# Therapeutic Strategy Combining Intravenous Cyclophosphamide Followed by Oral Azathioprine to Treat Worsening Interstitial Lung Disease Associated with Systemic Sclerosis: A Retrospective Multicenter Open-label Study

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***ABSTRACT.*** ***Objective***. To evaluate the effects and safety of 6-month intravenous cyclophosphamide (CYC) followed by 18-month oral azathioprine (AZA) therapy in patients with systemic sclerosis (SSc) and worsening interstitial lung disease (ILD).

***Methods.*** All patients presented with ILD and worsened forced vital capacity (FVC) and/or total lung capacity of more than 10% and/or DLCO of more than 15% during the previous year. Treatment was 6 monthly pulses of 0.6 g/m$^2$ CYC followed by oral AZA for 18 months on disease stabilization or improvement. The endpoint was the rate of percentage change in pulmonary function tests (PFT) after 6 and 24 months.

***Results***. Twenty-seven patients with SSc (20 females) were recruited. Age and disease duration before CYC therapy were (mean ± SD) 49.4 ± 15 years and 75.5 ± 87.8 months, respectively. Mean baseline FVC was 67% ± 19% of predicted value. At 6 months, in 7 (26%) patients disease was improved, in 12 (44%) stabilized, and in 8 (30%) worsened. Among the 19 (70%) responders, 15 received AZA and 4 declined. Twenty-three completed 2-year followup, 3 died, and one dropped out. Six (22.2%) had improved, 8 (29.6.%) were stable, and 13 (48.2%) had worsened. Evolution of the slope of FVC (in % per year) varied from –15.5 prior to treatment to +3 ($p = 0.004$) at 6 months and to +1 ($p < 5 \times 10^{-5}$) at 24 months.

***Conclusion***. Intravenous CYC followed by oral maintenance immunosuppressive therapy for worsening ILD was well tolerated and was associated with stable or improved PFT in 70% and 51.8% of SSc patients at 6 months and 2 years, respectively. (First Release May 1 2008; J Rheumatol 2008;35:1064–72)

*Key Indexing Terms:*
SYSTEMIC SCLEROSIS CYCLOPHOSPHAMIDE AZATHIOPRINE
MYCOPHENOLATE MOFETIL INTERSTITIAL LUNG DISEASE

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Interstitial lung disease (ILD) is a common manifestation of systemic sclerosis (SSc) and may be responsible for severe restrictive lung disease[1]. It represents, together with pulmonary arterial hypertension (PAH), one of the 2 main causes of disease-related death in SSc patients[2,3].

Various therapeutic strategies have been proposed to treat ILD in SSc patients[4-6]. Since 1993, retrospective studies of SSc-related ILD have found a beneficial effect of oral[7-14] or intravenous (IV)[11,13,15-23] cyclophosphamide (CYC), sometimes in association with corticosteroids[7,16,19,24], with improved pulmonary function test (PFT) and/or chest computed tomography (CT) results at 1 year. In 2000, White and colleagues confirmed these results in a large retrospective study of 103 patients and further showed that patients with alveolitis were more likely to worsen their lung function, and that lung function outcomes and survival were improved at 16 months in patients with alveolitis who received CYC[10].

The results of 2 prospective randomized trials were recently reported. The Scleroderma Lung Study, a prospective randomized placebo-controlled trial, included 158 patients of whom 145 completed at least 6 months of treatment[25]. Patients were randomized to receive oral CYC or placebo at least 6 months and no more than 12 months. Forced vital capacity (FVC; primary outcome) adjusted at 1 year was significantly better in the group treated with oral CYC ($p < 0.03$), as was the secondary outcome measure of total lung capacity (TLC), the Mahler transitional dyspnea index, the Health Assessment Questionnaire (HAQ) disability index, the Rodnan skin score, and several components of the Medical Outcomes Study 36-item Short-Form Health Survey (SF-36)[26]. However, at 2 years, overall differences between groups were minor and did not differ significantly, especially for PFT[27]. The Fibrosing Alveolitis in Scleroderma Trial (FAST) included 45 patients with SSc-related ILD who were randomized to receive low-dose prednisolone (20 mg/day) and 6 infusions of CYC followed by oral azathioprine (AZA) or placebo. This trial did not demonstrate significant improvement but did show a trend toward improvement of the primary or secondary endpoints with treatment versus placebo[28]. Thus, none of these trials demonstrated a major benefit of CYC over placebo[27,28].

With the exception of 10 out of 14 patients in the study by Silver, *et al*[7], no patients included in retrospective or prospective studies were selected on the basis of progression of ILD, which may explain the difficulties encountered in demonstrating a clinically relevant benefit of CYC for patients with SSc-related ILD.

To test whether CYC can benefit SSc patients with deteriorated lung function, we investigated patients with significantly worsened PFT results over the 12 months preceding presentation who were treated with pulses of IV CYC for 6 months, then oral AZA for 18 months.

