Systemic Sclerosis and Interstitial Lung Disease: A Pilot Study Using Pulse Intravenous Methylprednisolone and Cyclophosphamide to Assess the Effect on High Resolution Computed Tomography Scan and Lung Function

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ABSTRACT. ***Objective.*** To document the effectiveness, including the longterm effect, of a course of intravenous (IV) pulses of methylprednisolone (MP) and cyclophosphamide (CYC) in patients with scleroderma (SSc) who had evidence of lung inflammation on high resolution computer tomographic (HRCT) scan of the chest.

Methods. Fourteen consecutive patients with SSc and lung involvement were treated with 6 pulses of IV MP (10 mg/kg) and IV CYC (15 mg/kg) given at 3–4 weekly intervals. HRCT scans and lung function tests were performed at baseline and after the 6th pulse. Further lung function tests were repeated at 12 months and annually thereafter.

Results. Modified Rodnan skin scores improved significantly by 35% from a median baseline score of 17 (IQR 14–26.5) to a posttreatment score of 13 (IQR 10.5–18.5; p = 0.0058). HRCT scan scores improved significantly (p = 0.04). Twelve of 13 patients experienced either improvement or stabilization of the HRCT score. Median DLCO and lung volumes remained stable during the first 12 months. After a median followup of 26 months (IQR 19–43), 67% of patients experienced deterioration in DLCO. Median deterioration was 23% (IQR 44–0.6), with the median rate of deterioration of the predicted value of the DLCO/month being 0.87% (IQR 1.24–0.02). The treatment was safe and well tolerated.

Conclusion. This IV regimen stabilized lung disease in patients with SSc. When treatment was stopped, or reduced in intensity, a deterioration in lung function occurred in the majority of patients. Rate of deterioration of DLCO may be a useful marker for determining the intensity of treatment. These findings have implications for treating lung disease and designing clinical trials in patients with SSc. (J Rheumatol 2002;29:2371–8)

Key Indexing Terms:
SYSTEMIC SCLEROSIS
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Patients with systemic sclerosis (SSc) experience significant morbidity and mortality. Pulmonary fibrosis occurs in about 80% of patients with SSc[1]. Lung disease is now the commonest cause of death in these patients, since the introduction of angiotensin converting enzyme inhibitors has improved the prognosis of renal crises[2,3]. Evidence suggests that the deterioration in lung function starts in the early years, and therefore a regimen that influences this early deterioration would be clinically important.

Lung function tests are more sensitive than auscultation of the chest or a chest radiograph in detecting early interstitial disease in SSc[4]. A reduced diffusing capacity of the lung for carbon monoxide (DLCO) is the most sensitive measure and detects a defect in gas exchange[5]. Lung function tests may also show a restrictive pattern with decreased total lung capacity (TLC), vital capacity (VC) and/or forced vital capacity (FVC), forced expiratory volume (FEV_1), and residual volume. Pulmonary disease has been defined as being present if the TLC is < 80% of the predicted value and/or the DLCO is < 75% of the predicted value[6]. If the lung function tests are abnormal or deteriorating, then a high resolution computer tomographic (HRCT) scan of the lungs provides a sensitive and reproducible method of quantifying

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the morphological extent of disease to aid the clinical management of fibrosing alveolitis associated with SSc[7,8]. HRCT abnormalities seen in patients with SSc predominantly affect the lower lobes, particularly in a peripheral and subpleural location, and include intralobular opacities, parenchymal and subpleural opacities, areas of ground glass, and honeycombing[7,9]. The presence of ground glass changes on the HRCT correlates with the number of inflammatory cells in the bronchoalveolar lavage fluid[4,10] and the percentage predicted DLCO[11] and indicates that the disease may be reversible[7,12].

No drug has been shown in a randomized controlled prospective trial to be effective in altering the course of lung disease in SSc. Several drugs have been evaluated and include D penicillamine[13,14], aminobenzoic acid, colchicine, griseofulvin[15], and chlorambucil[16]. Oral cyclophosphamide (CYC) has probably been the most promising in observational studies and has been shown to improve lung function[17-23].

We investigated whether intravenous (IV) pulses of methylprednisolone (MP) and CYC could stabilize and/or improve the HRCT scan score and lung function as measured by FVC and DLCO. As well, we assessed if this treatment could improve the modified Rodnan skin scores in patients with SSc.

