Effects of 1-Year Treatment with Cyclophosphamide on Outcomes at 2 Years in Scleroderma Lung Disease

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Rationale: The Scleroderma Lung Study enrolled 158 patients with scleroderma-related interstitial lung disease in a placebo-controlled trial of oral cyclophosphamide (CYC). Although treatment-related benefits in pulmonary function, skin scores, and patient-centered outcomes were demonstrated after 1 year of therapy, the duration of benefit beyond 1 year was unclear.

Objectives: A second year of follow-up was performed to determine if these effects persisted after stopping treatment.

Methods: A detailed analysis of data obtained over the two years of the study was performed.

Measurements and Main Results: Using a longitudinal joint model, we analyzed FVC, total lung capacity, transitional dyspnea index, Rodnan skin scores, and the Health Assessment Questionnaire–Disability Index during the second year, after adjusting for baseline values, baseline fibrosis score, and nonignorable missing data. Evaluable subjects (72 CYC; 73 placebo) included 93 who completed all visits plus 52 who completed at least 6 months of therapy and returned at 24 month or had their 24-month data imputed. The beneficial effects of CYC on pulmonary function and health status continued to increase through 18 months, after which they dissipated, whereas skin improvements dissipated after 12 months. In contrast, the positive effect on dyspnea persisted through 24 months. Adverse events were uncommon.

Conclusions: One year of CYC improved lung function, skin scores, dyspnea, and health status/disability, effects which either persisted or increased further for several months after stopping therapy. However, except for a sustained impact on dyspnea, all of these effects waned and were no longer apparent at 24 months. Treatment strategies aimed at extending the positive therapeutic effects observed with CYC should be considered.

Clinical trial registered with www.clinicaltrials.gov (NCT 000004563).

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

The Scleroderma Lung Study was the first randomized, placebo-controlled trial to demonstrate the efficacy of 1 year of treatment with oral cyclophosphamide in scleroderma interstitial lung disease with active alveolitis.

What This Study Adds to the Field

The present report provides the first evidence that, during an additional year of follow-up in the same patients off of study drug, the benefits of cyclophosphamide persist for several additional months, but are generally no longer apparent at 2 years.

Keywords: cyclophosphamide; interstitial lung disease; scleroderma; systemic sclerosis

Scleroderma (systemic sclerosis [SSc]) is a connective tissue disorder of unknown etiology with underlying microvascular injury, excessive cutaneous fibrosis, and characteristic visceral changes involving the lung, heart, kidneys, and gastrointestinal tract. Pulmonary involvement, including interstitial lung disease (ILD) and/or pulmonary hypertension, develops in up to 80% of patients with SSc, and is currently the leading cause of death (1). A total of 40% of all patients with SSc develop at least moderate restrictive ventilatory impairment, and 15% develop severe restrictive ILD (FVC < 50% predicted) that is associated with a 10-year survival rate of only 40–50% (1, 2). There is a well defined need to identify and effectively treat early stages of SSc-ILD.

Although several agents have been evaluated as treatments for SSc-ILD, including D-penicillamine, prednisone, relaxin, methotrexate, IFN-γ, and cyclophosphamide (CYC), only CYC has been shown to slow the loss of FVC over time (3–11). The Scleroderma Lung Study (SLS) is a multicenter, National Institutes of Health–sponsored, randomized, controlled trial comparing a 1-year treatment of oral CYC (up to 2 mg/kg) with placebo. This trial was recently performed in 158 patients with symptomatic SSc-ILD and evidence of active alveolitis, as identified by either thoracic high-resolution computed tomography (HRCT) or

bronchoalveolar lavage (BAL), or both. As recently reported (11), assignment to the CYC arm was associated with statistically significant but modest benefits at the 12-month evaluation point, including placebo-adjusted improvements in FVC % predicted (2.53%; $P < 0.03$), total lung capacity (TLC) % predicted (4.09%; $P = 0.026$), the Mahler Transition Dyspnea Index (TDI; +1.4 vs. −1.5 in the placebo group; $P < 0.001$), Rodnan skin thickness scores in the 85 patients with diffuse SSc (−3.06; $P = 0.008$), and the Health Assessment Questionnaire–Disability Index (HAQ-DI; −0.16; $P = 0.009$). Active therapy was limited to 1 year due to concerns regarding increased toxicity from prolonged administration of CYC (12–15). Some adverse but not serious events (e.g., leukopenia and hematuria) were more common in the CYC patients during the double-blind treatment period.