## MATERIALS AND METHODS

*Patients*. Twenty-seven patients from 11 centers involved in the care of SSc patients through the network of the National Reference Center for Systemic Sclerosis were included in this retrospective, multicenter, open-label study between January 1998 and March 2005. To be eligible for the study, SSc patients had to fulfill the American College of Rheumatology criteria for SSc[29] and show progression of ILD. ILD was defined as high-resolution computed tomography (HRCT) of the chest that included one or more of the following features: isolated ground-glass opacities, honeycombing and concurrent presence of ground-glass attenuation, and traction bronchiectasis and/or bronchiolectasis. Lung fibrosis included architectural distortion with honeycombing and/or intralobular reticulation, traction bronchiectasis, distorted interlobular septal reticulations, or irregular linear opacities. Progression of ILD was defined as a decrease of FVC and/or TLC of more than 10% and/or decrease of carbon monoxide diffusing capacity (DLCO) of more than 15% of predicted values during the previous 12 months.

Exclusion criteria were CYC treatment during the previous 2 years, prior treatment with autologous stem cell transplantation, history of severe side effects under CYC therapy, evidence of another connective tissue disorder in association with SSc, severe left-ventricular involvement (ejection fraction < 40%), and age < 18 years. To account for any potential bias, we excluded patients with isolated pulmonary arterial hypertension (PAH), defined as systolic pulmonary artery pressure (PAP) at rest > 35 mm Hg detected by echocardiography and confirmed by right-heart catheterization. Patients who had PAH in association with ILD who had a drop of more than 10% FVC and/or TLC were interpreted as worsening ILD and were included.

Limited cutaneous SSc (lcSSc) was defined by skin thickening in areas solely distal to the elbows and knees, with or without facial involvement, and diffuse SSc (dSSc) by the presence of skin thickening proximal as well as distal to the elbows and knees, with or without facial or trunk involvement[30]. Esophagus involvement was defined by dysphagia, heartburn, and regurgitation, and bowel involvement by malabsorption, pseudo-obstruction, and/or bacterial overgrowth.

The following variables were recorded at baseline: age, sex, ethnicity, tobacco use, year of onset of Raynaud's phenomenon (RP), age at diagnosis, year of onset of the first non-RP manifestation, disease duration, disease form (lcSSc or dSSc), dyspnea (assessed by the New York Heart Association 4-point scale), blood pressure, pitting scars, digital ulcers, calcinosis, digestive involvement (esophagus and bowel), joint involvement, and myopathy defined by the presence of muscle weakness (assessed by manual muscle testing) and/or myalgia, together with at least one of the following: creatine kinase (CK) and/or aldolase level elevation above the upper limit of normal; muscular involvement seen on electromyographic examination (low voltage and/or short duration potential during maximal contraction, fibrillation or sharp wave); evidence of muscle involvement on muscle biopsy (myofiber atrophy, myofiber necrosis/regeneration process, inflammation, fibrosis, endomysial microangiopathy); heart involvement defined by cardiac insufficiency and/or conduction block or arrhythmia; ILD; elevated systolic PAP, maximal serum creatinine level, creatinine clearance, white blood cell count, platelet count, and hemoglobin level; presence of schistocytes, hematuria, proteinuria, granular cast, and antinuclear, anticentromere and antitopoisomerase 1 antibodies; and alveolitis as assessed by bronchoalveolar lavage (BAL) if performed. Alveolitis was diagnosed when the percentage of neutrophils in the BAL fluid was > 3% or that of eosinophils was > 2.5%, or both, in agreement with American Thoracic Society guidelines[31]. All BAL were performed as described[32].

*Therapeutic regimen*. Patients received one pulse of 0.6 g/m$^2$ CYC per month for 6 months. Monthly hematological monitoring was performed throughout CYC therapy. If the neutrophil count fell below 1500/mm$^3$, the CYC dose was decreased to 50%. In patients older than 65 years, the CYC dose was lowered to 0.5 g/m$^2$. Mesna (Uromitexan) was systematically given to prevent CYC-induced cystitis according to standard recommendations.

After 6 months of CYC therapy, a maintenance therapy was given for 18 months. In case of stabilization or improvement as defined above, oral

AZA (2–3 mg/kg/day) was prescribed. In case of significant worsening of PFT results at 6 months, patients were switched to another treatment depending on physician and patient's choice.

*Outcome measure*. The response to CYC therapy was analyzed according to PFT. PFT were performed prior to baseline and at baseline, 6 months, and 2 years, in the absence of respiratory infection or any other event that would perturb measurements of lung volumes or DLCO. Increase of FVC and TLC by more than 10% and increase of DLCO by more than 15% was considered as improved disease, change of less than 10% of FVC and/or TLC and/or 15% of DLCO as stabilized disease, and decrease of more than 10% of FVC or TLC or 15% of DLCO as worsened disease, following the International Consensus Statement[31]. In case of discrepancy between FVC, TLC, and/or DLCO, we took into account the most unfavorable measure. For patients who died or were lost to followup, disease was considered as worsened. Responders were defined as improved or stabilized disease.

*Statistical methods. Evolution of PFT results.* The evolution of pulmonary function was calculated for the following 4 periods: (1) between the pre-enrollment evaluation time (M –x) and the start of CYC treatment (M0); (2) between M0 and the end of CYC treatment (M6); (3) between M0 and month 24 of evaluation (M24); and (4) between M6 and M24.

