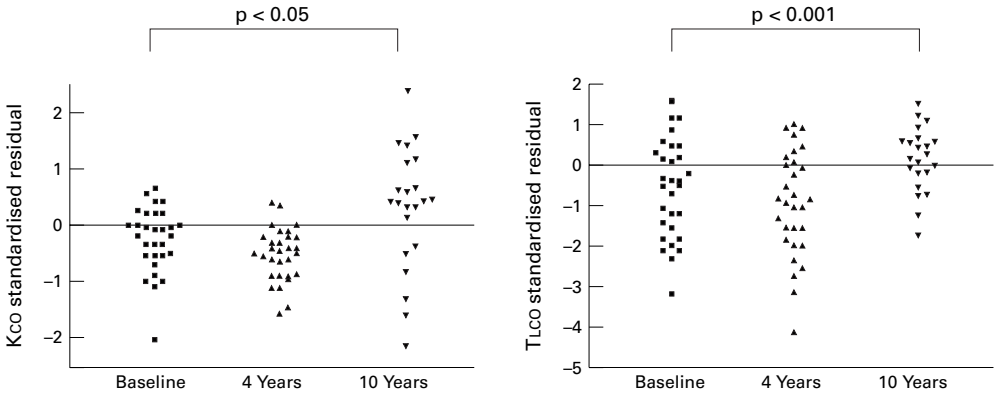

Figure 1 Transfer coefficient (KCO) and carbon monoxide transfer factor (TLCO) expressed as standardised residuals in patients with primary Sjögren's syndrome within six months of diagnosis and at four and 10 years' follow up.

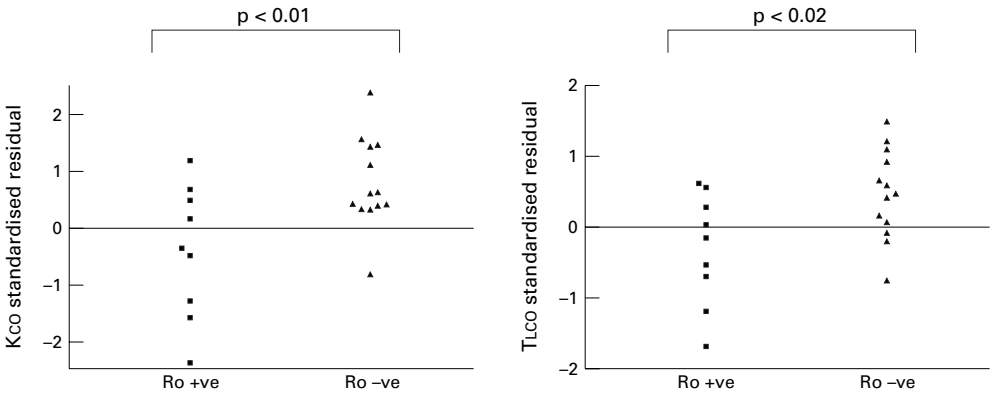

Figure 2 Transfer coefficient (KCO) and carbon monoxide transfer factor (TLCO) expressed as standardised residuals in Ro positive and Ro negative patients with primary Sjögren's syndrome at 10 years' follow up.

Standardised residuals[9] were used to express changes in pulmonary function with time, to take account of differences in predicted values with age and between patients. The paired *t* test was used to assess changes in lung function with time and the unpaired *t* test to compare anti-Ro positive and anti-Ro negative groups.

Results

Table 1 gives biographical details of the 30 patients studied. At baseline 13/30 patients reported dyspnoea. Five patients were current smokers. Bilateral fine basal crackles were present in four patients. Two had evidence of fibrosing alveolitis on plain chest radiograph. Five patients had a TLCO more than two standardised residuals below the predicted value (fig 1). After four years' follow up a further four patients developed dyspnoea. Three were now smokers, two having stopped since the initial assessment. Bilateral fine basal crackles were noted in nine patients, and one had features of a pleural effusion. The chest radiographs had become abnormal in a further two patients. All showed evidence of alveolitis, with associated persistent pleural effusions in one patient. There were significant reductions in TLCO ($p<0.02$) and KCO ($p<0.02$) compared with the baseline measurements (fig 1).