After completing the treatment phase of the SLS, subjects underwent an additional year of monitoring to investigate whether or not the beneficial effects from CYC persisted after discontinuing therapy. This report represents the first comprehensive analysis of the second-year outcomes from the SLS and identifies a unique pattern of disease modification. This modification persisted, or, in many cases, continued to improve, for up to 6 months after stopping CYC, but then deteriorated to placebo levels by the end of 2 years. The only exception was for the sensation of dyspnea, which maintained its treatment-related benefit throughout the entire second year. These results provide important insight into the disease process and its response to immunosuppressive therapy. Some of the results of this study have been previously reported in the form of an abstract (16).

METHODS

Subjects

Patients with SSc (as defined by the American College of Rheumatology [17]), either limited or diffuse (18), were enrolled if they met criteria described previously (11). All subjects provided written informed consent according to medical institutional review board guidelines.

Screening and Randomization

Screening methods have been described in detail previously (11). Subjects meeting all eligibility criteria were randomized by clinic to receive either CYC (2 mg/kg; Bristol-Myers Squibb, New York, NY) or identical-appearing placebo once daily for 12 months, followed by another year of follow-up off study medication.

Baseline Measurements

Baseline measures before initiating therapy included, among others: spirometry (FVC and FEV_1) (19, 20); FRC and TLC by whole-body plethysmography (21, 22); diffusing capacity of carbon monoxide (D_{LCO}) and ratio of D_{LCO} to alveolar volume (D_{LCO}/V_A) (23, 24); modified Rodnan skin thickness score (25); baseline dyspnea index (BDI) (26); and the 20-item HAQ-DI modified for scleroderma (27, 28). All pulmonary function technicians were certified by the study and performance monitored by site visits and a pulmonary function quality assessment core.

Aside from being used for eligibility purposes, HRCT scans were scored by two independent radiologists, blinded to treatment assignment, for extent of parenchymal abnormality (including pure ground glass opacity and lung fibrosis) in each of three lung zones using a four-point Likert scale. Further details are given in the online supplement.

Treatment with CYC or Placebo

Treatment with CYC (in 25-mg gel caps) or placebo was initiated at 1 mg/kg/day (to the nearest 25 mg) and increased every month by one capsule up to a maximum dose of 2 mg/kg/day or the next-highest tolerable dose. Methods of monitoring drug toxicity and criteria for discontinuing or adjusting study drug in response to drug-related toxicities have been described previously (11). A data safety and monitoring board provided oversight of the study.

Serial Monitoring and Outcome Measures

All of the baseline measurements were repeated at 3, 6, 9, 12, 15, 18, 21, and 24 months of the study, except for the BDI, which was replaced by the TDI.

Management of Treatment Failures

Treatment failure was defined as a decrement of 15% (absolute) or more in FVC % predicted from baseline, occurring at least 3 months into treatment and sustained for at least 1 month. Patients meeting this definition were unblinded, offered open-labeled therapy with CYC if on placebo, or advised to seek further treatment from their treating rheumatologist, and encouraged to continue with scheduled visits.

Statistical Analysis

Analysis of the first 12-month data has already been described (11). For assessment of the 24-month data, a longitudinal model was used for analysis of FVC % predicted and TLC, TDI, and skin score, adjusted for: baseline values; worst fibrosis score from the baseline HRCT scan; and nonignorable values missing due to death, treatment failure, or drop-out (29). Comparison of the two treatment groups at 9, 12, 15, 18, 21, and 24 months was performed by Huber's robust regression analysis (30) after imputing the missing observations using multiple imputation (31, 32). HAQ scores were analyzed using a permutation model (33, 34). The online supplement provides further details regarding the statistical analysis.

RESULTS

Disposition of Randomized Participants throughout the 24-Month Trial

A total of 158 study-eligible patients were randomized into the trial, 79 in each treatment group. The disposition of randomized participants throughout the 24-month trial is shown in Figure 1. Of the 54 CYC and 55 placebo patients who completed the 12-month visit, 48 and 45, respectively, subsequently completed visits up to and including the 24-month visit. An additional 9 CYC and 11 placebo patients returned for the 24-month visits after having withdrawn or failed treatment at earlier time points in the study. Thus, 24-month data were available in 57 CYC and 56 placebo patients. For the primary and secondary 24-month outcomes (FVC % predicted, TLC % predicted, TDI, skin score, and HAQ), evaluable data from 6–24 months were available on 69–72 CYC and 69–73 placebo patients for the Huber's robust regression analysis after imputing missing observations.

Although study drugs were discontinued after the first 12 months, participants were allowed to be treated with any medication that was believed to be indicated by their primary treating physician during the second year. Based on concurrent medication records, 14 patients originally assigned to the placebo group and 10 patients assigned to the CYC group were noted to be on some form of therapy during the second "off study drug" year that might have disease-modifying effects: 12 on prednisone (≥10 mg; average dose = 11.6 mg) and 2 on CYC (average dose = 72.5 mg) for the placebo group; 10 on prednisone (≥10 mg; average dose = 14 mg); and none on CYC for the CYC group. No patients received azathioprine or mycophenolate during this time. Analysis using Huber's robust regression after multiple imputation with the Markov Chain Monte Carlo method (31, 32) failed to identify any independent effect of such treatment on any of the outcome measures.