The rate of evolution of FVC was calculated as follows: [(FVC at time 2 – FVC at time 1)/FVC at time 1]/(time 2 – time 1) × 100 = rate of evolution[33]. Since time 1 and time 2 were measured in months, the rate of evolution was multiplied by 12 to be expressed in percentage per year. TLC and DLCO were calculated similarly to FVC. The evolution rates for the other PFT (TLC and DLCO) were calculated using the same formula. The evolution rates of 2 different time periods were compared by Wilcoxon signed-rank test.

*Prognostic factors for evolution of pulmonary function under CYC treatment*. We looked for factors predicting FVC evolution under treatment. The dependent variable was the difference of FVC evolution rates during the M–x to M0 and M0 to M6 periods. The following explanatory variables, measured at M0, were evaluated: age, sex, disease form (lcSSc or dSSc), anti-Scl70, active myopathy, disease duration, duration of lung involvement, associated corticosteroid treatment, heart failure, PAH, alveolitis, as well as groundglass and fibrosis HRCT scores at M0. Images were evaluated in a blinded way by a radiologist (MB) according to Desai, *et al*[34] using a 5-level grading system: origin of great vessels, aortic arch, carina, pulmonary venous confluence, and 1 cm above the dome of the right hemidiaphragm. The overall extent of disease (i.e., the combined extent of reticular abnormalities or ground-glass attenuation) was estimated to the nearest 5% for the 5 levels. Scores were summed to provide a final score of ground-glass and fibrosis.

At each level, we also estimated the proportions of ground-glass, attenuation, and reticular abnormalities, and the coarseness of reticular abnormalities, graded semiquantitatively as (0) ground-glass opacification alone; (1) predominantly fine intralobular fibrosis; (2) predominantly microcystic honeycombing (comprising air spaces < 4 mm in diameter); and (3) predominantly macrocystic honey-combing (air spaces > 4 mm in diameter). The severity of bronchial dilatation within a reticular pattern and areas of ground-glass opacification were also graded semiquantitatively (0 = none, 1 = mild, 2 = severe).

Data were analyzed by Wilcoxon rank-sum test. All statistical analyses involved use of SAS, version 8.0 (SAS Institute Inc., Cary, NC, USA).

## RESULTS

*Clinical and immunological characteristics of the 27 patients*. Between January 1998 and March 2005, 27 patients with SSc (20 female) fulfilling inclusion criteria were recruited. Pretreatment demographic, clinical, and immunological features of patients are summarized in Table 1. Mean ± SD age and disease duration were 49.4 ± 15 years and 75.5 ± 87.8 months, respectively. Two patients also had proximal skin involvement occurring less than 3 years after disease onset. Mean ± SD duration of ILD was 42.3 ± 49.6 months at the first CYC infusion. Twenty (74%) patients had dSSc and 16 (60%) had anti-Scl70. Mean FVC was 67% ± 19% and mean DLCO was 38% ± 10%. Prior to initiation of CYC treatment, 17 (63%) patients had received low-dose oral prednisone (< 15 mg/day throughout the study), 4 (15%) oral methotrexate and 1 (3.7%) subcutaneous injection of alpha interferon. One (3.7%) patient, who had no evidence for ILD at that time, received 6 CYC pulses 4 years prior to inclusion, for severe early diffuse SSc.

*Table 1.* Baseline demographic, clinical, and immunological characteristics of 27 patients with systemic sclerosis (SSc) and worsened ILD.

| Measures | Patients with SSc |
|---|---|
| Age, yrs, mean ± SD | 49.4 ± 15 |
| Sex, F (%) | 20 (76) |
| Ethnicity | |
| White, n (%) | 22 (81.5) |
| Black, n (%) | 5 (18.5) |
| Tobacco use, yes/no/NA | 5/16/6 |
| Disease duration of SSc, mo, mean ± SD | 75.5 ± 87.8 |
| Disease duration of ILD, mo, mean ± SD | 42.3 ± 49.6 |
| Diffuse SSc, n (%) | 20 (74) |
| Limited cutaneous SSc, n (%) | 7 (26) |
| RSS, mean ± SD | 19 ± 14 |
| Digital ulcers, n (%) | 7 (26) |
| Esophagus involvement, n (%) | 21 (78) |
| Bowel involvement, n (%) | 3 (11) |
| Muscle involvement, n (%) | 4 (15) |
| sPAP, mm Hg, mean ± SD | 37 ± 9 |
| SRC, n (%) | 0 (0) |
| Alveolitis, n (%) | 3 (11) |
| FVC, %, mean ± SD | 67 ± 19 |
| TLC, %, mean ± SD | 70 ± 19 |
| DLCO, %, mean ± SD | 38 ± 10 |
| $PAO_2$, mm Hg, mean ± SD | 83 ± 13 |
| Antinuclear antibodies, n (%) | 23 (85) |
| Anticentromere, n (%) | 1 (4) |
| Anti-Scl70, n (%) | 16 (60) |
| Anti-RNP, n (%) | 2 (7.4) |

DLCO: carbon monoxide diffusing capacity, FVC: forced vital capacity; ILD: interstitial lung disease; NA: not applicable; sPAP: systolic pulmonary arterial pressure; RNP: ribonucleoprotein; RSS: Rodnan skin score; SRC: scleroderma renal crisis; TLC: total lung capacity.

