

Cyclophosphamide Is Associated with Pulmonary Function and Survival Benefit in Patients with Scleroderma and Alveolitis

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Background: Lung inflammation (alveolitis) may cause lung fibrosis in scleroderma.

Objective: To determine whether cyclophosphamide treatment is associated with retention of lung function and improved survival in scleroderma patients with alveolitis.

Design: Retrospective cohort study.

Setting: Johns Hopkins and University of Maryland Scleroderma Center.

Patients: 103 patients with scleroderma who had bronchoalveolar lavage or lung biopsy.

Intervention: Cyclophosphamide therapy.

Measurements: 1) Serial measurement of forced vital capacity (FVC) and carbon monoxide diffusing capacity and 2) survival.

Results: During a median follow-up of 13 months after bronchoalveolar lavage or biopsy, patients with alveolitis who did not receive cyclophosphamide therapy experienced a decrease in FVC (mean difference, -0.28 L [95% CI, -0.41 to -0.16 L] and -7.1% of the predicted value [CI, -10.9% to -4.0%]). Carbon monoxide diffusing capacity also decreased in these patients (mean difference, -3.3 $\text{mmol} \cdot \text{min}^{-1} \cdot \text{kPa}^{-1}$ [CI, -4.6 to -2.1 $\text{mmol} \cdot \text{min}^{-1} \cdot \text{kPa}^{-1}$] and -9.6% of the predicted value [CI, -16.7% to -2.4%]). During a median follow-up of 16 months, patients with alveolitis who received cyclophosphamide were more likely to have a good outcome (stabilization or improvement) in FVC (relative risk, 2.5 [CI, 1.5 to 4.1]) and diffusing capacity (relative risk, 1.5 [CI, 1.0 to 2.2]). These patients also had improved survival; the median survival rate was 89% (25th, 75th percentiles, 84%, 94%) compared with 71% (25th, 75th percentiles, 55%, 86%) in untreated patients ($P = 0.01$, log-rank test).

Conclusions: The presence of lung inflammation identifies patients with scleroderma who are more likely to have worsening lung function. Lung function outcomes and survival are improved in patients with alveolitis who receive cyclophosphamide.

Interstitial lung disease is the major cause of death in patients with systemic sclerosis (scleroderma) (1). Pathologic studies of early disease show inflammation in the pulmonary interstitium that spills into alveolar spaces (2). Bronchoalveolar lavage fluid obtained from patients with scleroderma who have lung inflammation (alveolitis) may contain increased numbers of total cells, T cells, neutrophils, eosinophils, and mast cells (3–7). Alveolitis has been associated with subsequent deterioration of pulmonary function in scleroderma (3, 4).

Silver and colleagues (3) tested the theory that suppressing alveolitis with cyclophosphamide may prevent loss of pulmonary function. Both oral (3, 8–10) and intravenous cyclophosphamide (11) have been reported to be beneficial. Previous studies included small numbers of patients treated with cyclophosphamide (3, 8–11) or no concurrently followed groups of untreated patients with alveolitis or patients without alveolitis (3, 8, 10, 11). In some studies, no attempt was made to diagnose lung inflammation in all patients; it was therefore not clear how many patients were at risk for deterioration of pulmonary function (9, 10).

We performed a retrospective analysis of pulmonary function and survival in patients with scleroderma and alveolitis, as identified by using bronchoalveolar lavage or lung biopsy. The cohort includes patients with alveolitis who were and those who were not treated with cyclophosphamide and patients without alveolitis.

Methods

Patients

We included patients seen at the Johns Hopkins and University of Maryland Scleroderma Center between March 1991 and December 1998 who met classification criteria for scleroderma (12) and had pulmonary function tests and bronchoalveolar lavage or lung biopsy done during workup for alveolitis. To be included, patients had to be followed until death or until at least one set of follow-up pulmonary function tests was done a minimum of 6 months after bronchoalveolar lavage or lung biopsy.

Patients were categorized as having limited or diffuse cutaneous systemic sclerosis (13). Disease

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duration was defined as the number of months from the first symptom that was clearly attributable to scleroderma (14). Significant renal involvement was defined as new or worsening hypertension associated with an increase in serum creatinine concentration to greater than 150% of the baseline value. Pulmonary artery pressures of more than 35 mm Hg, as estimated by Doppler echocardiography, were considered high.