MATERIALS AND METHODS

Patients and assessment. Fourteen consecutive patients with SSc (defined by the American College of Rheumatology criteria[24]) and with lung disease who were new referrals to the Connective Tissue Clinic at Leeds General Infirmary from January 1996 to December 1998 were studied prospectively. A HRCT scan was performed if the TLC was < 80% of the predicted value and the DLCO was < 75% of the predicted value or if serial 3 monthly lung function tests showed a deterioration. To enter the study, a patient had to have an abnormal HRCT of the lungs with some ground glass changes[25]. Patients were fully assessed at baseline and at 6 months (after receiving the 6 IV pulse treatments). The assessment included the modified Rodnan skin score[26]. Skin thickness was assessed clinically in each of 17 body surfaces, using a 0–3 scale, where 0 = normal, 1 = mild thickness, 2 = moderate thickness, and 3 = severe thickness (maximum score = 51). Urinalysis, blood tests, lung function tests (lung volumes and transfer factor), electrocardiograph, Doppler echocardiography, and HRCT of the lungs were also performed. Blood tests included an autoantibody profile, for example antinuclear antibody (ANA), anticentromere antibody, anti-Scl-70 and other extractable nuclear antigens (ENA), anti ds-DNA antibodies, immunoglobulins, full blood cell count, creatinine, plasma viscosity, and C-reactive protein (CRP). The HRCT was performed using the standard protocol of 1.0–1.5 mm cuts at 15–20 mm intervals from lung base to apex. All scans were scored independently by 2 consultant chest radiologists, who were unaware of the clinical information but knew the chronological order of the scans. The average score was used for the analysis. The scans were assessed for disease extent, ground glass change, and/or established fibrosis, using a validated HRCT scoring system for pulmonary fibrosis in patients with asbestos related disease[27]. This system has 4 gradings for the severity of disease: no disease (score 0–6), minor disease (7–18), moderate disease (19–30), and advanced disease (> 30). The maximum score is 72. The lung function tests and HRCT scans were performed within 4 weeks of completing the pulse regimen. Longterm followup was continued and included at least annual lung function tests.

Treatment protocol. Patients were given 6 IV pulses of MP 10 mg/kg and CYC 15 mg/kg. The first 3 pulses were given at 3 weekly intervals and the remaining 3 pulses were administered at 4 weekly intervals. This regimen was adapted from the Birmingham Vasculitis Protocol[28]. Patients were also reviewed prior to receiving each pulse, and in particular the presence of an intercurrent infection was excluded. In view of the high dose of IV corticosteroids, all patients were prescribed a gastric protectant, either a proton pump inhibitor or H2 antagonist. They were also advised to drink 3 l of fluid on the day of the pulse and prescribed three 400 mg mesna tablets, 1 h pre-CYC and 4 and 12 h post-CYC, to reduce the risk of hemorrhagic cystitis. All patients were offered antiemetics and used either metoclopramide or granisetron. They were also given a supply of amphoteracin should they develop oral thrush around the time of the neutrophil nadir level, roughly 10 days post-CYC. All patients were taking low dose lisinopril (typically 2.5 mg daily) as a renal protectant.

Statistical analysis. Statistical analysis was performed using SPSS 6.0 software (SPSS Inc., Chicago, IL, USA). For nonparametric data analysis the Mann Whitney U Test was used for ordinal variables, Fisher's exact test for dichotomous variables, and the Wilcoxon rank sum test for paired variables. The following definitions were applied to changes from entry values for the lung volumes and DLCO, as in previous studies. Improved was defined as ≥ 10% increase; stable if < 10% increase or < 10% decrease; and worsened if ≥ 10% decrease. The definition of change for the skin scores was similar: improved if ≥ 10% decrease; stable if < 10% decrease and < 10% increase; and worsened if ≥ 10% increase.