Among the 27 patients, prior to CYC therapy, the mean annual decrease in FVC was –12% (± 12%) of predicted value and in TLC –11% (± 10%) of predicted value. The mean decrease in DLCO was –20% (± 18%) of predicted value (Table 2). Twelve patients had a decrease in 1 measure, including 4 who were included on the basis of an isolated drop in DLCO. Eleven patients had a decrease in 2 measures, and the 4 remaining had a decrease in 3 measures. Ten patients underwent BAL; only 3 had an alveolitis.

Four among the 27 patients included into the study had systolic PAP > 35 mm Hg as detected by echocardiography

*Table 2.* Rate of change from baseline at 6 and 24 months for pulmonary function tests (in percentage of predicted value) in 27 patients with SSc. Data are mean ± standard deviation.

| | Baseline | 6 Months | | | | 24 Months | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | All Patients, n = 27 | Improved, n = 7 | Stabilized, n = 12 | Worsened, n = 8 | All Patients, n = 27 | Improved, n = 6 | Stabilized, n = 8 | Worsened, n = 13 |
| FVC (% of predicted) | N = 27 | N = 24 | N = 7 | N = 11 | N = 6 | N = 22 | N = 6 | N = 8 | N = 8 |
| | –12 ± 12 | 4 ± 16 | 14 ± 18 | 1 ± 13 | –4 ± 15 | 3 ± 4 | 19 ± 14 | 13 ± 17 | –20 ± 18 |
| TLC | N = 27 | N = 27 | N = 7 | N = 12 | N = 7 | N = 21 | n = 5 | N = 8 | N = 8 |
| | –11 ± 10 | 2 ± 11 | 10 ± 16 | 2 ± 4 | –7 ± 9 | –1 ± 13 | 12 ± 5 | 3 ± 4 | –13 ± 12 |
| DLCO | N = 27 | N = 21 | N = 5 | N = 9 | N = 5 | N = 13 | N = 3 | N = 7 | N = 3 |
| | –20 ± 17 | 0 ± 19 | 13 ± 23 | 5 ± 10 | –21 ± 11 | –2 ± 20 | 4 ± 28 | –3 ± 9 | –15 ± 30 |

FVC: forced vital capacity; TLC: total lung capacity; DLCO: carbon monoxide diffusing capacity.

and underwent a right-heart catheterization. Two of them, who had normal left ventricular ejection fraction upon echocardiography, had a left ventricular involvement as assessed by elevated pulmonary capillary pressure. In the 2 others, a right-heart catheterization confirmed the presence of PAH with mean PAP values of 38 and 47 mm Hg, respectively.

*Response to therapy*. Twenty-five (92.5%) patients completed the 6 IV CYC pulses. In one, CYC was discontinued after 4 infusions and in another, after 5 infusions, because of cardiac and bowel toxicity, respectively. These 2 patients underwent the same evaluation as the others. After 6 months of treatment, the disease was improved in 7 (26%) patients, stabilized in 12 (44%), and worsened in 8 (30%) (Figure 1). Based on changes observed in FVC and/or TLC, out of the 27 patients included into the study, at 6 months, 7 (26%) were improved, 11 (40.7%) were stabilized, and 9 (33.3%) worsened. If we analyze responders and nonresponders on