Pulmonary Function Tests

In most patients, forced vital capacity (FVC) and carbon monoxide diffusing capacity were measured in the Hopkins Bayview Pulmonary Function Laboratory by using standard procedures (15, 16) under the supervision of Dr. Wise. Normal values were derived from those in published articles by Goldman and Becklake (17) and Burrows and associates (18). Normal values on tests done elsewhere were consistent with values in this laboratory; thus, no adjustments were made.

Bronchoalveolar Lavage

Bronchoalveolar lavage was done as described elsewhere (19). Cell counts were obtained by using a hemocytometer. Cytochrome slides of cells were stained by using a modified Giemsa stain. Cell differential was performed on 500 cells; inflammation was indicated if neutrophils were more than 3.0% of total cells or eosinophils were more than 2.2% of total cells. These cutoff values are 3 SDs above the mean of those in controls in our laboratory and are consistent with published reports (20).

All patients gave informed written consent for bronchoalveolar lavage or lung biopsy. Eighty patients had testing solely for clinical indications, which included dyspnea on exertion and, usually, restrictive lung disease on pulmonary function tests. Twenty-three patients had bronchoalveolar lavage as part of a research protocol that was approved by the institutional review boards at the Johns Hopkins School of Medicine and the University of Maryland School of Medicine. These 23 patients had disease duration of less than 3 years and some dyspnea on exertion. That research protocol was separate from any treatment decision and from the current retrospective analysis of the clinical course of patients in our center, whose lung inflammation status was known.

Cyclophosphamide Therapy

The initial daily dose of oral cyclophosphamide was 1 to 1.5 mg/kg of body weight. The daily dose was increased as tolerated, usually in increments of 25 mg every 3 to 4 weeks, up to 2 mg/kg per day; a goal was to avoid neutropenia. Intravenous cyclophosphamide was administered monthly, with intra-

venous hydration, in doses of 800 to 1400 mg for 6 to 9 months.

Statistical Analysis

Statistical analyses were done by using StatView 5 software (SAS Institute, Inc., Cary, North Carolina). Repeated-measures analysis of variance was used to compare the rate of change in lung function over time between pulmonary function tests in different patient groups. The Cox-Mantel log-rank test was used to test differences in survival (21).

Results

Patient Groups

We included 103 patients in our study. Four more patients, none of whom had alveolitis, met the inclusion criteria but were lost to follow-up. Evaluation for lung inflammation was done by bronchoalveolar lavage in 94 patients and lung biopsy in 9 patients. Sixty-nine patients had alveolitis and 34 patients did not.

Of the patients with alveolitis, 39 received cyclophosphamide and 30 did not. The judgment to treat was made by consensus among Dr. White or Dr. Wigley, Dr. Wise, the patient, and the referring physician. Thirty-five patients received oral cyclophosphamide; 4 received intravenous cyclophosphamide because of the preference of the referring physician. As documented in the chart, the most common reason why patients did not receive cyclophosphamide was the judgment that alveolitis was mild and that close follow-up with or without prednisone therapy might be adequate (18 patients). Other reasons were patient unwillingness to take cyclophosphamide (8 patients), unwillingness of the referring physician to give cyclophosphamide (2 patients), and active substantial renal involvement (2 patients).

The median daily dose of oral cyclophosphamide was 100 mg/d (25th, 75th percentiles, 81.5, 150 mg/d). The median duration of therapy was 10.8 months (25th, 75th percentiles, 6.5, 14.5 months). Four patients (10%) were hospitalized for infection while receiving cyclophosphamide, and two developed hemorrhagic cystitis (5%). Alopecia prompted one patient (3%) to wear a wig.

The two groups of patients with alveolitis were similar in age, sex, ethnicity, disease type, disease duration, smoking status, pulmonary hypertension, anti-Scl 70 antibodies, renal involvement, bronchoalveolar lavage for research purposes, receipt of prednisone therapy, and prednisone dose ($P > 0.2$ for all comparisons) (Table 1). Compared with untreated patients with alveolitis, patients who re-

