Cyclophosphamide for Systemic Sclerosis-related Interstitial Lung Disease: A Comparison of Scleroderma Lung Study I and II

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ABSTRACT. ***Objective.*** To compare safety and efficacy outcomes between the cyclophosphamide (CYC) arms of Scleroderma Lung Study (SLS) I and II.

Methods. Participants enrolled in the CYC arms of SLS I (n = 79) and II (n = 69) were included. SLS I and II randomized participants to oral CYC for 1 year and followed patients for an additional year off therapy (in SLS II, patients received placebo in Year 2). Eligibility criteria for SLS I and II were nearly identical. Outcomes included the forced vital capacity (FVC%)-predicted and DLCO%-predicted (measured every 3 mos) and quantitative radiographic extent of interstitial lung disease (measured at 1 and 2 yrs for SLS I and SLS II, respectively). Joint models were created to evaluate the treatment effect on the course of the FVC/DLCO over 2 years while controlling for baseline disease severity.

Results. SLS I and II CYC participants had similar baseline characteristics. After adjusting for baseline disease severity, there was no difference in the course of the FVC%-predicted (p = 0.535) nor the DLCO%-predicted (p = 0.172) between the SLS I and II CYC arms. In both groups, treatment with CYC led to a significant improvement in the FVC%-predicted from 3 to 12 months, but no significant improvement beyond this point. Treatment with CYC had no effect on the DLCO for either group.

Conclusion. Treatment with 1 year of oral CYC led to similar improvements in lung function in both SLS I and II, although the effects were not sustained following cessation of CYC. These results suggest that increasing the duration of ILD therapy may improve outcomes for patients with systemic sclerosis–ILD. (First Release February 15 2019; J Rheumatol 2019;46:1316–25; doi:10.3899/jrheum.180441)

Key Indexing Terms:
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Interstitial lung disease (ILD) is the leading cause of death in patients with systemic sclerosis (SSc)[1,2]. Randomized controlled trials have favored the use of cyclophosphamide (CYC) for treating SSc-ILD[3,4,5]. Compared with placebo, 1 year of CYC improved lung function in patients with SSc-ILD in Scleroderma Lung Study (SLS) I[3]. However, the effects of CYC waned after monitoring patients for an additional year off therapy[6]. In SLS II [comparing CYC and mycophenolate mofetil (MMF)], treatment with 1 year of CYC appeared to have a more sustained effect on lung

function over 2 years[5]. Following the publication of SLS II, a number of SSc experts have questioned whether the CYC arm of SLS II performed better than the CYC arm of SLS I.

However, because SLS I[3] and II[5] used different analytic approaches, comparing efficacy outcomes reported in these publications has inherent limitations. In SLS I[3], the analysis of the primary endpoint [forced vital capacity (FVC)] was based on a longitudinal model that included terms for treatment and time and an interaction term[3]. In contrast, in SLS II[5], the analysis of the primary endpoint (FVC) was performed using an inferential joint model combining a mixed effects model for longitudinal outcomes and a survival model to handle non-ignorable missing data[7,8].

To further understand the effects of CYC on SSc-ILD outcomes, our present study directly compared efficacy outcomes between the CYC arms of SLS I and II using an inferential joint model approach. In using a uniform analysis approach, our present analysis aimed to test the hypothesis that the CYC arm of SLS I and II had similar clinical outcomes regarding the course of the FVC and DLCO. This study also aimed to compare the safety profiles for patients in these 2 groups.

MATERIALS AND METHODS

Study participants. All participants enrolled in the CYC arm of SLS I[3] and II[5] were included in this analysis. Participating centers, investigators, and eligibility criteria were similar for both trials[3,5]. The protocol was approved by a Data and Safety Monitoring Board constituted by the US National Heart, Lung, and Blood Institute, National Institutes of Health. The institutional review board (IRB) at the main coordinating center, University of California, Los Angeles, approved this study (11-002659-CR-00005). In addition, each of the participating centers (n = 12 for SLS I and n = 14 for SLS II) had IRB approval to conduct this study. All participants gave written informed consent. Prior SLS publications describe inclusion and exclusion criteria[3,5].

SLS I and II study design. SLS I consisted of 162 participants randomized between September 2000 and January 2004 to receive either oral CYC (titrated to 2.0 mg/kg once daily) or matching placebo for 1 year, followed by an additional year of observation off treatment as previously published[3]. In SLS II, 142 patients were randomized between September 2009 and December 2012 and assigned to receive either MMF (titrated as tolerated to 3.0 g/day in divided doses) for 2 years or oral CYC (titrated as tolerated to 2 mg/kg once daily) for 1 year followed by an additional year on placebo[5].