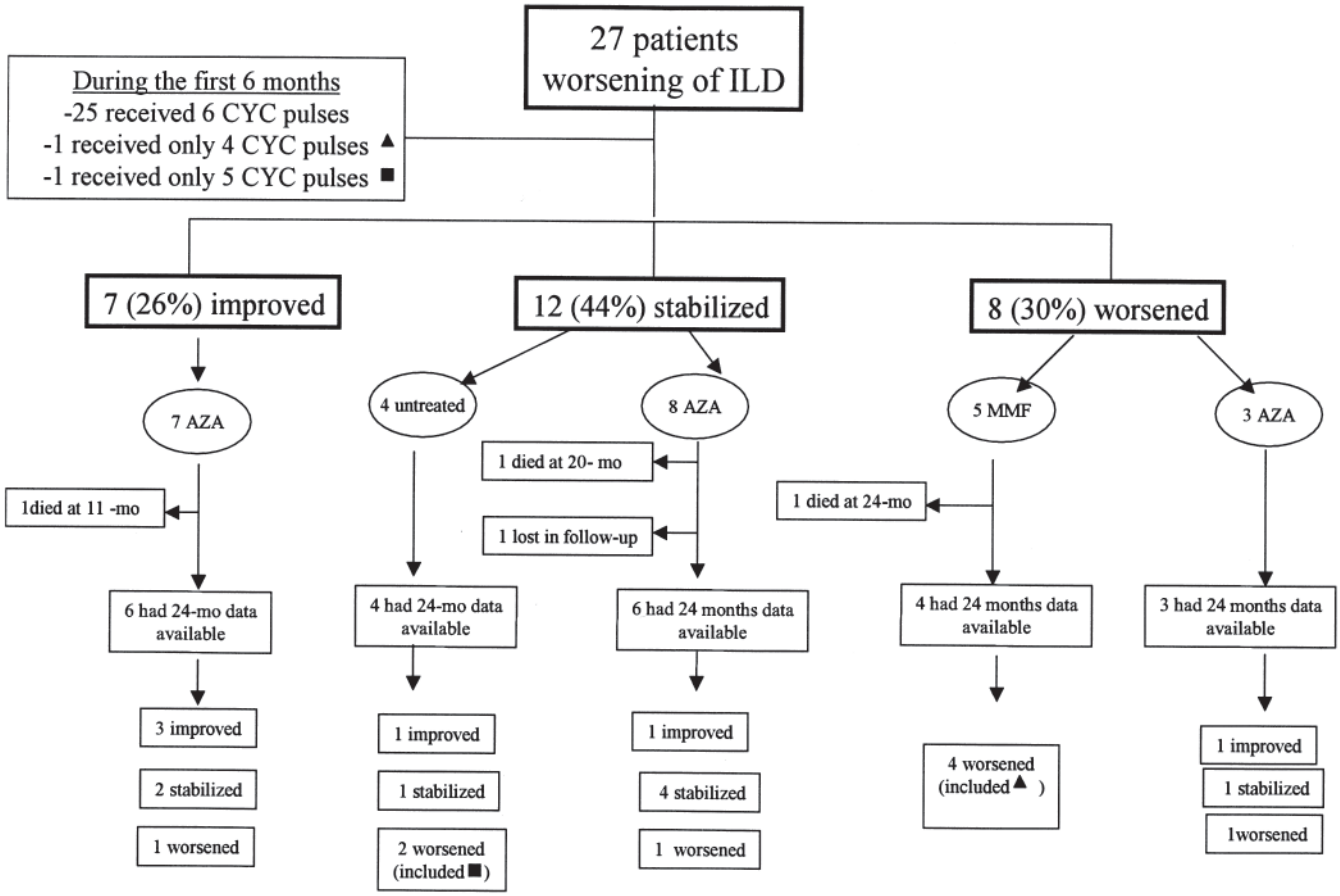


*Figure 1.* Disposition of all patients with SSc and ILD at 6 months and 2 years.

the basis of changes in DLCO, among the 19 patients in whom DLCO was available, 4 (21.1%) were improved, 10 (52.6%) were stabilized, and 5 (26.3%) worsened.

Among the 19 responders, 15 (79%) received AZA, whereas 4 (21%) declined the therapy and continued low-dose prednisone alone. Among the 8 patients whose disease failed to respond to CYC, 5 received mycophenolate mofetil (MMF), 2 g/day, and 3 AZA, 2–3 mg/kg/day, on the basis of patient and/or physician decision. At 2 years, only one of 27 patients was lost to followup. Disease improved in 6 (22.2%), stabilized in 8 (29.6%), and worsened in 13 (48.2%), including 3 patients who died (only one due to end-stage ILD progression) and one patient lost to followup (Figure 1). At 24 months, based on changes observed in FVC and/or TLC only, 9 (33.3%) were improved, 5 (18.5%) were stabilized, and 13 (48.2%) worsened. Among the 19 patients in whom DLCO was available, 2 (10.5%) were improved, 8 (42.1%) were stabilized, and 9 (47.4%) worsened.

Among the 4 patients whose disease responded to CYC and who declined AZA treatment, disease at 2 years was worsened in 2, stabilized in one, and improved in one. Overall, IV CYC followed by oral maintenance immunosuppressive therapy was associated with stable or improved FVC and TLC in 70% and 51.8% of patients at 6 months and 2 years, respectively.

*Evolution of pulmonary function.* Measures of FVC, TLC, and DLCO before CYC, at initiation, and at 6 and 24 months are shown in Figure 2. The slope of FVC (median in % per year) varied from –15.5 (interquartile range) prior to treatment to +3 (IQR) at 6 months and +1 (IQR) at 24 months. The differences in evolution rates between the pre-enrollment period and the first 6 months of therapy or 24 months of followup were highly significant (respectively, $p = 0.004$ and $p = 0.005$ in both cases), with no significant difference between rates at 6 months and the following 18 months' maintenance therapy ($p = 0.43$). Significant benefit was also observed for rates of TLC and DLCO prior to treatment and during the first 6 or 24 months treatment, with again no significant difference between rates at 6 months and 2 years (Table 3). Mean FVC, TLC, and DLCO rates were 67% (± 19%), 70% (± 19%) and 38% (± 10%) prior to initiation of CYC treatment; 68% (± 18%), 71% (± 19%), and 41% (± 12%) at 6 months; and 65% (± 19%), 67% (± 20%), and 38% (± 12%) at 24 months and they did not differ significantly.

Only 4 of the 27 (14.8%) patients were included on the basis of an isolated drop in DLCO. Interestingly, none of them had a PAP > 35 mm Hg on echocardiography at baseline and none developed PAH. After excluding these 4 patients, we obtained results similar to those shown in Table 3 (data not shown).

Alveolitis upon BAL was the only variable associated with a statistically significant correlation with the slope of FVC ($p = 0.004$). However, this result should be interpreted with caution since only 8 patients were evaluated at 24 months.