Table 1. Patient Characteristics*

Characteristic	Patient Group		
	Group 1: Alveolitis, Cyclophosphamide Therapy (n = 39)	Group 2: Alveolitis, No Cyclophosphamide Therapy (n = 30)	Group 3: No Alveolitis, No Cyclophosphamide Therapy (n = 34)
Age, y	49 (41, 56)	49 (41, 59)	47 (30, 54)
Female, n (%)	26 (67)	19 (63)	26 (76)
Ethnicity			
White, n (%)	21 (54)	18 (60)	18 (53)
Black, n	16	10	15
Asian, n	2	2	1
Diffuse cutaneous systemic sclerosis, n (%)	24 (62)	20 (67)	26 (76)
Disease duration, mo	30 (10, 63)	26 (11, 63)	22 (16, 64)
Current smoker, n (%)	1 (3)	1 (3)	3 (9)
Significant renal involvement, n (%)	3 (8)	2 (7)	4 (12)
Pulmonary hypertension, n (%)†	15 (39)	18 (60)	12 (39)
Anti-Scl 70 antibodies, n (%)‡	12 (32)	6 (21)	10 (31)
Bronchoalveolar lavage done for research purposes, n (%)	4 (10)	3 (10)	16 (47)§
Prednisone therapy, n (%)	25 (64)	19 (63)	8 (24)§
Prednisone dose, mg/d	10 (0, 14)	10 (0, 20)	0 (0, 0)
Time from first pulmonary function test to bronchoalveolar lavage, mo	2 (0, 11)	7 (3, 25)¶	0 (0, 17)
Time from bronchoalveolar lavage to last pulmonary function test, mo	16 (11, 34)	13 (7, 36)	21 (12, 32)
Bronchoalveolar lavage or lung biopsy result			
Forced vital capacity, L	2.1 (1.7, 2.4)**	2.3 (1.7, 3.2)	2.5 (2.1, 3.0)
Forced vital capacity, % predicted	58 (45, 67)††	69 (53, 80)	68 (60, 83)
Carbon monoxide diffusion capacity, mmol · min ⁻¹ · kPa ⁻¹	10.0 (7.8, 12.7)	8.7 (6.8, 12.4)	13.4 (11.7, 16.9)‡‡
Carbon monoxide diffusing capacity, % predicted	42 (28, 53)	43 (33, 59)	61 (52, 73)§§
Bronchoalveolar lavage fluid composition			
Total cells, × 10 ⁴ /mL	50.0 (34.6, 65.1)	39.1 (26.0, 73.0)	29.9 (24.1, 37.3)
Neutrophils, % total cells	5.2 (4.0, 10.6)¶¶	4.0 (3.4, 6.1)	1.3 (0.6, 1.7)***
Eosinophils, % total cells	1.2 (0.2, 3.0)	1.2 (0.6, 3.5)	0.6 (0.1, 1.2)†††
Lymphocytes, % total cells	7.6 (5.0, 13.0)	8.2 (4.7, 11.7)	7.0 (4.1, 11.4)

* Data for continuous variables are given as the median (25th, 75th percentiles).

† No data were available on 3 patients in group 3.

‡ No data were available on 2 patients each in groups 1 and 2 and 1 patient in group 3.

§ $P < 0.001$ compared with groups 1 and 2 (chi-square test).

|| $P = 0.001$ compared with groups 1 and 2 (Mann-Whitney test).

¶ $P = 0.05$ compared with group 1; $P = 0.04$ compared with group 3 (Mann-Whitney test).

** $P = 0.15$ compared with group 2; $P = 0.003$ compared with group 3 (Mann-Whitney test).

†† $P = 0.05$ compared with group 2; $P = 0.002$ compared with group 3 (Mann-Whitney test).

‡‡ $P < 0.001$ compared with group 1; $P = 0.003$ compared with group 2 (Mann-Whitney test).

§§ $P < 0.001$ compared with group 1; $P = 0.001$ compared with group 2 (Mann-Whitney test).

||| $P = 0.003$ compared with groups 1 and 2 (Mann-Whitney test).

¶¶ $P = 0.05$ compared with group 2 (Mann-Whitney test).

*** $P < 0.001$ compared with groups 1 and 2 (Mann-Whitney test).

††† $P = 0.02$ compared with group 1; $P = 0.003$ compared with group 2 (Mann-Whitney test).

ceived cyclophosphamide had shorter follow-up of pulmonary function before undergoing bronchoalveolar lavage or lung biopsy (mean difference, 4.1 months [95% CI, -4.5 to 12.9 months]). Follow-up after bronchoalveolar lavage or lung biopsy and total follow-up of pulmonary function did not differ among the three patient groups ($P > 0.2$, Mann-Whitney test) (Table 1).

At the time of bronchoalveolar lavage or lung biopsy, most patients with alveolitis had moderate to severe restrictive lung disease and severe impairment in gas transfer (Table 1). Compared with cyclophosphamide-treated patients, untreated patients with alveolitis had higher FVC (mean difference, 0.15 L [CI, 0.02 to 0.65 L] and 5.6% of the predicted value [CI, -2.1% to 13.9%]) (Table 1). Compared with untreated patients with alveolitis, cyclophosphamide-treated patients had a higher percentage of neutrophils in bronchoalveolar lavage fluids (Table 1) (mean difference, 1.5% [CI, -1.9% to 5.0%]) but similar total cell counts (cells/mL) and percentages of eosinophils and lymphocytes.