SLS I and II assessment measurement. Completed pulmonary function tests were performed at baseline. The FVC (primary SLS I/II endpoint) and DLCO (secondary SLS I/II endpoint) were measured every 3 months during the trials. Dyspnea was assessed using the Mahler Dyspnea Index at baseline (BDI) and every 3 months thereafter for SLS I and every 6 months thereafter for SLS II using the Transition Dyspnea Index (TDI)[9,10]. In SLS I, an interview-administered paper version of the BDI/TDI was used[9], while in SLS II a self-administered computer-assisted version of the BDI/TDI was used[10]. The modified Rodnan skin score (mRSS)[11] was used to assess cutaneous sclerosis. The mRSS[11] was performed every 3 months in SLS II and every 6 months in SLS I.

High-resolution computed tomography (HRCT) thoracic imaging was obtained at baseline and at 12 and 24 months in SLS I and II, respectively. Both studies used similar HRCT acquisition and analysis methods[12,13] except that, in SLS I, nonvolumetric CT scans of 1–2 mm slice thickness were acquired at 10-mm increments, while in SLS II, volumetric CT scans of 1–1.5 mm slice thickness were acquired contiguously. We report the quantitative lung fibrosis score, representing the percentage of counts with reticular opacity with architectural distortion, and the quantitative ILD (QILD) score, representing the sum of all abnormally classified scores, including scores for fibrosis, ground-glass opacity, and honeycombing. Scores were summed for the whole lung (WL) and for the 1 zone of maximal involvement.

Baseline characteristics. Summary statistics were generated for baseline characteristics from the 2 cohorts. Group comparisons were performed using a 2-sample T test, Wilcoxon rank-sum test, and a chi-square test.

Primary outcome: FVC%-predicted. An intention-to-treat principle was applied to all analyses using an inferential joint model consisting of a mixed-effects model for longitudinal outcomes and a survival model to handle non-ignorable missing data due to study dropout, treatment failure, or death[7,8]. The joint model was used as our primary inferential approach because it can provide unbiased and efficient estimates when there are non-ignorable missing data in the outcomes due to dropouts, treatment failures, and deaths. Consistent with the intention-to-treat principle, treatment failures and others who prematurely withdrew from the double-blind treatment phase were encouraged to return for monitoring.

Repeated measurements of the FVC%-predicted were characterized by a linear mixed effects submodel in the joint model, and intrasubject data correlation among multiple measurements over time was accounted for by random intercept and random time trend. Fixed effects were prespecified covariates for the primary outcome including baseline FVC %-predicted, baseline QILD-WL, a time trend, treatment assignment, treatment-time trend interactions, and treatment-QILD interaction. The time trend was modeled by linear splines with knots at 12 and 21 months. The location of knots was determined by preliminary examination of the data using descriptive statistics. Treatment assignment was coded as a binary variable with SLS I–CYC group as the reference. Thus, the model estimates 3 piecewise linear trends for the SLS I–CYC group in 3–12 months, 12–21 months, and 21–24 months, and change in these time trends in the SLS I–CYC group compared with the SLS II–CYC group.

Secondary outcomes: DLCO%-predicted, TDI, mRSS, and safety. Secondary efficacy endpoints were also analyzed using a joint model with no adjustment for multiple comparisons. For safety analyses, descriptive statistics were used to compare the incidence of adverse events (AE) and serious AE (SAE) between treatment arms. The definitions of specific AE (leukopenia, anemia, etc.) were identical between SLS I and SLS II[3,5].

All tests were 2-sided. Group comparisons of baseline characteristics were performed using SAS 9.4 (SAS Institute). The joint modeling analysis was implemented in the C statistical program.

RESULTS

Baseline characteristics. Patients assigned to CYC in SLS I and II exhibited similar baseline demographic features except for a slight difference in age (Table 1). The FVC%-predicted, disease duration, and mRSS were similar for the CYC arms of each trial. Patients assigned to CYC in SLS I had lower DLCO%-predicted and a trend for more extensive QILD than patients assigned to CYC in SLS II. Moreover, the BDI was lower in SLS I-CYC compared with SLS II-CYC, perhaps owing to discrepancies in the mode of administration of the BDI in SLS I and II as described under Materials and Methods.

Disposition of study participants. In SLS II, 32 (46.4%) CYC patients prematurely withdrew from the study drug, 2 failed treatment, and 11 died during the 24-month study period. In SLS I, 25 (31.6%) CYC patients prematurely withdrew from the study drug, 4 failed treatment, and 4 died during the 24-month study period (Supplementary Figure 1, available with the online version of this article).