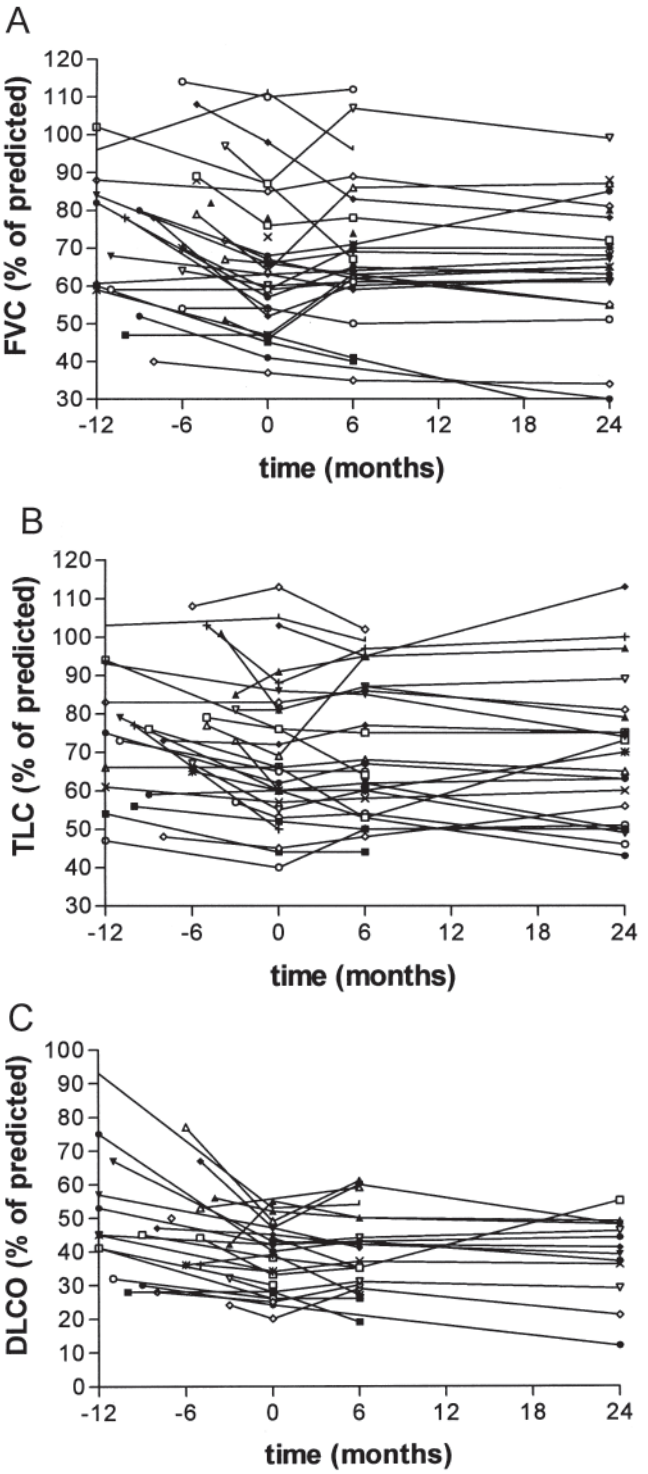


*Figure 2.* Measures of FVC (A), TLC (B), and DLCO (C) before, at initiation, and after 6 and 24 months of therapy in 27 SSc patients with ILD.

The median slope of FVC between 0 and 6 months was higher in patients who had a lower fibrosis score [+6.8 (IQR 5.3; 28.0) when the fibrosis score was < 10 vs –7.3 (IQR

*Table 3.* Comparison of the evolution of pulmonary function tests (in percentage per year) between different periods.

| Variable | Period 1 | Period 2 | No. of Patients | Evolution Period 1, Median (IQR), % per year | Evolution Period 2, Median (IQR), % per year | Wilcoxon Signed-Rank p |
|---|---|---|---|---|---|---|
| FVC | M–x to M0 | M0 to M6 | 25 | –15.5 (7.5) | +3.0 (24.6) | 0.004 |
| | M–x to M0 | M0 to M24 | 23 | –15.5 (7.5) | +1.0 (10.4) | 0.005 |
| | M0 to M6 | M6 to M24 | 21 | +1.0 (10.4) | –0.0 (5.0) | 0.430 |
| TLC | M–x to M0 | M0 to M6 | 26 | –10.0 (15.16) | +2.0 (13.5) | 0.003 |
| | M–x to m0 | M0 to M24 | 21 | –10.0 (15.16) | +0.1 (6.0) | 0.002 |
| | M0 to M6 | M6 to M24 | 21 | +2.0 (13.5) | +0.0 (6.6) | 0.272 |
| DLCO | M–x to M0 | M0 to M6 | 19 | –11.5 (18.3) | +0.0 (14.0) | 0.023 |
| | M–x to M0 | M0 to M24 | 13 | –11.5 (18.3) | +0.1 (3.0) | 0.021 |
| | M0 to M6 | M6 to M24 | 11 | +0.0 (14.0) | –0.7 (2.6) | 0.638 |

IQR: interquartile range; M–x: pre-enrollment evaluation; M0: start of CYC treatment; M6: end of CYC treatment; M24: 24th month after M0.