Medically Meaningful Changes in Forced Vital Capacity and Carbon Monoxide Diffusing Capacity

Our two primary outcomes were medically meaningful changes in FVC and carbon monoxide diffusing capacity. Results of pulmonary function tests done at the time of bronchoalveolar lavage or biopsy were compared with the results of the last tests done. A good outcome was defined as improvement (increase of 10% or more) or stabilization in values, and a bad outcome was defined as worsening (decrease of 10% or more) pulmonary function values or death. These criteria were defined before data analyses were done and were chosen because within-individual variation in pulmonary function results may be as high as 10%, although it is usually closer to 3% to 5% in persons with experience in taking pulmonary function tests (22).

Patients who received cyclophosphamide were more likely than untreated patients with alveolitis to have a good outcome in FVC (72% and 23%; relative risk, 2.5 [CI, 1.5 to 4.1]) (Table 2). Treated

Table 2. Medically Meaningful Changes in Pulmonary Function

Outcome	Patient Group			Total
	Group 1: Alveolitis, Cyclophosphamide Therapy	Group 2: Alveolitis, No Cyclophosphamide Therapy	Group 3: No Alveolitis, No Cyclophosphamide Therapy	
Percentage of predicted forced vital capacity*				
Good (improved/stable), <i>n</i>	28 (11/17)	7 (2/5)	27 (7/20)	62 (20/42)
Bad (worse/dead), <i>n</i>	11 (4/7)	23 (9/14)	7 (2/5)	41 (15/26)
Percentage of predicted carbon monoxide diffusing capacity†				
Good (improved/stable), <i>n</i>	19 (5/14)	8 (3/5)	22 (10/12)	49 (18/31)
Bad (worse/dead), <i>n</i>	20 (13/7)	22 (8/14)	12 (7/5)	54 (28/26)

* $P < 0.001$ for group 1 compared with group 2 and for group 2 compared with group 3 (chi-square test). The relative risk for a good outcome in forced vital capacity in group 1 was 2.5 (95% CI, 1.5 to 4.1) compared with group 2 and 0.8 (CI, 0.5 to 1.3) compared with group 3. The relative risk for a good outcome in forced vital capacity in group 2 was 0.3 (CI, 0.1 to 0.5) compared with group 3.

† $P = 0.06$ for group 1 compared with group 2, $P = 0.2$ for group 1 compared with group 3, and $P = 0.002$ for group 2 compared with group 3 (chi-square test). The relative risk for a good outcome in diffusing capacity in group 1 was 1.5 (CI, 1.0 to 2.2) compared with group 2 and 0.5 (CI, 0.3 to 0.9) compared with group 3. The relative risk for a good outcome in diffusing capacity in group 2 was 0.4 (CI, 0.2 to 0.8) compared with group 3.

patients had a better outcome in diffusing capacity than untreated patients (49% and 27%; relative risk, 1.5 [1.0 to 2.2]) (Table 2).

Changes in Pulmonary Function Test Results over Time

Additional analyses examined absolute changes in the FVC and carbon monoxide diffusing capacity. Both groups of patients with alveolitis had similar decreases in FVC and carbon monoxide diffusing capacity before bronchoalveolar lavage or biopsy was done (Table 3). The rates of change in these variables before bronchoalveolar lavage or biopsy did not differ between the two groups ($P > 0.2$ for all comparisons, repeated-measures analysis of variance).

After bronchoalveolar lavage or biopsy, patients with alveolitis who did not receive cyclophosphamide

had further decreases in FVC (mean difference, -0.28 L [CI, -0.41 to -0.16 L] and -7.1% of the predicted value [CI, -10.9% to -4.0%]). In these patients, carbon monoxide diffusing capacity also decreased (mean difference, -3.3 $\text{mmol} \cdot \text{min}^{-1} \cdot \text{kPa}^{-1}$ [CI, -4.6 to -2.1 $\text{mmol} \cdot \text{min}^{-1} \cdot \text{kPa}^{-1}$] and -9.6% of the predicted value [CI, -16.7% to -2.4%]) (Table 3). In contrast, FVC increased in cyclophosphamide-treated patients (mean increase, 0.11 L [CI, -0.01 to 0.24 L] and 4.3% of the predicted value [CI, 0.9% to 7.7%]), but diffusing capacity did not change significantly (Table 3).