Table 1. Baseline characteristics of participants assigned to CYC in SLS I and SLS II.

Characteristics	SLS I–CYC, n = 79	SLS II–CYC, n = 69	p
Age, yrs			0.040††
Mean	48.4 ± 12.3	52.2 ± 9.6	
Range	28–81	28–71	
Female sex, %	76.0	74.6	0.853£
SSc duration, yrs, median (IQR) †	2.4 (1.3–4.6)	1.9 (1.2–4.0)	0.308**
Limited/diffuse, %	38.0/62.0	46.2/53.9	0.322£
Race, %			0.220£
White	67.1	67.7	
African American	15.2	23.1	
Asian	3.8	4.6	
Other	13.9	4.6	
FVC, % of predicted	67.6 ± 11.4	66.9 ± 9.9	0.704††
DLCO, % of predicted	47.2 ± 13.7	54.5 ± 14.6	0.002††
Mahler Dyspnea Index (focal score)*	5.6 ± 1.8	7.1 ± 2.4	0.0002††
Skin thickness score (mRSS)◊			
All patients			0.302**
Median (IQR)	12 (7–22)	12 (5–20)	
Range	2–51	2–46	
Patients with dcSSc			0.545**
Median (IQR)	21 (14–25)	19 (12–26)	
Range	7–51	6–46	
Patients with lcSSc			0.894**
Median (IQR)	5 (3–9)	5 (2–8)	
Range	2–16	2–18	
QLF-WL, median (IQR)	7.5 (2.8–12.8)	7.4 (3.1–13.1)	0.816**
QLF-ZM, median (IQR)	23.5 (6.8–46.0)	18.2 (6.3–34.3)	0.244**
QILD-WL	35.8 ± 17.1	30.6 ± 14.2	0.066††
QILD-ZM	58.1 ± 22.3	51.1 ± 20.0	0.055††
Positive antinuclear antibody, n (%)	NA	65/70 (92.9)	
Positive anticentromere antibody, n (%)	NA	2/70 (2.9)	
Positive anti-Scl70 antibody, n (%)	NA	31/70 (44.3)	
Positive RNA polymerase III antibody, n (%)	NA	9/70 (12.6)	

Values are mean ± SD, unless otherwise indicated. † Based on the onset of the first non-Raynaud symptom attributable to SSc. †† T test. £ Chi-square test. ** Wilcoxon rank-sum test. * Can range from 0 to 12, with lower scores indicating worse dyspnea. ◊ Can range from 0 to 51, with higher scores indicating more severe thickening. CYC: cyclophosphamide; SLS; Scleroderma Lung Study; SSc: systemic sclerosis; FVC: forced vital capacity; mRSS: modified Rodnan skin score; IQR: interquartile range; QLF: quantitative extent of lung fibrosis on high-resolution computed tomography; WL: whole lung; ZM: zone of maximal involvement; QILD: quantitative extent of total interstitial lung disease (including fibrosis, honeycomb, and ground glass opacity); dcSSc: diffuse cutaneous SSc; lcSSc: limited cutaneous SSc; NA: not available.

Use of potential disease-modifying therapy. Of the 54 CYC-arm patients followed during Year 2 of SLS I, 10 began treatment with a glucocorticoid (GC; e.g., prednisone, prednisolone, methylprednisolone) at a dosage ≥ 10 mg daily (mean dose 14 mg daily) during this year "off study drug." None of these patients consumed any other immunosuppressant therapies during this time.

Among the CYC arm patients in SLS II, 32 began treatment with a GC at a dosage ≥ 10 mg daily (mean dose 18.0 mg) during the 24-month study period. In addition, 10 began treatment with potentially disease-modifying immunosuppressant therapy during Year 2 of the study (azathioprine: n = 2, MMF: n = 7, CYC: n = 1).

For both studies, the type, duration, and dosage of GC used varied widely. Moreover, many patients did not receive a stable dosage, frequently stopping and starting GC therapy or enduring long or short tapers.