RESULTS

Fourteen white Caucasian patients were entered into the study, 11 women and 3 men. Their median age at the onset of SSc was 46.5 years (interquartile range 32–60). Onset of SSc was defined by the development of the first SSc manifestation other than Raynaud's, which was skin involvement in this study. All patients had Raynaud's (median duration 6.0 yrs, IQR 3.5–12) and 12 (86%) had gastrointestinal involvement, which was typically esophageal dysmotility. The median duration of symptomatic lung disease, at entry into the study, was 1 year (IQR 1–3). The lung examination was normal in 9 (64%) patients. Half of the patients were smokers. All patients were positive for ANA at presentation. Forty-three percent of individuals were anti-Scl-70 positive and one patient was anticentromere antibody positive. Twenty seven percent of patients were known to be rheumatoid factor positive, 15% of patients had other positive ENA besides anti-Scl-70, e.g., RNP, Ro and La antibodies. The creatine kinase was mildly raised in 43% of patients, the CRP was increased in 39%, and immunoglobulins were raised in 46%. These abnormalities improved with treatment. All patients had normal serum creatinine and no significant proteinuria. No patient had pulmonary hypertension determined by Doppler echocardiography.

Table 1 summarizes the patients' individual characteristics and the absolute values for skin scores, HRCT scans, and lung function tests. The median skin score at baseline was 17 (IQR 14–26.5), and it improved significantly by a median of 35% (IQR 3.5–46) to a posttreatment value of 13 (IQR 10.5–18.5; p = 0.0058, Wilcoxon rank sum test). On an individual basis, 61% of patients improved, 39% were stable, and none deteriorated.

Table 1a. Patient demographics and individual results for the HRCT scan scores and skin scores.

Patient	M/F	Age at Onset, yrs	Duration, yrs*	Lung Disease**	Chest Examination	Scl-70 Status	HRCT Score, Baseline	HRCT, Post-therapy	Skin Score, Baseline	Skin Score, Post-therapy
1	F	42	1	1	Normal	+	25	14	16	7
2	F	48	5	3	Abn	–	54.5	55.5	22	15
3	M	29	3	1	Normal	+	40.5	27.5	11	6
4	F	74	0	1	Normal	–	25.5	25.5	15	15
5	F	30	11	4	Abn	–	54	54.5	14	9
6	F	45	0	1	Abn	–	21.5	18.5	17	18
7	M	38	1	1	Normal	+	34.5	20	26	26
8	F	69	2	0	Normal	–(ACA+)	18	NA	13	12
9	M	30	1	3	Normal	–	52	47	23	13
10	F	56	4	0	Normal	–	41.5	32.5	14	13
11	F	55	7	1	Abn	–	41.5	36	27	13
12	F	64	2	1	Normal	+	24.5	22	31	20
13	F	58	2	3	Abn	+	39.5	34	NA	NA
14	M	33	5	0	Normal	+	28	40	36	19

* Disease duration from first non-Raynaud's symptom at start of pulse therapy. **Duration of lung disease (yrs). Abn: abnormal, ACA: anticentromere, NA: not available.

Table 1b. Individual function results.

Patient	FVC, Baseline	FVC, Post-therapy	% Rate of Change, FVC†	FEV1, Baseline	FEV1, Post-therapy	TLC, Baseline	TLC, Post-therapy	DLCO, Baseline	DLCO, Post-therapy	% Rate of Change, DLCO††
1	90	98	1.5	82	89	93	107	76	88	2.6
2	48	43	–1.7	50	50	58	59	18	27	8.3
3	95	94	–0.18	86	96	116	96	85	72	–2.5
4	70	104	3.3	84	110	NA	80	NA*	67	
5	34	35		35	37	NA	37	NS*	26	
6	106	105	–0.16	96	94	124	96	110	94	–2.42
7	102	100	–0.33	93	93	111	94	63	50	–3.4
8	152	154	–0.22	134	125	121	116	54	55	0.31
9	75	75	0.00	75	72	88	88	62	58	–1.1
10	102	99	–0.49	99	93	81	86	65	60	–1.28
11	70	N/A		70	N/A	71	NA	48	48	0
12	72	70	–0.46	75	75	NA	73	NA	53	
13	100	101	0.17	106	113	95	106	69	81	2.9
14	96	91	–0.87	86	78	100	99	95	80	–2.6

† % change of % predicted FVC/month. †† % change of % predicted DLCO/month. * Patients unable to adequately expire all lung volumes and DLCO are quoted as percentage of predicted.