–23.0; –5.3) when the fibrosis score was ≥ 10]. However, this difference was not statistically significant (p = 0.13), and we found no significant association between the evolution rate of FVC after 6 months' CYC treatment and the fibrosis score, whether the score had a quantitative (p = 0.40) or a binary (cutoff of 10, p = 0.19) encoding. There was no correlation between quantitative or binary (cutoff of 20) final score of ground-glass sign and the evolution rate of FVC at 6 months (p = 0.4 and p = 0.28, respectively). The other variables we investigated did not influence the slope of FVC.

After a 6-month followup, a high PAP was detected by echocardiography in 2 additional patients who had a normal PAP at baseline, and right-heart catheterization confirmed PAH in one of them. Thus, at 6 months, 3 patients had PAH. All of these 3 patients received a specific treatment based on bosentan in 2 and a combination of bosentan and inhaled prostacyclin in one. At 6 months, after 6 CYC pulses, on a basis of FVC and TLC, one of these patients stabilized, while the 2 others worsened. At 24-month followup, one of them died because of worsening of PAH and the 2 others worsened, with significant reduction in FVC and/or TLC. DLCO could not be evaluated in one patient because of insufficient volume obtained.

*Adverse effects*. Overall, the therapeutic strategy of combined CYC and AZA or MMF was well tolerated. CYC was discontinued in 2 patients before the sixth IV infusion because of side effects attributed to CYC: severe diarrhea in 1 and myocardial toxicity in another, with discontinued therapy after 4 and 5 perfusions, respectively.

Among the 18 patients who received AZA, one had severe liver toxicity, and AZA therapy was discontinued after 6 months, whereas 18-month treatment was achieved in others. Among the 5 patients who received MMF, only one had moderate diarrhea. No severe secondary effects occurred in these patients.

In 2 patients (7.4%), severe infectious complications developed during the first 3 CYC infusions: in one, *Staphylococcus aureus* septicemia secondary to central venous catheter infection, and in the other, extensive Varicellae zona virus infection. These infectious complications were not associated with neutropenia or lymphopenia. Hemorrhagic cystitis was not observed.

*Survival*. Survival rate at 2 years was 88.8%. Three SSc patients died, at 11, 20, and 24 months, respectively. All had completed the 6 CYC infusions. Causes of death were severe PAH, respiratory insufficiency secondary to lung fibrosis, and undetermined cause 11 months after therapy began.

## DISCUSSION

We investigated SSc patients with significant worsening of ILD as identified by PFT results during the 12 months before presentation. Six monthly IV pulses of CYC, then 18 months of oral immunosuppressive maintenance therapy, was well tolerated and was associated with stable or improved PFT measures in 70% and 51.8% of SSc patients at 6 months and 2 years, respectively. Although only one of the 3 observed deaths was due to worsening ILD, we considered the 3 cases as treatment failures, despite the lack of evidence of worsened PFT.

The results of 2 prospective randomized trials comparing CYC to placebo were recently reported. In the North American Scleroderma Lung Study, the course of FVC (primary outcome) was significantly better at 1 year with CYC treatment (p = 0.05). Transition dyspnea index, HAQ, skin score, and vitality and health transition scales of the SF-36 were also significantly improved ($p < 0.05$)[25]. However, at 2 years, overall differences between treatment groups were small, especially for PFT results (evolution rate of FVC –2.0% for CYC vs –2.3% for placebo), with no significant beneficial effect demonstrated[27]. In the UK Fibrosing Alveolitis in Scleroderma Trial (FAST), in which 45 patients with SSc-related ILD were randomized to receive prednisolone (20 mg/day) and 6 CYC infusions (0.6 g/m$^2$ monthly) followed by oral AZA or placebo, estimation of

the relative treatment effect (active treatment vs placebo) adjusted for baseline FVC and treatment center revealed a favorable FVC outcome of 4.19%; this between-group difference showed a trend toward statistical significance (p = 0.08). No improvements in DLCO or secondary outcome measures were identified[28]. Thus, these trials demonstrated a limited beneficial effect of CYC as compared with placebo for SSc with ILD[27,28].

In our study, where patients were selected on the basis of worsened PFT results during the previous year, a 6-month course of CYC plus 18 months of oral maintenance therapy stabilized or improved FVC and TLC in 70.3% and 51.8% of patients at 6 months and 2 years, respectively. Among these patients, after 6 months of CYC therapy, 7 (26%) improved their FVC and/or TLC by more than 10% and/or DLCO by more than 15%, 12 (44%) were stabilized, and 8 (30%) worsened their FVC and/or DLCO by more than 10%. The evolution slope of FVC (in % per year) in the 27 patients varied from –15.5 prior to treatment to +3 during the first 6 months' treatment, to +1 during the 24 months of immunosuppressive treatment, which corresponds to a highly significant improvement. In the absence of a control group, we cannot rule out the possibility that this improvement was due to the natural history of ILD. Indeed, SSc patients with longterm lung disease can stabilize spontaneously[33]. Nevertheless, although Steen and Medsger reported that patients lose their FVC primarily in the first 4–6 years of evolution and do not change much after that, they also reported that the proportion of patients with SSc who died of pulmonary fibrosis increased from 6% to 33% of scleroderma-related deaths and from 5% to 16% of all deaths between 1972 and 2002[3]. Thus, the current natural history of SSc-associated ILD is probably not comparable to the history that was reported in the early 1990s, and we observed that some patients who had a slow progression over several years, presented a phase of rapid clinical decline after 5–10 years of evolution. In addition, the importance of the improvement during a short period (6 mo) makes us believe that the observed benefit is likely to be due to CYC treatment. This interpretation should be confirmed by a randomized controlled trial using the same inclusion criteria of progressive lung disease.