There is no difference in the course of the FVC between CYC arms. After controlling for baseline FVC%-predicted and baseline QILD-WL, there was no difference in the course of FVC%-predicted over 24 months between the CYC arms of SLS I and II (Table 2, Figure 1). From 3 to 12 months, patients in both CYC arms experienced an increase in the FVC%-predicted, with no between-arm differences. There appeared to be a persistent increase in the FVC%-predicted from 12 to 21 months in the CYC arm of SLS II; however, there was no significant difference in the course of the FVC%-predicted between CYC arms from 12 to 21 months, nor from 21 to 24 months (Table 2). At 24 months, the mean values for the FVC%-predicted were essentially unchanged

in the SLS I–CYC arm (Figure 1). In contrast, at 24 months, the mean values for the FVC%-predicted in the SLS II–CYC arm improved by an average of +2.88% for the CYC arm (95% CI 1.19–4.58; $p < 0.05$).

The joint model also revealed that patients with a higher FVC%-predicted at baseline had an improved course of FVC%-predicted over 24 months (Table 2). Baseline QILD-WL score was not associated with the course of the FVC%-predicted.

There is no difference in the course of the DLCO between CYC arms. After controlling for baseline DLCO%-predicted and baseline QILD-WL, there was no difference in the course of DLCO%-predicted over 24 months between the CYC arms of SLS I and II (Supplementary Table 1, available with the online version of this article; Figure 2). In SLS I, the DLCO%-predicted declined from baseline to 12 months and subsequently stabilized in the following 12 months (Figure 2). In SLS II, the DLCO%-predicted appeared to increase from 12 to 21 months (Supplementary Table 1), but there was no difference in the course of the DLCO%-predicted between CYC study arms at 3–12 months, 12–21 months, or 21–24 months. Of note, one developed pulmonary hypertension (PH), requiring therapy in the CYC arm of SLS II; no patients developed PH requiring therapy in the CYC arm of SLS I during the 24-month study period.

The joint model also revealed that patients with a higher DLCO%-predicted at baseline had an improved course of DLCO%-predicted over 24 months (Supplementary Table 1, available with the online version of this article). Baseline QILD-WL score was not associated with the course of the DLCO%-predicted. Regardless of the baseline severity in the interstitial diseases measured by QILD-WL, subjects who were treated by CYC improved in FVC%- and DLCO%-predicted values.

Treatment with CYC is associated with improved course of mRSS in both CYC arms. In all patients [those with diffuse (dcSSc) and limited cutaneous (lcSSc) SSc combined], after adjusting for baseline mRSS, there was a steady decline in the mRSS over 24 months (Figure 3; Supplementary Table 2, available with the online version of this article). There was no significant difference in the course of the mRSS between CYC arms at 3–12 months, 12–21 months, or 21–24 months (Supplementary Table 2).

In patients with dcSSc (n = 49 for SLS I; n = 35 for SLS II), the rate of decline of the mRSS was greater within the first 12 months for both groups (Supplementary Figure 2 and Supplementary Table 3, available with the online version of this article). There was no significant difference in the course of the mRSS between CYC arms at 3–12 months, 12–21 months, or 21–24 months among patients with dcSSc (Supplementary Table 3).

In patients with lcSSc (n = 32 for SLS I; n = 30 for SLS II), the mRSS did not substantially change in either group (Supplementary Figure 3, available with the online version of this article). Further, there was no significant difference in the course of the mRSS between CYC arms at 3–12 months, 12–21 months, or 21–24 months among patients with dcSSc (Supplementary Table 4).

Not surprisingly, patients with a higher mRSS at baseline had a greater improvement in the course of the mRSS over 24 months for all patients ($p = 0.017$) and for patients with dcSSc ($p = 0.032$).

Table 2. Results of joint model analysis comparing the course of the FVC%-predicted between patients assigned to CYC in SLS I and II (n = 111).

Covariate	Estimated Effect	SE	p
Time (3–12 mos)*	0.251	0.111	0.024
Time (12–21 mos)*	0.034	0.114	0.766
Time (21–24 mos)*	–0.434	0.348	0.212
Baseline FVC%-predicted	1	0.053	< 0.0001
Baseline QILD-WL	0.026	0.048	0.588
Treatment arm assignment†	1.980	3.185	0.534
Treatment arm assignment × time interaction (3–12 mos) **	–0.012	0.172	0.944
Treatment arm assignment × time interaction (12–21 mos) **	0.214	0.171	0.211
Treatment arm assignment × time interaction (21–24 mos) **	–0.104	0.624	0.868
Treatment arm assignment × baseline QILD-WL	0.023	0.071	0.746

* The reference group is the CYC arm of SLS I; therefore, these time trends represent the trends observed in the CYC arm of SLS I. From 3 to 12 months, there was an increase in the FVC%-predicted in the CYC arm of SLS I (estimated effect –0.49), although this was not statistically significant. † Estimate for baseline differences in FVC%-predicted by treatment arm. **Trends observed in the CYC arm of SLS II compared with the CYC arm of SLS I. There were no significant between-group differences in these trends over the course of 24 months. FVC: forced vital capacity; CYC: cyclophosphamide; SLS: Scleroderma Lung Study; SE: standard error; QILD: quantitative extent of total interstitial lung disease; WL: whole lung.