Figure 1 shows the HRCT scans of Patient 7 before and after treatment. The pretreatment scan showed ground glass change in both lower lobes consistent with acute alveolitis. In the posttreatment scan the ground glass change had largely resolved. The interobserver variability correlation for the HRCT scan scores was very good, with a Pearson rank correlation coefficient of 0.99. The baseline HRCT extent scores showed that one patient had minor disease, 5 had moderate disease, and 8 had advanced disease, according to the HRCT scoring system[27]. The median baseline HRCT score was 37.0 (IQR 24.9–44.1) and the median posttreatment HRCT score was 32.5 (IQR 21.0–43.5). Pre- and posttreatment HRCT scans were available for scoring in 13 patients. The median percentage improvement was 13.0 (IQR –0.45 to 23.5), which was significant (p = 0.04). The HRCT improved in 7 (54%) patients, remained stable in 5 (38%), and deteriorated in one patient (8%). Patients 2, 5, and 9 all had advanced disease, but had stabilization of their disease. Greatest improvement in the CT score was seen in Patients 1, 7, and 10. Patients 7 and 10 had very early lung disease.

Table 2 summarizes lung function test results. There was no overall significant change in the DLCO at baseline and after pulse 6, but there was a trend toward greater improvement in the DLCO in patients with early lung disease (< 2 years) compared with longer duration disease (p = 0.053). The overall DLCO results fulfilled the definition of stable, but within the cohort 3 patients improved (27%), 4 were

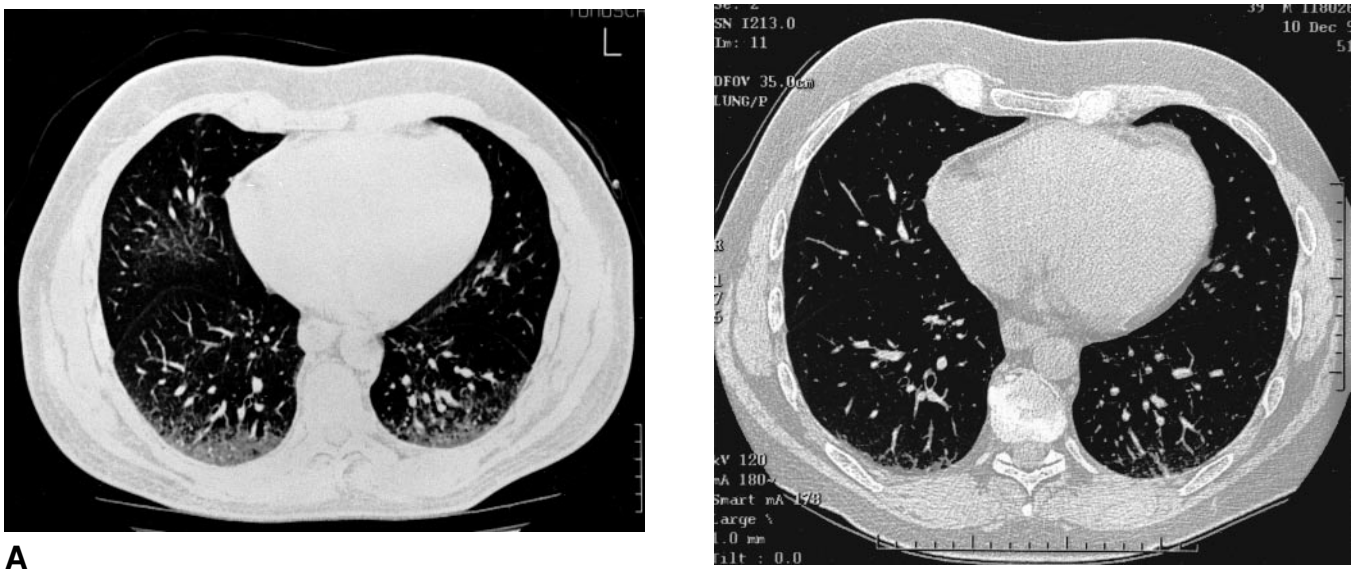

Figure 1. (A) Pretreatment and (B) post-therapy HRCT scans.

Table 2. Cohort lung function test results. Data are median percentage of predicted (interquartile range).