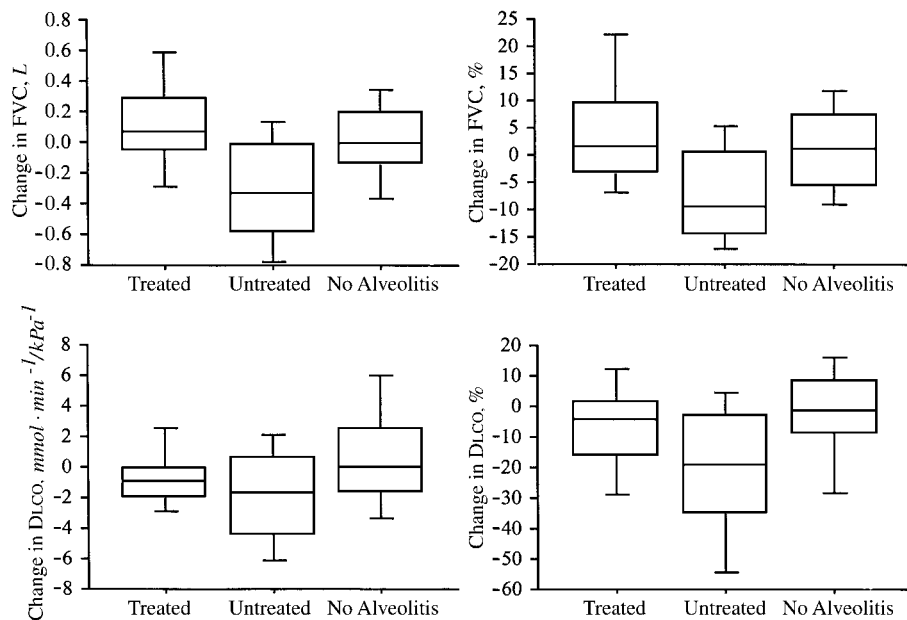
After bronchoalveolar lavage or biopsy, the change in percentage of predicted FVC and diffusing capacity differed for treated and untreated patients with alveolitis ($P = 0.05$ for FVC; $P = 0.02$ for diffusing capacity, repeated-measures analysis of variance). The rates of change also differed in un-

Table 3. Mean Differences in Pulmonary Function over Time*

Pulmonary Function	Patient Group		
	Alveolitis, Cyclophosphamide Therapy	Alveolitis, No Cyclophosphamide Therapy	No Alveolitis, No Cyclophosphamide Therapy
Forced vital capacity			
Difference between first value and that obtained by BAL, <i>L</i>	-0.19 (-0.30 to -0.07)	-0.28 (-0.41 to -0.16)	-0.16 (-0.27 to -0.04)
<i>P</i> value	0.002	<0.001	0.01
Difference between value obtained by BAL and last value, <i>L</i>	1.1 (-0.1 to 2.4)	-3.1 (-4.8 to -1.4)	0.10 (-0.80 to 1.1)
<i>P</i> value	0.07	0.001	
Difference between first value and that obtained by BAL, % predicted	-0.52 (-0.84 to -0.20)	-0.71 (-1.01 to -0.40)	-0.41 (-0.77 to -0.04)
<i>P</i> value	0.002	<0.001	0.03
Difference between value obtained by BAL and last value, % predicted	4.3 (0.9 to 7.7)	-7.1 (-10.9 to -3.4)	1.5 (-1.2 to 4.3)
<i>P</i> value	0.02	0.001	
Carbon monoxide diffusing capacity			
Difference between first value and that obtained by BAL, $\text{mmol} \cdot \text{min}^{-1} \cdot \text{kPa}^{-1}$	-1.8 (-3.1 to -0.5)	-3.3 (-4.6 to -2.1)	-1.9 (-3.3 to -0.4)
<i>P</i> value	0.008	<0.001	0.02
Difference between value obtained by BAL and last value, $\text{mmol} \cdot \text{min}^{-1} \cdot \text{kPa}^{-1}$	-0.6 (-1.4 to 0.3)	-1.8 (-3.3 to -0.4)	0.6 (-0.6 to 1.8)
<i>P</i> value		0.02	
Difference between first value and that obtained by BAL, % predicted	-8.4 (-15.0 to -1.8)	-10.1 (-16.3 to -3.6)	-3.2 (-8.9 to -2.5)
<i>P</i> value	0.02	0.003	
Difference between value obtained by BAL and last value, % predicted	1.0 (-5.7 to 7.7)	-9.6 (-16.7 to -2.4)	2.0 (-2.1 to 6.1)
<i>P</i> value		0.01	

* Numbers in parentheses are 95% CIs. *P* values compare the two sets of pulmonary function tests. A positive value indicates an increase in lung function and a negative value indicates a decrease. BAL = bronchoalveolar lavage.