Baseline Characteristics

Baseline features of the 145 subjects (72 CYC and 73 placebo) whose data were included in the 24-month analysis were similar to those of the entire group of randomized participants, as previously reported (11), and are shown in Table 1. Briefly, 69.7%
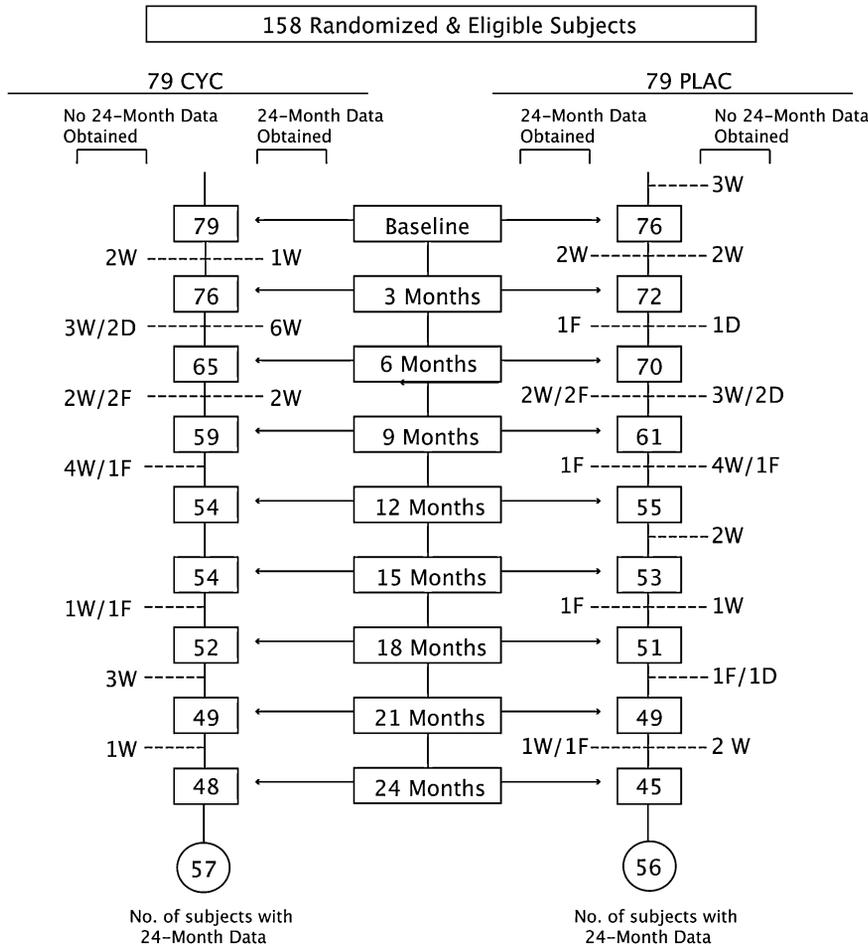
Figure 1. Disposition of the 158 randomized participants in the Scleroderma Lung Study over the 24 months of the trial. CYC = cyclophosphamide; D = died; F = failed treatment; PLAC = placebo; W = withdrew from the study.

of the patients were female, with an average age of 48 ($\pm$1.0 SE) years and an average duration of SSc from the onset of the first non-Raynaud's symptom of 3.2 years. A total of 62% of the patients had diffuse disease. Mean baseline values for respiratory parameters were as follows: FVC, 68 ($\pm$0.9) % predicted; TLC, 69 ($\pm$1.1) % predicted; FRC, 73 ($\pm$1.6) % predicted; D_{LCO}, 47 ($\pm$1.2) % predicted; and Mahler BDI focal score, 5.6

($\pm$0.2; scale, 0–12, with lower scores indicating worse dyspnea). Mean baseline skin thickness score was 15 ($\pm$0.9; scale, 0–51, with higher scores indicating greater thickness); baseline skin thickness was significantly greater in those with diffuse than in those with limited disease (21 $\pm$ 1.0 and 6 $\pm$ 0.5, respectively; $P < 0.0001$). Mean baseline HAQ-DI was 0.8 ($\pm$0.06; range, 1–3, with higher scores indicating more disability). None of the

TABLE 1. BASELINE CHARACTERISTICS OF THE 145 PARTICIPANTS RANDOMIZED INTO THE SCLERODUALE LUNG STUDY WITH 24-MONTH EVALUABLE DATA