	Baseline (0 mo)	Post-treatment (6 mo)	% Change from Baseline	Wilcoxon Rank p	6 mo Post-therapy (12 mo)	% Change from 6 mo	Wilcoxon Rank p
DLCO	65 (54–85)	60 (52–81)	–7.4 (–16–16)	0.24	60 (45–77)	–1.2 (–16–4.7)	0.39
TLC	95 (81–116)	94 (77–103)	–0.9 (–16–7.6)	0.41	93 (71–111)	3.4 (–6.7–5.7)	0.72
FVC	93 (70–102)	98 (73–103)	0.00 (–2.4–4.2)	0.66	91 (74–111)	3.3 (–12–10.5)	0.33
FEV_1	85 (74–97)	93 (74–103)	0.00 (–5.1–7.6)	0.77	85 (75–97)	1.6 (–8.6–3.5)	0.65

stable (36%), and 4 deteriorated (36%). The findings were similar for the TLC, FVC, and FEV_1. Lung function tests 6 months after completing the course of pulses showed that the group median DLCO and lung volumes had remained stable.

The DLCO and HRCT scan scores showed a nonsignificant negative correlation at baseline (r = –0.59, p = 0.056). This relationship became more significant after treatment (r = –0.67, p = 0.012). However, of the patients who improved on HRCT only a couple fulfilled the criteria for the definition of improvement in DLCO.

The treatment was safe and well tolerated. Only one patient (Patient 1) had a decreased white blood cell count 10 days post-pulse and therefore required a dose reduction at subsequent pulses. On 5 occasions, the pulse had to be postponed by one week due to an intercurrent infection, typically a lower respiratory chest infection. Six patients (43%) continued to take low dose oral prednisolone, but treatment with the pulses enabled these patients to reduce their maintenance dose of oral corticosteroids. No patient developed episodes of scleroderma renal crisis during the period of observation or followup.

Preliminary longterm data. Followup has continued in all patients for a median of 26 months (IQR 19–43) (Table 3). The patients have been monitored with regular lung function tests (Figure 2). If there was a deterioration in lung function, particularly in the transfer factor, then the patient was invited to have a further course of pulses. If the deterioration continued despite additional therapy, then the patient received maintenance pulse therapy at 6 (3 pulses), 9 (3), and then 12 weekly (continuous) intervals. Patients 1, 3, and 6 have followed this protocol. They are now 48, 54, and 60 months past their first pulse. Their transfer factors are 84%, 45%, and 59% of predicted values, respectively. Patients 5, 7, and 14 deteriorated significantly and were given 4 high dose pulses of CYC (22.5 mg/kg) with MP at 4 weekly intervals, which stabilized their transfer factors. Patients 4, 8, 10, 11, and 13 received no further pulses during the followup period. Further pulses were planned for Patient 13, but she died suddenly. Patient 11 started a second course of pulses after the final assessment in this study because of a recent deterioration in her DLCO. Patients 4 and 8 are symptomatically well and have declined further lung function tests.

However, for the patients with complete lung function

Table 3. The longterm results.

Patient	Duration Followup, mo	Final DLCO*	% Change DLCO from Baseline	% Change DLCO/mo	Number of Pulses	Time to Next Pulse After Pulse 6, mo	Cumulative, mg/kg	CYC, mg/kg/mo
1	43	84	10.5	0.24	23	9	260	6.05
2						0	195	
3	54	45	–47.0	–0.87	20	27	300	5.56
4					6	No further	90	
5	11	18			10	4	195	17.7
6	58	59	–46.4	–0.8	32	2	406	7.00
7	21	48.4	–22.5	–1.07	9	0	117	5.57
8					6	No further	90	
9	33	58	–6.5	–0.2	12	12	240	7.27
10	26	70	7.7	0.3	5	No further	75	2.88
11	26	30	–37.5	–1.4	6	No further	60	2.73
12	27	55			12	8	172	6.37
13	19	40	–42	–2.2	6	No further	51.6	2.7
14	16	79	–17.2	–1.08	9	4	157.5	9.8

* Percentage of predicted DLCO value. CYC cyclophosphamide.