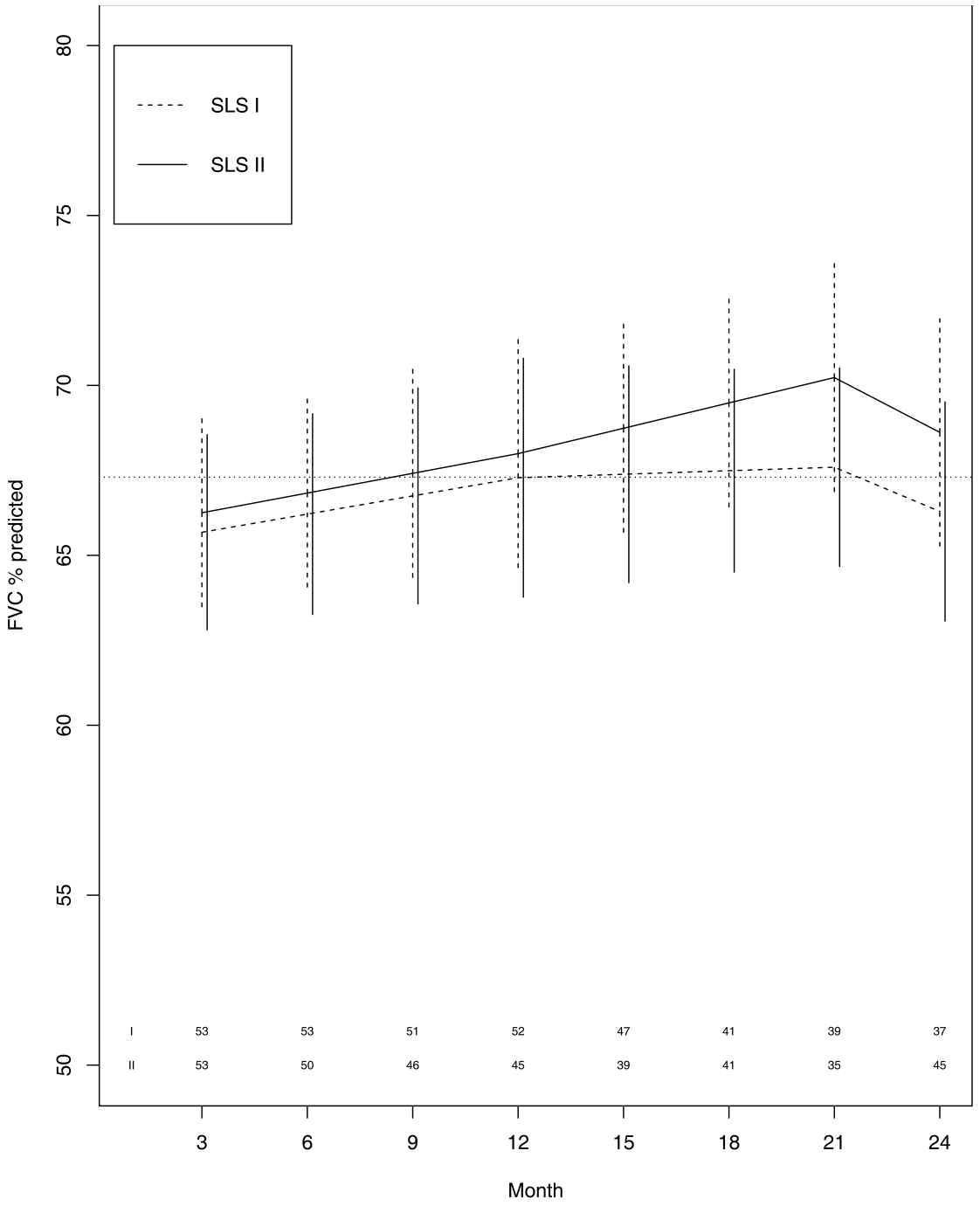

Figure 1. Course of the FVC% from 3 to 24 months in CYC patients in SLS I and II using joint model analysis. Prespecified covariates for this model included the baseline FVC%-predicted and baseline QILD-WL. The dotted line represents the mean baseline value for the entire cohort. FVC: forced vital capacity; CYC: cyclophosphamide; SLS: Scleroderma Lung Study; QILD-WL: radiographic extent of interstitial lung disease for the whole lung.