Figure 1. Change in forced vital capacity (FVC) (top left and right) and carbon monoxide diffusing capacity (DLCO) (bottom left and right) over time in patients with scleroderma. Results of pulmonary function tests done at the time of bronchoalveolar lavage or lung biopsy were compared with those of the last tests done in a patient. "Treated" indicates patients with alveolitis who received cyclophosphamide, and "untreated" indicates patients with alveolitis who did not receive cyclophosphamide. The line in the middle of each box shows the 50th percentile, the limits of the box show the 25th and 75th percentiles, and the limits of the bar show the 5th and 95th percentiles.



treated patients and patients without alveolitis ($P = 0.09$ for percentage of predicted FVC; $P = 0.001$ for diffusing capacity, repeated-measures analysis of variance). Rates of change did not differ in treated patients and patients without alveolitis ($P > 0.2$ for percentage of predicted FVC and diffusing capacity). Changes in FVC and carbon monoxide diffusing capacity in individual patients are shown in **Figure 1**; results of pulmonary function tests at the time of bronchoalveolar lavage or biopsy are compared with those of the last tests done.

Serial Pulmonary Function Tests in Untreated Patients Who Began Receiving Cyclophosphamide

Seven patients with alveolitis did not initially receive cyclophosphamide, but therapy was begun after follow-up pulmonary function tests. These patients are not included in the analysis of treated patients above. The median duration of pulmonary function follow-up was 22 months (25th, 75th percentiles, 12, 47 months) before cyclophosphamide therapy and 22 months (25th, 75th percentiles, 17, 36 months) after cyclophosphamide therapy was begun. Forced vital capacity and diffusing capacity decreased before cyclophosphamide therapy was started. After cyclophosphamide was given, additional changes in FVC and diffusing capacity were not statistically significant ($P > 0.2$ for all comparisons, two-tailed paired t -test). Before cyclophosphamide therapy, the mean decrease in FVC was -0.56 L (CI, -0.34 to -0.77 L) and -12.6% of the predicted value (CI, -18.2 to -7.1). In contrast, after cyclophosphamide therapy, the mean increase in FVC was 0.27 L (CI, -0.40 to 0.94 L) and 9.5% of the predicted value (CI, -12.0% to 30.9%). Be-

fore therapy, the carbon monoxide diffusing capacity decreased by -2.5 $\text{mmol} \cdot \text{min}^{-1} \cdot \text{kPa}^{-1}$ (CI, -4.3 to -0.8 $\text{mmol} \cdot \text{min}^{-1} \cdot \text{kPa}^{-1}$) and -12.2% of the predicted value (CI, -20.1% to -4.4%); after therapy, these values increased by 0.7 $\text{mmol} \cdot \text{min}^{-1} \cdot \text{kPa}^{-1}$ (CI, -2.4 to 1.0 $\text{mmol} \cdot \text{min}^{-1} \cdot \text{kPa}^{-1}$) and 0.9% of the predicted value (CI, -10.5% to 8.7%). The rates of change in percentage of predicted FVC and diffusing capacity differed before and after cyclophosphamide therapy ($P = 0.03$ and 0.07 , respectively, by repeated-measures analysis of variance). These crossover data support the group data indi-