Silver and colleagues conducted an open prospective study in SSc patients with early disease and evidence of alveolitis who received oral CYC and low-dose prednisone[7]. Patients were selected based on the findings of an abnormal BAL cell analysis in association with declining PFT (12 of 14), or recent deterioration in FVC without BAL analysis (2 of 14). At 6 months FVC and DLCO improved or stabilized in 13/14 and 5/13 patients, respectively. These results were maintained at 12 months and 24 months. Prior to inclusion, patients had a more severe reduction in FVC in Silver's study[7] than in our study, whereas Scleroderma Lung Study patients had a similar FVC, and FAST Study patients had a higher FVC. Indeed, the selection of patients with nonprogressive and mild disease, especially for the FAST study[28], may have attenuated the significance of the primary endpoints of the 2 recent prospective randomized trials comparing CYC to placebo. Indeed, as reported by Steen, *et al*, only a small proportion of patients with SSc-related ILD develop severe worsened ILD[33]. Although ILD represents the main cause of mortality in SSc patients[3], patients with worsened ILD should be focused on, while those with stable PFT results should be followed up without initiating immunosuppressive therapy.

Of note, at the time of inclusion, patients of all 3 previous studies[7,25,28] had a less severe reduction in DLCO compared to our patients. This might be the consequence of greater vascular involvement in our patients, but this finding would have negatively influenced our results, since CYC has no efficacy in pulmonary vascular disease in SSc patients. The fact that we included mostly patients with longterm disease (mean disease duration of 78 mo) and low FVC may also have negatively affected the study outcome.

Although a limited number of our patients underwent BAL, presence of alveolitis was associated with a more severe degradation than were other measures before the initiation of CYC therapy and with a better response to treatment. Our data are in accord with previous results showing that patients with alveolitis respond better to CYC than those without alveolitis[10,21,35]. However, in the Scleroderma Lung Study, evidence of alveolitis on BAL was not associated with response to CYC[25]. Thus, further evidence is needed to recommend the use of BAL as a prognostic marker in SSc ILD.

We chose IV CYC therapy on the basis of literature results and our experience with this route of administration as first-line treatment in patients with small- and/or medium-size systemic vasculitides and poor prognosis criteria[36]. To reduce the risk of side effects with CYC therapy, since the dosage of CYC by the oral route is 2 to 3 times higher than that by the intravenous route, we treated patients with only 6 IV CYC infusions, followed by oral AZA for 18 months.

Very few data are available on the use of AZA for SSc. AZA was proposed in the FAST trial as maintenance therapy, and the association of IV CYC followed by oral AZA failed to demonstrate a beneficial effect compared with placebo[28]. In a prospective randomized study comparing oral CYC to AZA, with both groups receiving 15 mg prednisone, oral CYC reduced the frequency of RP attacks and erythrocyte sedimentation rate, and AZA led to worsened condition[14]. Among the 4 patients who did not receive AZA therapy, all with stable disease after 6 months of CYC, one improved, one maintained a stable condition, and 2 worsened. Eight patients were stabilized after 6 months of CYC and then received AZA. Among these, one died at 20 months and another was lost to followup. Among the 6 others avail-

able at 24 months, one improved, 4 were stabilized, and one worsened. However, because of the very small sample size of each subgroup, we cannot draw any conclusions concerning the efficacy or inefficacy of AZA following CYC treatment.

Among the 5 patients who received MMF in our study, only one showed improvement, 3 worsened, and one died of a cause unrelated to ILD. Thus, no conclusion can be inferred regarding MMF as a maintenance therapy. Finally, 70% of our patients received low-dose oral prednisone, and further studies are needed to document the efficacy of corticosteroids in SSc-associated ILD. Overall, we cannot draw conclusions about the efficacy of oral maintenance therapy in our study. Nevertheless, even if the evolution of the FVC slope was statistically not significant between Month 6 and Month 24, we observed that this slope decreased slightly again after the end of the CYC treatment. Therefore, the possibility of increasing the duration of CYC therapy to 1 year or using another immunosuppressive drug to maintain the result obtained with CYC could be entertained.

It is important to recall that we performed an open and noncomparative study, so these results need to be confirmed in a prospective randomized comparative trial in patients with SSc with worsening ILD. In addition, our followup was limited to 2 years, longer than in reported retrospective or prospective randomized studies, but longterm followup is necessary to assess longterm efficacy of our therapeutic strategy.

In conclusion, we showed that a therapeutic strategy associating intravenous CYC followed by oral maintenance immunosupressive therapy for worsening ILD was well tolerated and at 2 years stabilized 51.8% of patients with progressive ILD. Although further studies are needed to confirm our results, the use of CYC might be restricted to SSc patients presenting with worsening ILD. However, more effective therapies are needed.

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