Safety analysis. In terms of predefined AE that would warrant clinical intervention and a change in therapy, there were similar rates of neutropenia (SLS I: 7; SLS II: 5) and pneumonia (SLS I: 6; SLS II: 4) between the CYC arms of SLS I and II (Table 3). However, hematuria occurred in numerically more CYC patients in SLS I compared with SLS II (SLS I: 10; SLS II: 2), while leukopenia (SLS I:19; SLS II: 30) and anemia (SLS I: 4; SLS II: 13) occurred in numerically more CYC patients in SLS II compared with SLS I. The majority of the anemia (70%) and leukopenia (91%) in SLS II–CYC patients occurred during the first year of the study.

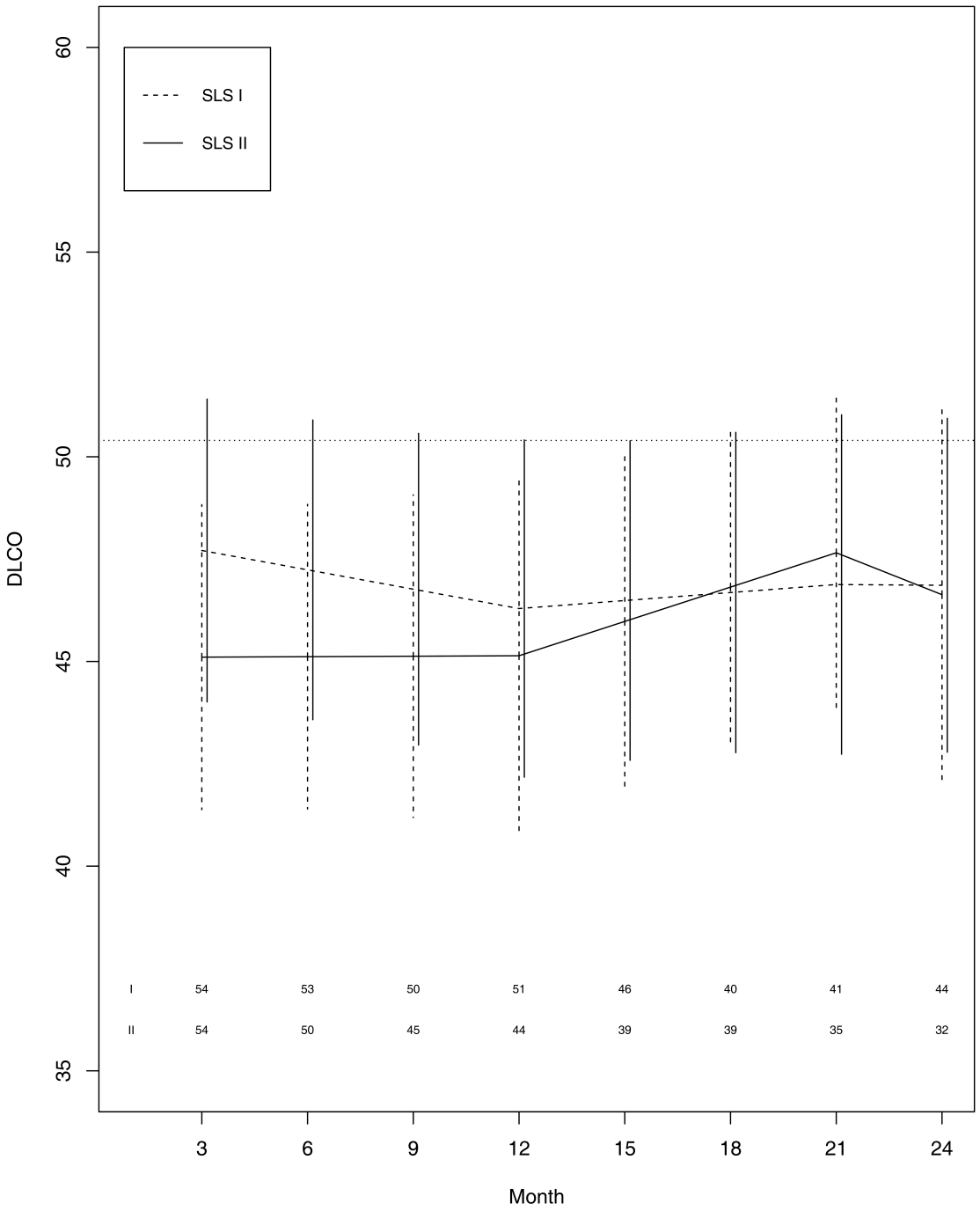

Figure 2. Course of the DLCO% from 3 to 24 months in SLS II patients assigned to MMF versus SLS I patients assigned to placebo using joint model analysis. Prespecified covariates for this model included the baseline DLCO%-predicted and baseline QILD-WL. The dotted line represents the mean baseline value for the entire cohort. SLS: Scleroderma Lung Study; QILD-WL: radiographic extent of interstitial lung disease for the whole lung.