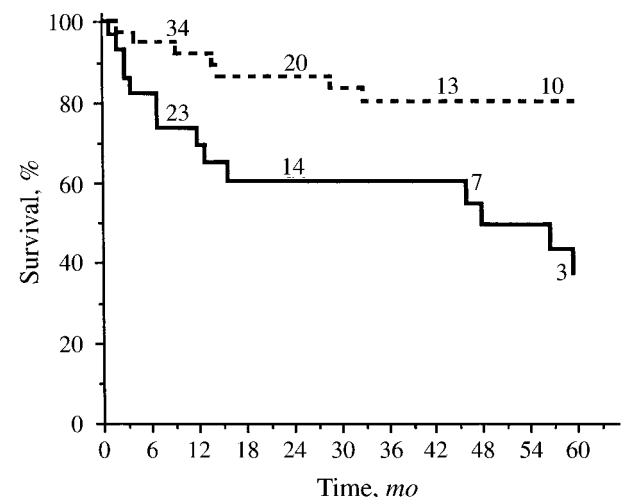


Figure 2. Survival in patients with scleroderma and alveolitis. Survival was better among patients with alveolitis who received cyclophosphamide (dashed line) than among patients with alveolitis who were not treated (solid line) ($P = 0.01$, Cox-Mantel log-rank test). The numbers above the lines are the number of patients at risk at the indicated time point. The median survival rate was 89% (25th, 75th percentiles, 84%, 94%) in treated patients and 71% (25th, 75th percentiles, 55%, 86%) in untreated patients.

cating that cyclophosphamide therapy stabilizes lung function.

Survival

Survival was a secondary outcome. The survival rate was greater among patients with alveolitis who received cyclophosphamide than among untreated patients ($P = 0.01$, Cox-Mantel log-rank test) (**Figure 2**). The survival rate was also greater among patients without alveolitis than among untreated patients with alveolitis ($P = 0.009$). The major cause of death in all patients was pulmonary disease; variable degrees of restrictive lung disease and pulmonary hypertension contributed to death in individual patients. Pulmonary deaths accounted for 5 of 7 deaths among patients treated with cyclophosphamide, 13 of 14 deaths among untreated patients with alveolitis, and 3 of 5 deaths among patients without alveolitis.

Discussion

Our major findings are that patients with scleroderma who have alveolitis, as indicated by abnormal bronchoalveolar lavage or lung biopsy results, experience excessive deterioration in lung function and increased mortality compared with patients without alveolitis. In our retrospective cohort study, patients with alveolitis who received cyclophosphamide did not experience such deterioration in lung function and had improved survival.

Silver and colleagues (23) reported that patients with scleroderma and neutrophilic or eosinophilic alveolitis had lower carbon monoxide diffusing capacity and more radiographic fibrosis than did patients without alveolitis. Alveolitis has also been associated with greater lung fibrosis on chest computed tomography (24). Subsequent studies have shown that alveolitis persists if untreated, and patients with alveolitis have greater deterioration in lung function than do patients without alveolitis (3–5). These reports support the idea that persistent alveolitis contributes to the severity of scleroderma lung disease.

Our study extends the findings of previous studies in larger numbers of patients. It confirms that patients with alveolitis who are not treated with cyclophosphamide experience excessive deterioration in lung function compared with patients without alveolitis. It also shows that survival is worse in patients with scleroderma and alveolitis.

Silver and colleagues (3) reported on use of cyclophosphamide plus prednisone to treat patients with scleroderma and alveolitis. They found improvement in dyspnea and less deterioration in lung function in four patients compared with a preceding

observation period (3). In a retrospective analysis, Steen and coworkers (25) found that 14 patients given cyclophosphamide showed improvement in FVC, whereas those given prednisone, other immunosuppressive drugs, D-penicillamine, or no treatment had deterioration in pulmonary function. Five of these patients had alveolitis on bronchoalveolar lavage. Behr and colleagues (5) reported on 14 patients with alveolitis who were treated with cyclophosphamide after their lung function deteriorated while receiving prednisolone. After 43 weeks of follow-up, their patients had less deterioration of pulmonary function than did patients with alveolitis who received no treatment.

Our study extends the results of previous studies of cyclophosphamide in scleroderma lung disease. We followed more patients for longer periods and included two comparison groups that were followed concurrently: untreated patients with alveolitis and patients without alveolitis. Bronchoalveolar lavage or lung biopsy was done in all patients to determine the presence of lung inflammation, and only patients with alveolitis received cyclophosphamide. Some patients with alveolitis were not given cyclophosphamide because of physician or patient decision. These patients appeared to have less intense alveolitis, as assessed by the degree of neutrophilia in bronchoalveolar lavage fluids. However, they experienced greater deterioration in lung function and increased mortality compared with cyclophosphamide-treated patients. In comparison, patients without alveolitis had stable lung function and better survival. Of note, we show that the differential outcomes of pulmonary function are reflected in the survival rates in the patient groups.

Our results imply that alveolitis causes lung fibrosis in scleroderma, which is associated with a greater risk for death. The relative stability of lung function in patients with scleroderma but no alveolitis suggests that cyclophosphamide therapy for restrictive lung disease in patients with scleroderma is not warranted, unless these patients have proven lung inflammation.