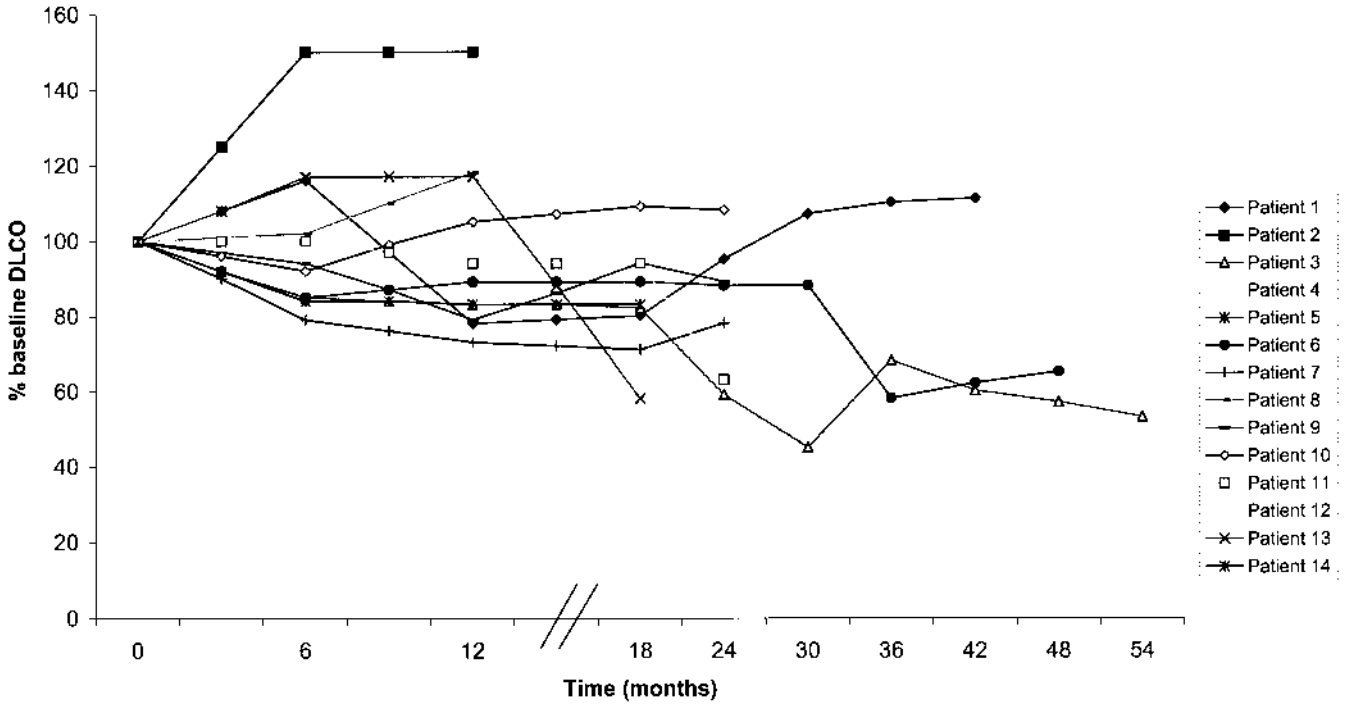

Figure 2. Longterm DLCO results showing percentage change from baseline.

data (9 patients) over this longer period of followup, there was a marked deterioration in the median DLCO. The median final DLCO was 55% predicted (IQR 40–70), compared with 65% at baseline. Six (67%) patients had deteriorated. The median deterioration in DLCO was 23% (IQR 44–0.6%). This deterioration was occurring at a median rate of 0.87% predicted value of DLCO per month (IQR 1.24–0.2). The median number of pulses administered per patient was 10 (IQR 6–20). The median cumulative dose of CYC per patient was 165 mg/kg (IQR 86–245). The median rate of CYC dosing was 6.1 mg/kg/month (IQR 2.9–7.3).

Three patients in this cohort have subsequently died. One was aged 60 and died of a cerebral hemorrhage (Patient 13); one aged 66 died of generalized SSc (Patient 12); and one aged 42 died of a chest infection and pulmonary fibrosis

(Patient 5). They died 24, 30, and 12 months, respectively, after completing the initial course of pulses. Patients 12 and 5 received additional pulses of MP and CYC after a further deterioration in lung function tests. Patient 5 had advanced disease of long duration (11 years) when she started pulse therapy.

DISCUSSION

This study has shown that treatment with IV MP and CYC in patients with SSc and interstitial lung disease (ILD), as confirmed on the HRCT, may stabilize disease activity during the course of treatment and for 6 months after treatment. However, in the long term, when patients were not undergoing therapy or were receiving less aggressive therapy, deterioration still occurred in most patients, sometimes at a significant rate. Early aggressive therapy should therefore be considered in poor prognosis patients with scleroderma with evidence of alveolitis, in order to have the greatest effect on disease outcome.