In terms of SAE, 47 patients experienced an SAE in the SLS I–CYC arm compared with 22 patients in the SLS II–CYC arm. In both CYC arms, the majority of these SAE were judged by the Morbidity and Mortality Committee to not be related to treatment (72.3% for SLS I and 73.0% for SLS II) as described in Table 3. The number of deaths was greater in the SLS II–CYC patients (n = 11) compared with the SLS I-CYC patients (n = 6).

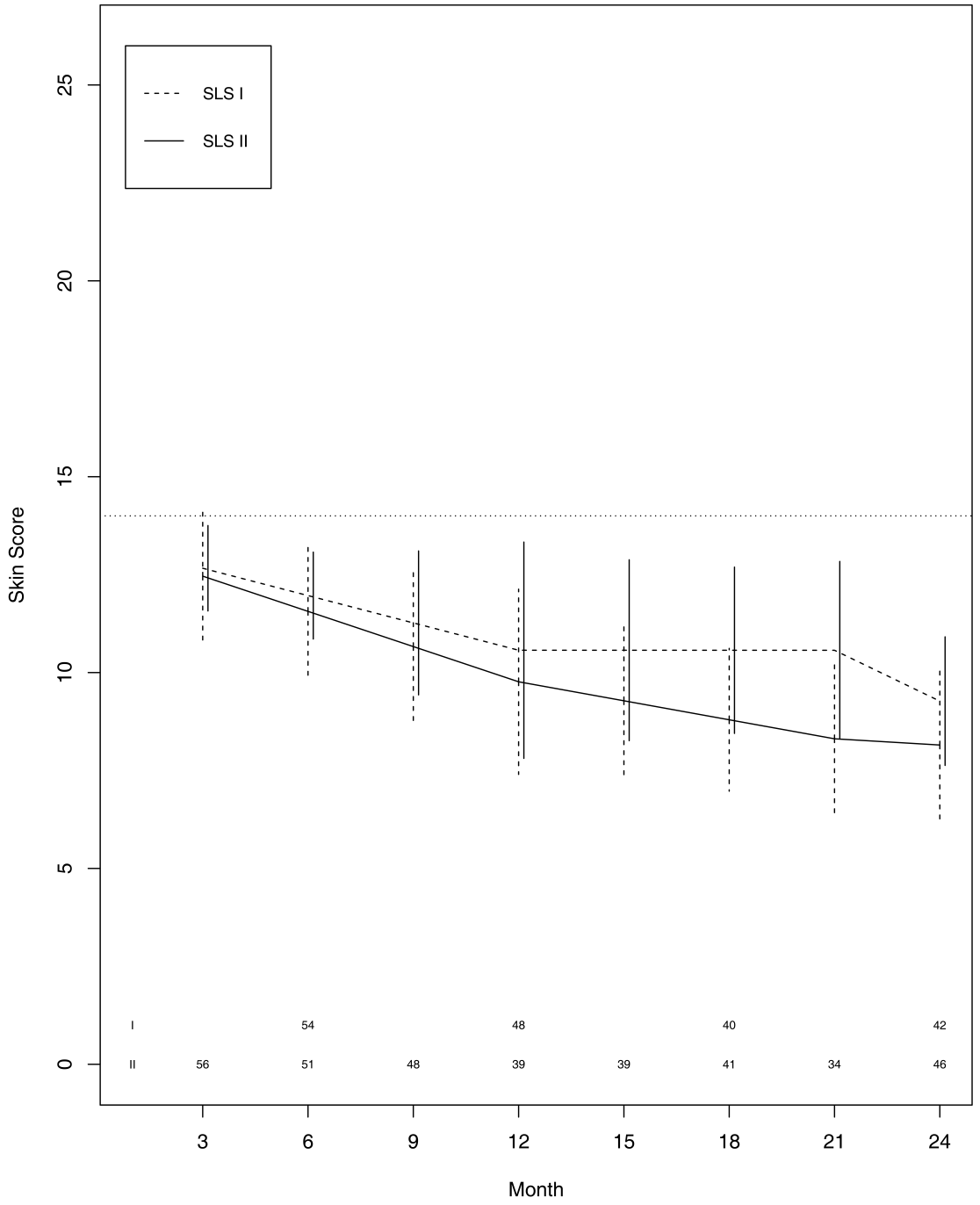

Figure 3. Course of the mRSS from 3 to 24 months in CYC patients in SLS I and II using joint model analysis. Prespecified covariates for this model included the baseline mRSS. The dotted line represents the mean baseline value for the entire cohort. SLS: Scleroderma Lung Study; mRSS: modified Rodnan skin score; CYC: cyclophosphamide.