At 10 years, of the original 30 patients, four had died and four were lost to follow up. One patient died from bronchopneumonia complicating fibrosing alveolitis; two from cerebrovascular events, and the other from metastatic spread of a transitional cell carcinoma of the bladder. A total of 16/22 patients reported dyspnoea, of whom 12 had a persistent non-productive cough; three were current smokers. There were no new cases of pulmonary fibrosis identified on plain chest radiograph. The TLCO and KCO did not deteriorate further from the results at four years' follow up, with significant improvement in both TLCO and KCO between baseline and 10 years ($p<0.001$ and $p<0.05$ respectively) and between four years' and 10 years' follow up ($p<0.001$).

SEROLOGY

At initial documentation, 10 patients were anti-Ro or anti-La antibody positive, or both, seven ANA positive (but anti-Ro and anti-La antibody negative), two RF positive, and 11 seronegative. There were no changes in the patients' serology when repeated after 10 years. The one patient who died of an infective complication of fibrosing alveolitis was ANA positive. Anti-Ro antibody positive patients otherwise had significantly lower transfer factors ($p<0.02$) and transfer coefficients ($p<0.01$) than patients with primary SS without this serological marker (fig 2).

Discussion

The clinical significance of pulmonary disease in primary SS is uncertain and the reported prevalence from cross sectional studies ranges from 9% to 60%.[10–12] This wide range is partially due to variation in the sensitivity of

tests employed. High resolution computed tomography can identify parenchymal abnormalities in patients free of respiratory symptoms,[5] suggesting subclinical pulmonary disease, whereas plain chest radiography and simple tests of pulmonary function, such as TLCO and KCO, are relatively insensitive techniques.

The significance of early parenchymal changes is best assessed by longitudinal studies. In our original report[7] we described a significant reduction in TLCO and KCO over four years. Other follow up studies have found that lung function does not deteriorate to the same extent. Although Mialon *et al* demonstrated a statistically significant decrease in TLCO and KCO over 55 months' follow up of 18 patients with primary SS,[13] the reduction was not considered to be large enough to be clinically significant. Linstow *et al* followed up 27 patients with primary SS previously reported to have reduced pulmonary diffusing capacities and found the TLCO and KCO increased significantly after seven years.[6]

Our 10 year follow up data suggest that the observed fall in TLCO and KCO seen at four years has not continued. There were statistically significant increases in both the TLCO and KCO between baseline and four year follow up results and those at 10 years' follow up. Radiological evidence of fibrosing alveolitis was present in four patients at year four. One patient with fibrosing alveolitis died of bronchopneumonia, but no new cases were identified between four and 10 years' follow up. However, respiratory symptoms remained prevalent, with 16/22 reporting breathlessness on minimal exertion and 12/22 a chronic non-productive cough.

The wide range in the reported prevalence of pulmonary disease in primary SS may also result from differences in patient groups. We have previously found that the anti-Ro antibody identifies a subgroup of patients with primary SS with more systemic disease,[1] and the TLCO and KCO were significantly lower in our anti-Ro antibody positive patients at 10 years' follow up.

It is difficult to explain the apparent improvement in lung function in these patients beyond four years' follow up. This improvement was seen both in patients treated with oral corticosteroids, where there was radiological evidence of interstitial lung disease, and in those where there was no therapeutic intervention. The improvement in lung function found by Linstow *et al*[6] was also independent of treatment. We have recently reported[14] a reduction towards normal in serum IgG levels in patients with primary SS followed up for 10 years, again in the absence of treatment, suggesting a reduction in disease activity. Longitudinal studies involving bronchoalveolar lavage are required to see if the natural history of the lung disease in these patients is characterised by a reduction in infiltrating inflammatory cells with time.

Although our original paper[7] had concluded that pulmonary complications of primary SS represented a significant threat to health and accounted for considerable morbidity, our long term follow up of these patients is reassuring, and suggests that most patients with primary SS do not develop progressive lung disease. Pulmonary complications occur predominantly in anti-Ro antibody positive patients and present early in the course of the disease.

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