The natural history for these patients with SSc with alveolitis is progression with increased morbidity and mortality[29]. However, the severity and progression of pulmonary fibrosis is very variable and cannot always be predicted by the initial lung function tests, chest radiographs, or demographic findings[30-32]. The DLCO and FVC are probably the most important prognostic factors in determining survival in SSc patients with ILD[33]. Most patients in this study had diffuse disease and a significant number were anti-Scl-70 positive, 2 predictors for the development of pulmonary fibrosis[34,35]. The pattern for loss of lung function in patients with SSc has varied in different series[31,32,36-38]. Steen, *et al* showed that SSc patients with severe ILD experienced greatest loss in lung volume during the first 4 years of their disease[36]. Colp, *et al* also concluded that lung abnormalities occurred early and then stabilized[31], while Bagg, *et al* found pulmonary involvement to be uniformly progressive[37]. In contrast, Peters-Golden, *et al* found no significant difference in the rate of change in lung volumes and DLCO compared with healthy subjects, although there was heterogeneity within the small group of patients with a restrictive defect[32]. Importantly, our study showed that in the short term the deterioration in the DLCO and lung volumes could be halted and sometimes improved with intensive treatment. However, in the long term the DLCO deteriorated in over half of the patients, including those with late disease, and was therefore more in keeping with the findings of Bagg, *et al*. The results of this study therefore endorse early aggressive treatment in patients with poor prognosis. The longer term followup data was disappointing. Various regimens (no further treatment, an increasing interval between pulses, and high dose pulses) were used following the initial course of pulses. Although the numbers were small, the impression from these preliminary results suggests that continued aggressive therapy is required in patients with poor prognosis. The percentage rate of deterioration of the percentage predicted DLCO may be a useful gauge to determine the intensity of therapy, e.g., if the DLCO is deteriorating more than 0.9% of predicted value per month, then perhaps therapy should be stepped up.

Complex mechanisms underlie the pathogenesis of ILD, including epithelial and endothelial injury, vascular leakage, production of inflammatory cells and their mediators, and fibroblast activation. CYC suppresses both B and T cell function, is cytotoxic to lymphocytes, and directly suppresses immunoglobulin production, and so seems to be an appropriate drug to use in the treatment of scleroderma. In small uncontrolled prospective and retrospective studies, treatment with oral CYC has improved lung function in patients with SSc[17-23]. The 14 patients in a prospective study from Silver, *et al* had bronchoalveolar lavage proven alveolitis and relatively early disease (mean duration 23 mo)[17]. They were treated with a mean daily dose of 100 mg CYC and < 10 mg per day oral prednisolone for up to 24 months. The mean FVC was 51.4% of the predicted value at baseline and improved significantly to 63.6% after treatment. Steen's retrospective study also showed improvement in the FVC in 14 patients treated with oral CYC, particularly if they had early disease[18]. In Akesson's prospective study, 18 patients were treated with oral CYC and prednisolone for one year[19]. The greatest improvement was seen in those patients with elevated acute phase serum proteins. One very small study of 5 patients evaluated the effect of 1 g IV CYC given at monthly intervals for 48 weeks[22]. The percentage predicted FVC increased by 7%, but the percentage predicted DLCO still decreased by 12%, and there was no change on the HRCT. In White's recent larger retrospective study in patients with bronchoalveolar lavage proven alveolitis, the patients who received oral CYC had greater improvement in FVC, DLCO, and survival compared with untreated patients[21]. Another recent study evaluated oral CYC (2.0–2.5 mg/kg/day) versus IV monthly CYC (750 mg/m^2) over 12 months in 16 patients[23]. Unfortunately, the patients in the 2 groups had different degrees of baseline lung involvement, making comparison difficult, but the greatest improvement was seen in those with ground glass changes alone, i.e., early disease, as in our study. The patients in these studies had more advanced lung disease at baseline, with lower mean or median FVC and DLCO, compared with our patients. All studies were evaluating oral CYC rather than IV CYC as in our study, except studies from Varai, *et al* and Davas, *et al*, which had very small numbers of patients (5 and 8, respectively)[22,23].