	All (n = 145)	CYC (n = 73)	Placebo (n = 72)	P Value (CYC vs. Placebo)
Age, yr	47.9 ± 1.0	47.9 ± 1.3	47.8 ± 1.5	0.9322
Female, %	69.7	76.7	62.5	0.0627
SSc duration, yr	3.2 ± 0.2	3.3 ± 0.3	3.1 ± 0.2	0.5974
With diffuse SSc, %	62.1	63.0	61.1	0.8134
FVC, % predicted	67.9 ± 0.9	67.6 ± 1.3	68.3 ± .5	0.7250
FEV$_1$/FVC, %	82.9 ± 0.7	82.8 ± 1.0	83.1 ± 0.9	0.8038
TLC, % predicted	69.0 ± 1.1	69.4 ± 1.5	68.7 ± 1.5	0.7308
FRC, % predicted	73.3 ± 1.6	74.6 ± 2.1	71.9 ± 2.3	0.3905
D$_{LCO}$, % predicted	46.9 ± 1.2	47.1 ± 1.5	45.8 ± 1.5	0.5356
Mahler BDI focal score (range, 0–12)	5.6 ± 0.2	5.6 ± 0.22	5.6 ± 0.23	0.8504
Skin score (range, 0–51)	15.2 ± 0.9	15.9 ± 1.3	14.5 ± 1.2	0.4232
Diffuse SSc	20.9 ± 1.0	21.7 ± 1.5	20.2 ± 1.4	0.4619
Limited SSc	5.9 ± 0.5	6.1 ± 0.7	5.7 ± 0.6	0.6969
HAQ-DI (range, 0–3)	0.82 ± 0.06	0.96 ± 0.08	0.68 ± 0.08	0.0131

Definition of abbreviations: BDI = baseline dyspnea index; CYC = cyclophosphamide; D$_{LCO}$ = diffusing capacity of carbon monoxide; HAQ-DI = Health Assessment Questionnaire–Disability Index; SSc = systemic sclerosis.
Plus/minus values represent means ($\pm$SEM).

baseline characteristics differed between the CYC and placebo treatment groups, except for the HAQ-DI, which was significantly higher in the CYC than in the placebo group (0.96 ± 0.08 vs. 0.68 ± 0.08, respectively; $P = 0.013$). In addition, a greater percentage of the participants in the CYC group were female, although the gender difference did not reach statistical significance ($P = 0.0627$).

The 24-Month Outcomes

Mean values (± SE) of FVC % predicted and TLC % predicted (adjusted for baseline % predicted values and maximal HRCT-scored fibrosis) from 6 to 24 months are shown graphically by treatment group in Figures 2A and 2B. As with the other data presented in subsequent figures, the mean adjusted values shown are derived from the joint longitudinal model, and the P values for comparison of the two treatment groups were calculated using Huber's robust regression analysis to minimize the impact of outliers. For both FVC % predicted and TLC % predicted, a significant CYC treatment effect was observed at 12 months, and was still noted at 18 months, after which the effect waned. As such, by 24 months, the mean values of both variables were almost identical between the two treatment groups. No significant between-group differences were observed for D_{LCO} % predicted or D_{LCO}/V_A % predicted at either 12

months or over the 12- to 24-month course (data for D_{LCO} % predicted are presented in the online supplement).