Clinical judgment remains the basis for deciding which patients with scleroderma should undergo evaluation for lung inflammation and which method of evaluation should be used. We selected patients for evaluation because they had dyspnea on exertion, usually in the setting of diffuse cutaneous systemic sclerosis (70%); disease duration of less than 3 years (64%); and restrictive lung disease on pulmonary function tests (78%). Most of our patients (91%) underwent bronchoalveolar lavage, which carries lower risks and cost than lung biopsy. For assessment of treatment efficacy, cell differentials in bronchoalveolar lavage fluid are quantitative and easier to obtain serially than lung biopsies. How-

ever, the results of bronchoalveolar lavage may be difficult to interpret unless the operator has experience in using a particular lavage protocol for the diagnosis of lung inflammation, the laboratory has experience in doing cell counts and differentials in bronchoalveolar lavage fluids, and values in normal persons under those circumstances are known.

Our data suggest that cyclophosphamide therapy will be beneficial if alveolitis is present. Most of our patients with alveolitis received oral cyclophosphamide. Too few patients were treated with intravenous cyclophosphamide to allow us to meaningfully compare the efficacy of intravenous and oral administration. Oral and intravenous cyclophosphamide have similar pharmacokinetics (26) but can have different effects on lymphocyte subsets (27) and different clinical effects (28). The optimal duration of cyclophosphamide therapy is unknown. Our current practice is to give the drug for 12 to 18 months, stop therapy, and repeat bronchoalveolar lavage 4 to 8 weeks later. If alveolitis is still present, we repeat this cycle. Stability of pulmonary function should be considered a good outcome.

An alternative approach, used by Behr and associates (5), is to start prednisolone therapy in any patient with scleroderma who has abnormal results on lung function tests, then add cyclophosphamide if vital capacity or total lung capacity decreases more than 10% within 8 to 12 weeks. However, it is not possible to discern by pulmonary function tests alone which patients with scleroderma have alveolitis and therefore are at higher risk for deterioration in lung function. In our cohort, treatment with prednisone was not correlated with medically meaningful changes in lung function or survival in patients with alveolitis, regardless of whether those patients received cyclophosphamide. This is consistent with the results of studies by Silver (3) and Steen (9) and their colleagues. Even in the study by Behr and associates (5), the failure rate of prednisolone therapy alone was 37% in the first 2 months of therapy, and it might be as high as 50% if low-risk patients without alveolitis were excluded.

Additional studies are needed to assess the mechanisms of the clinical benefit of cyclophosphamide. Our preliminary data (not shown) suggest that cyclophosphamide therapy is associated with normalization of neutrophilia in bronchoalveolar lavage fluids, similar to that observed when this therapy is used to treat idiopathic pulmonary fibrosis (29). This finding suggests that cyclophosphamide may work in scleroderma by resolving pulmonary inflammation, thus preventing further decrease in lung function.

Our study had several limitations. First, selection of patients with alveolitis for cyclophosphamide treatment was biased by physician and patient

choice. The reason for not using cyclophosphamide most often documented in the chart was that alveolitis was too mild to warrant such aggressive treatment. Indeed, the percentage of neutrophils in bronchoalveolar lavage fluids was higher and FVC was lower in treated patients. Although this might bias against a treatment effect, we cannot be confident that other factors did not influence treatment assignment. Second, many patients with alveolitis were given prednisone. We could discern no difference in outcomes attributable to steroids; this finding is similar to those of Silver (3) and Steen (9) and their colleagues but differs from that of Behr and associates (5). Finally, all patients were seen in a scleroderma center and were selected to undergo bronchoalveolar lavage on the basis of clinical judgment of characteristics that would put them at risk for progressive lung disease, as outlined above. In addition, some patients had undergone bronchoalveolar lavage as part of an unrelated research protocol to assess immune abnormalities in the lungs in early scleroderma. Thus, caution is warranted in extrapolating the results of this study to the general population of patients with scleroderma.

One important finding of our study is the prognostic value of bronchoalveolar lavage in predicting which patients with scleroderma will experience excessive deterioration in pulmonary function and increased mortality. Whereas previous studies have shown that abnormal or rapidly deteriorating lung function is associated with increased mortality (30, 31), evidence of alveolitis may identify these patients before extensive lung disease has developed, thereby allowing earlier intervention. Our results support previous evidence suggesting that cyclophosphamide is an effective intervention in such at-risk patients. However, we cannot unequivocally recommend this treatment until its benefit is confirmed in a placebo-controlled clinical trial with randomized treatment allocation.

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