The modified Rodnan skin scores improved significantly during this study. This may be an additional clinical benefit secondary to this treatment, although it is noted that patients with scleroderma can experience an improvement in skin score due to the natural history of the disease. This is more common in patients with well established disease, but this

cohort of patients on the whole had early disease. Also, there was no control arm in this pilot study and this would have helped to determine if this improvement in the skin score was genuine. In Clements' high dose versus low dose D penicillamine randomized controlled trial (RCT) in early diffuse SSc, the patients in the low dose arm (125 mg alternate days) showed no significant improvement in skin scores until they had received the treatment for 12 months[14]. The patients in the high dose arm (750 mg or 1 g daily) showed no significant improvement until 18 months after starting therapy. These were longer periods than the 6 months observed in our study. This is interesting since the patients in Clements' study and our study had similar baseline disease duration and skin scores. In a previous RCT comparing chlorambucil versus placebo, skin thickening was shown to improve significantly in early, intermediate, and long duration diffuse disease at 24 and 36 months but not at 12 months[39]. Clements, *et al* concluded that the best time to study therapies designed to affect skin thickening may be in the first year. Again, the patients in our study did not follow this pattern of delayed improvement, emphasizing that the change seen may be a real one. Further, 69% of patients who had undergone a hemopoietic stem cell transplant, typically with hemoimmunoablative doses of CYC, experienced an improvement of > 25% in the skin score, which was consistent with our findings although we were using less toxic doses[40]. It should also be noted that our study was not blinded, although previous skin scores were not available to the examiner.

The treatment was well tolerated. The side effects were those expected with CYC, namely nausea and mild neutropenia. Nausea was successfully treated with antiemetics. The patient who developed neutropenia had a reduction in CYC at subsequent pulses. Importantly, no patient developed renal crisis during the observation or followup periods with this regimen. All patients were taking low dose lisinopril. In previous studies, fewer significant side effects have occurred when CYC was administered as IV pulses compared with continuous oral, but without losing the benefit[28,41-43]. The findings in our study were consistent with this, namely, that patients experienced fewer side effects compared with patients receiving oral CYC but still gained benefit from the treatment.

The 3 deaths that occurred in this cohort were not related to the treatment with CYC. Two were related to endstage scleroderma including lung disease. This was comparable with the mortality rate in previous series. Altman, *et al* found the median survival of patients with diffuse skin disease and lung disease without renal and cardiac involvement to be 78 months, with a 50% eight-year mortality rate[33]. Similarly, Steen, *et al* found the 5-year mortality rate in SSc patients with restrictive lung disease to be 58%[44].

There is no single commonly used validated HRCT scan scoring system for ILD, making it difficult to objectively quantify the degree of improvement between studies. Indeed, the change in HRCT scan score has been rarely used as an outcome measure in the response to treatment of alveolitis in patients with SSc, although HRCT scans have the advantage of being noninvasive and evaluating the whole of both lungs. We chose to use the validated HRCT scoring system for pulmonary fibrosis in patients with asbestos related disease because it has shown good intra- and inter-observer reliability and a good range of possible scores, so that a change can be determined[27]. Interestingly, over two-thirds of patients in this study had a transfer factor > 75% of the predicted and lung volumes > 80% of predicted at study baseline, but had marked changes on the HRCT scan. This finding emphasizes that these patients should be very closely monitored when they first present.

Wells, *et al* showed that patients with ground glass changes alone are more likely to show an improvement in lung function[12]. After treatment in that study only 21% of patients experienced an improvement in lung function. The CT scoring system used in our study classified patients as having either moderate or advanced disease in all but one case. This may explain why an improvement was seen in the HRCT scan scores, but not the lung function. The realistic hope may therefore be to stabilize the DLCO or reduce the rate of deterioration with treatment.

SSc is a rare disease, with an incidence of 2–20 per million of the population per year[45], so to date only small studies have been performed. Large prospective multicenter randomized controlled trials are therefore required to successfully evaluate therapies in such patients. One such study is now underway in the UK in SSc patients with alveolitis, to evaluate the effectiveness of IV CYC on lung disease and skin involvement. Future studies will need to evaluate the best maintenance therapy in these patients. Additional prognostic markers are also needed, so that the appropriate intensity of therapy can be given to these patients at risk of significant morbidity and mortality.

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