To assess whether the response to CYC might be linked to the extent of lung disease at baseline, an exploratory analysis was performed to examine treatment-related differences in FVC % predicted over time in subjects who presented with either an FVC of less than 70% predicted (n = 77: 40 CYC; 37 placebo) or at least 70% predicted (n = 64: 29 CYC; 35 placebo), using the joint longitudinal model. More severe restriction at baseline (FVC < 70% predicted) was associated with a greater difference in FVC % predicted at 12 months between the CYC and placebo groups (4.62% higher FVC % predicted in the CYC group; $P = 0.007$) than that observed when the entire cohort was used in the analysis, and the CYC treatment effect was even greater at 18 months (6.8% higher FVC % predicted; $P = 0.006$). In contrast, subjects who had less-severe disease at baseline (FVC ≥ 70% predicted) had decidedly smaller (and nonsignificant) treatment-related differences (0.55% higher FVC % predicted in the CYC group at 12 mo; $P = 0.82$; 2.67% higher FVC % predicted in the CYC group at 18 mo; $P = 0.35$). By 24 months, the outcome differences between the CYC and placebo arms had decreased substantially and were no longer significant, regardless of the baseline FVC % predicted (1.96% difference in FVC % predicted in the more severe group; $P = 0.49$; 1.11% difference in the less severe group; $P = 0.66$).
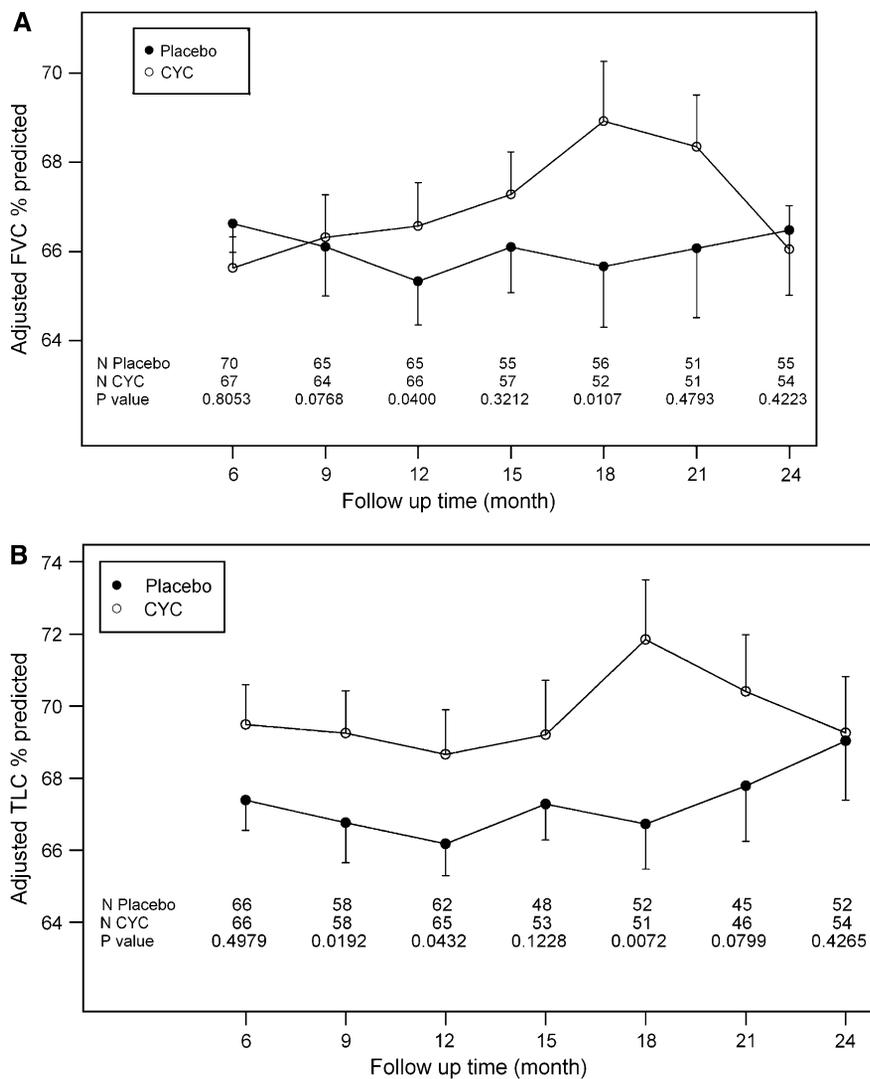

Figure 2. Time course from 6 to 24 months of mean values (±SE) for FVC % predicted (*A*) and TLC % predicted (*B*) of participants in the placebo and cyclophosphamide (CYC) treatment groups determined from a longitudinal model that adjusted for baseline % predicted values, maximal high-resolution computed tomography–scored fibrosis, and nonignorable missing data (29). For this and subsequent figures, numbers of patients in each treatment group at each visit are shown, along with the P values for the between-treatment differences obtained from Huber's robust regression analysis with multiple imputation (30).

A secondary analysis of response to treatment was also performed in which FVC % predicted, TLC % predicted, and TDI at Months 12, 18, and 24 were dichotomized as follows: the response was coded as "0" for the outcome below baseline (i.e., "worse"), treatment failure, dropout for any reasons after Month 6, or death; and "1" for the outcome at or above baseline (i.e., "not worse"). The treatment effect was evaluated by logistic regression to adjust for baseline values and maximum fibrosis score on the baseline HRCT scan. The results of the responder analysis indicated the following: a significant treatment effect for FVC favoring CYC at 12 months ($P = 0.013$), but not at 18 months ($P = 0.108$) or 24 months ($P = 0.364$); a significant treatment effect favoring CYC for TLC at 18 months ($P = 0.004$), but not at 24 months ($P = 0.67$); and no treatment effect for $D_{L_{CO}}$ or $D_{L_{CO}}/V_A$ at any time point.

Mean focal scores ($\pm SE$) for the TDI (adjusted for baseline fibrosis) for the two treatment groups are shown in Figure 3. Again, significant between-group differences favoring CYC are found at 12 months, but, in contrast to the physiologic results, the beneficial impact on dyspnea persists more or less to the end of follow-up (24 mo). The results of the responder analysis indicated a significant treatment effect for TDI favoring CYC at 12 months ($P = 0.025$), with responses approaching but not achieving statistical significance at 18 months ($P = 0.089$) and 24 months ($P = 0.074$).

In Figure 4, mean scores for skin thickness ($\pm SE$) adjusted for baseline skin scores and fibrosis on HRCT are shown only for the subset of patients with diffuse SSc, because (*1*) these patients had significantly greater skin thickness at baseline compared with those with limited SSc ($P < 0.0001$), and (*2*) significant treatment-related improvement in skin thickness scores was noted at 12 months only in the patients with diffuse disease ($P < 0.01$) (11). Among patients with diffuse SSc, skin thickness decreased continuously over the 24-month trial in the CYC group, but increased over the first year in the placebo group, resulting in a significant difference favoring CYC at 12 months ($P < 0.01$). From 12 to 18 months, however, skin thickness decreased in the placebo group at approximately the same rate as in the CYC group. By contrast, from 18 to 24 months, skin thickness scores remained relatively stable in the placebo group and increased slightly in the CYC group, so that, by 24 months, the between-group difference was no longer statistically significant ($P = 0.23$).

Mean values for the HAQ-DI declined (improved) progressively in the CYC group until Month 18, but increased (worsened) in the placebo group over the same time period, resulting in significant between-treatment differences favoring CYC at 12 and 18 months ($P < 0.003$ and $P < 0.007$, respectively). Thereafter, however, the HAQ-DI scores for the two treatment groups converged, so that the differences between the two groups were no longer significant at 24 months ($P = 0.275$). Similar findings were observed when the analysis was confined to patients with diffuse SSc.

Adverse events were uncommon during the second year of the trial after discontinuation of study medication. Although leukopenia and neutropenia were significantly more common in the CYC than in the placebo group during the first year of the trial, neither of these events was observed in either group during the second year. During Year 2, hematuria occurred in one CYC patient and two placebo patients (one of whom received CYC in the second year), anemia in two CYC patients (one of whom continued taking CYC in the second year) and 1 placebo patient, and pneumonia in one CYC patient and no placebo patients. Also during the second year, 27 serious adverse events (SAEs: four probably and four possibly treatment related) occurred in the CYC group and 22 SAEs (five possibly treatment related) occurred in the placebo group; the between-group differences in the frequency of SAEs were not significant. Five patients died during the first 12 months of the trial (two in the CYC group and three in the placebo group); an additional three deaths in the placebo group and four in the CYC group occurred in the second year of the trial. Most of the deaths were judged by an independent, three-person morbidity and mortality review committee to be disease related, but none was considered treatment related.

DISCUSSION

The SLS was the first randomized placebo-controlled clinical trial to demonstrate that patients with SSc-ILD and evidence of active alveolitis respond to a 1-year course of oral CYC with statistically significant improvements in lung function (FVC and TLC), dyspnea (TDI), skin thickness, functional disability, and some measures of health-related quality of life, as assessed at the 12-month visit (11). According to study design, CYC therapy was limited to 1 year due to concerns over the potential for increasing long-term toxicity with continued drug administration (12–15). Furthermore, we hypothesized that a 1-year treatment with CYC might lead to a remission of the autoimmune process, thereby preventing further disease progression without
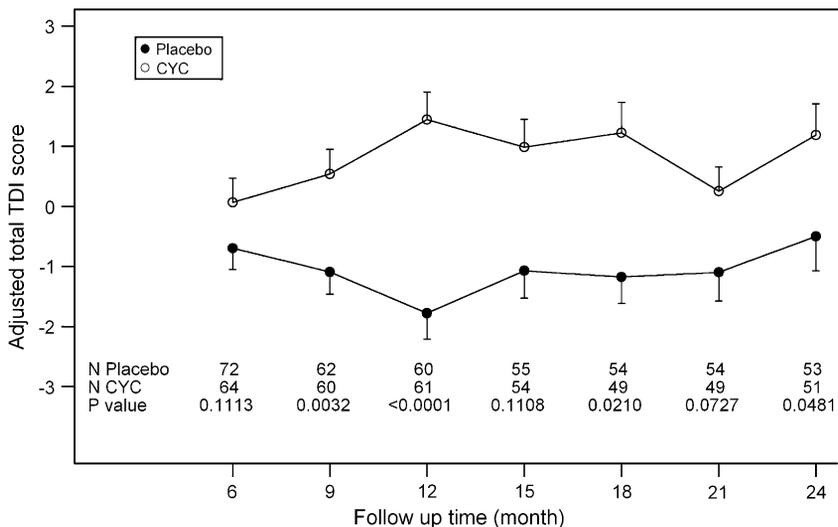

Figure 3. Time course from 6 to 24 months of mean values ($\pm SE$) for transition dyspnea index (TDI) determined from the longitudinal model (*see* legend for Figure 2). CYC = cyclophosphamide.
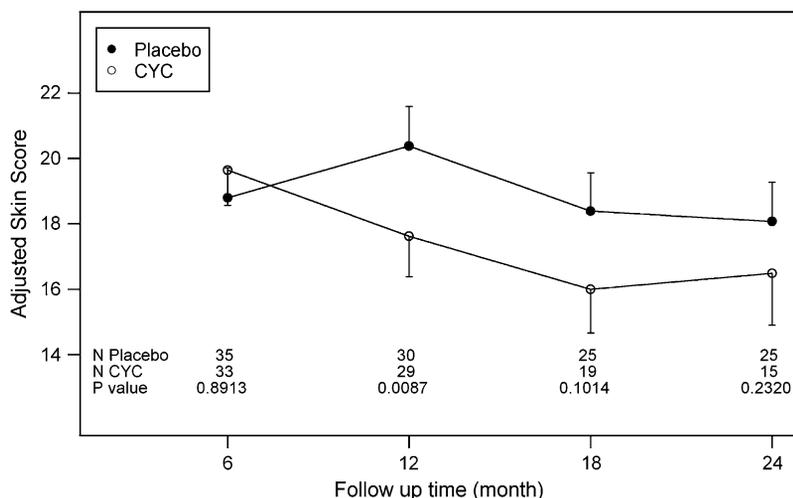
Figure 4. Time course from 6 to 24 months of mean values (±SE) for skin thickness scores (modified Rodnan) determined from the longitudinal model (*see* legend for Figure 2). CYC = cyclophosphamide.

the need for ongoing immunosuppressive therapy. To test this hypothesis, we followed our participants for an additional year, while off of study drugs, and monitored them at 3-month intervals for changes in both physiologic and patient-centered outcomes.

Our findings during the second year of observation provide important new insights into the nature of SSc-ILD and its response to immunosuppressive therapy. It was very interesting that the beneficial effects of CYC on lung function (FVC and TLC) continued to increase for 6 months after stopping CYC therapy (i.e., from 12 to 18 mo), compared with the physiologic changes over the same time interval in the placebo group (Figures 2A and 2B). These results are consistent with our hypothesis that inflammation begets fibrosis, and that suppression of inflammation for 1 year impedes its progression to fibrosis, extending beyond the actual duration of therapy. After 18 months, however, these physiologic improvements progressively waned, so that, by the end of the 2-year trial, the FVC and TLC of the two treatment groups were nearly the same. As such, even though the effects of CYC can persist for months after stopping therapy, the impact on lung function is ultimately time limited, and extended treatment may be required to obtain longer-term benefits.

The exploratory subanalysis, demonstrating that differences in FVC % predicted between the CYC and placebo arms at 12 and 18 months were much greater in subjects who exhibited more severe restrictive lung disease at baseline (FVC % predicted < 70%), suggests that the overall treatment effect was driven primarily by this subset of patients. Furthermore, these findings, along with the previously observed correlation between HRCT measures of fibrosis at baseline and response to treatment (11), reinforce the concept that the combination of significant restriction and existing fibrosis predicts a greater response to CYC relative to placebo.

Another interesting observation in those subjects who were assigned to receive placebo was that, after a progressive decline in lung function during the first year of the trial, both FVC and TLC stabilized, or even tended to improve, in the second year (Figures 2A and 2B). The reason for these second-year time trends in the placebo group is unclear, but could be related, at least in part, to previously reported observations that the greatest rate of decline in lung function in SSc-ILD occurs in early disease (within 3 yr of disease onset), after which the rate of further decline slows (1). The findings during the second year in the placebo group could also have been influenced by participant attrition between 12 and 24 months, particularly if those placebo

patients who might have exhibited the greatest lung function decline failed to return for clinic assessments during this time period. On the other hand, the attrition rate during the second year was similar in the CYC group. Another possible explanation is confounding by the use of potentially disease-modifying therapy by placebo patients during the second year. However, only two placebo patients used CYC during the second year (as well as during the later months of the first year), and repeat analyses that excluded these subjects yielded similar results. Also, an equivalent number of CYC and placebo patients (21 and 22, respectively) used prednisone during the second year, and a secondary analysis failed to demonstrate any impact of prednisone therapy on the results of the trial.

In contrast to the second-year results for FVC and TLC, the improvement in breathlessness (TDI) in the CYC group that was noted during the first year was maintained throughout most of the second year (Figure 3). In the placebo group, however, although dyspnea worsened progressively during the first year, it remained stable, or even improved slightly, in the second year, possibly for the same reasons discussed for the trends in FVC and TLC. The disparity between the effects of CYC on physiologic variables during the end of the second year (worsening) versus the effects on dyspnea (stable) may reflect the lack of correlation between dyspnea and lung function that has been noted in response to other therapies in other lung diseases, such as asthma and chronic obstructive pulmonary disease (25, 35–37). The perception of the sensation of breathlessness is influenced by a number of factors, in addition to alterations in lung mechanics, including ventilatory drive, respiratory muscle function, and sensory stimuli originating from the lung and other tissues, including skeletal muscle and skin (36, 38). Thus, skin and musculoskeletal changes, which improved with CYC therapy and either remained stable or continued to improve during the second year, could have accounted for the sustained improvement in breathlessness, independent of any alterations in lung function.

The opposing trends in skin changes during the year-long, double-blind treatment period between the CYC and placebo patients (decreasing and increasing skin thickness, respectively) were no longer observed during the second, off-treatment year, during which skin thickness decreased slightly but steadily in both treatment groups (Figure 4). It is possible that the parallel decreases in skin thickness in both treatment groups during the second year could simply reflect the general tendency for skin "softening" to occur later in the course of SSc, regardless of treatment.

The scores for the HAQ-DI improved in the CYC group and worsened in the placebo group during the active treatment period, resulting in significant differences between the two treatment groups at 12 months. Subsequently, in the CYC group, the scores continued to improve up to 18 months, after which they appeared to stabilize, whereas, in the placebo group, they remained more or less stable, with little between-group differences apparent at 24 months. Thus, the trends in the HAQ-DI, which may, in part, reflect musculoskeletal and skin involvement by SSc, paralleled those in the lung volumes, which most likely reflect a combination of lung inflammation and fibrosis. For both of these tissue-related outcomes, it appears that the benefits of 1 year of CYC therapy continue to accrue for several months after therapy is discontinued, after which they appear to wane, essentially disappearing by 24 months. It remains to be determined whether continued therapy with CYC or some other, less toxic, disease-modifying agent would lead to more sustained benefit in lung function and extrapulmonary measures.

A major limitation of the study was that only 93 (59%) of the 158 study-eligible, randomized participants completed both the study treatment during the first 12 months of the trial and all of the subsequent follow-up visits during the second year. Consequently, this relatively large attrition rate could have undermined our ability to show a significant treatment effect at 24 months. On the other hand, 145 (92%) of the 158 randomized subject had measurements performed at 6-month or later visits that permitted their 24-month data to be imputed; also, times to death, treatment failure, or dropouts due to disease progression were adjusted for as nonignorable missing data in our longitudinal analysis. A total of 113 (77.4%; 57 CYC and 56 placebo patients) of the 146 subjects known to be alive at 2 years had assessments performed at 24 months, even if they failed treatment or withdrew from the study at earlier time points. It is still unlikely, however, that our methods of statistical modeling for dealing with missing data completely eliminated the impact of attrition on the end results of the trial at 2 years.

Although the SLS did succeed in establishing the benefits of oral CYC administered for 1 year as a modestly effective treatment for SSc-ILD, the limited magnitude and duration of benefit, and the short-term and potential long-term toxicity, of oral CYC point to the need for a therapeutic alternative with greater and more durable efficacy and less toxicity. One alternative approach that has been tried involved a trial of CYC administered by intravenous infusion monthly for 6 months (to minimize the risk of hemorrhagic cystitis associated with the oral route), followed by azathioprine versus placebo in 45 patients with active fibrosing alveolitis due to SSc (39). This therapeutic strategy appeared to be an attempt to induce a "remission" with CYC and then to follow up with an immunosuppressive agent of lower potential toxicity that could permit more prolonged therapy. The results indicated a trend toward a favorable outcome in the azathioprine-treated group ($P = 0.08$) in the absence of any evidence of hemorrhagic cystitis or bone marrow suppression.

In summary, at the end of a 12-month course of treatment with oral CYC, FVC, TLC, dyspnea (TDI), skin thickness, and quality of life were all significantly improved relative to placebo in 158 patients with dyspnea with SSc-ILD and active alveolitis (11). Although beneficial effects in most of these outcomes were still apparent several months after withdrawal of therapy, at the end of one additional year off of treatment, FVC and TLC results were nearly identical for the CYC and placebo treatment groups, and none of the other outcomes, with the single exception of dyspnea, showed significant between-group differences. We conclude that the beneficial physiological effects of CYC in SSc-ILD with active alveolitis evident after 12 months of therapy are, in general, no longer apparent at 24 months. These results point to the need for studies of alternative treatment strategies in SSc-ILD, employing other potentially disease-modifying agents of sufficiently low toxicity that they can be administered over more prolonged periods, either alone or after a shorter course of CYC. These newer treatment approaches would need to be compared in randomized, controlled clinical trials with the already demonstrated benefits of a 1-year treatment regimen with CYC.

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