DISCUSSION

Historically, CYC was the treatment of choice for progressive ILD in patients with SSc. Two randomized controlled trials, SLS I and SLS II, evaluated the effects of 1 year of CYC therapy compared with placebo (SLS I) and MMF (SLS II). In SLS II, the results seemed to suggest that CYC use was associated with a more sustained effect on treatment outcomes compared with SLS I. However, the analytic approaches used in these 2 studies differed. To our knowledge, our present study is the first to provide an in-depth analysis of outcomes for patients in the CYC arms from these 2 studies using a uniform analytic approach. The results

Table 3. Number of patients with adverse events (AE) and serious AE (SAE) from baseline to 24 months.

Variables	SLS I–CYC, n = 79	SLS II–CYC, n = 69
AE*		
Leukopenia	19	30
Neutropenia	7	5
Anemia	4	13
Hematuria	10	2
Pneumonia	6	4
SAE		
No. patients with SAE	47	22
Related to treatment†	13	8
Not related to treatment†	34	16
Death	6	11

* Predefined by protocol as likely to be related to study drug and to warrant protocol-defined management (except for pneumonia): anemia = Hgb < 10 g/dl or < 9 for those with Hgb < 11 at enrollment; leukopenia = WBC < 2500; neutropenia = neutrophils < 1000; thrombocytopenia = platelets < 100,000; hematuria > 25 red blood cells (or 10–15 red blood cells on > 1 urinalysis) in absence of urinary tract infection or menses. † According to consensus classification by Morbidity and Mortality Committee. SLS: Scleroderma Lung Study; CYC: cyclophosphamide; Hgb: hemoglobin; WBC: white blood cells.

reported herein demonstrate that efficacy outcomes were similar for both CYC arms.

Patients assigned to CYC in both SLS I and II experienced an improvement in the course of the FVC%-predicted during the first year of therapy, with no differences between study arms (Figure 1). Following cessation of CYC, the FVC%-predicted appeared to continue to increase from 12 to 21 months in the SLS II–CYC arm; however, there was no significant difference in the course of the FVC%-predicted between CYC arms from 12 to 21 months. The mean values for the FVC%-predicted were unchanged from baseline to 24 months in the SLS I–CYC arm, while there was a slight improvement in the FVC%-predicted in the SLS II–CYC arm of 2.88%, although it is unknown whether this small change represents a clinically meaningful improvement.

The use of potentially disease-modifying therapies in the second year of the study may have influenced the course of the FVC%-predicted during this time frame. For example, in SLS I, other than prednisone, no CYC participants started immunosuppressant therapy during Year 2[6]. However, 10 patients in the SLS II–CYC arm began immunosuppressant therapy during Year 2, and the majority started taking MMF[5]. It is possible that continued immunosuppression may have led to improved outcomes, although the paucity of patients receiving continued immunosuppression limits our ability to perform any meaningful analyses on this small subgroup. Further, there is likely a strong selection bias because patients were probably more likely to receive continued immunosuppression if they experienced progression of their ILD.

In addition to the FVC%-predicted, there was no difference in the course of the DLCO%-predicted between the CYC arms after controlling for baseline disease severity (Figure 2). In both studies, the DLCO%-predicted remained essentially unchanged from baseline to 24 months. Very few patients in either study developed PH during the 2-year study period.

In both joint models, higher baseline FVC and higher baseline DLCO were associated with an improved course of the FVC and DLCO, respectively. While the radiographic extent of ILD for the whole lung (QILD-WL) was associated with the course of the FVC and DLCO in univariate analysis, QILD-WL was not significantly associated with the course of the FVC and DLCO in the multivariate joint model analysis when the baseline FVC and DLCO measures were included as covariates. This may have resulted from collinearity because the QILD scores correlated with the FVC and DLCO.

Regarding cutaneous sclerosis, the mRSS declined to a similar degree in both CYC arms over 2 years (Figure 3). Patients with dcSSc experienced the greatest decline in the mRSS (Supplementary Figures 2 and 3, available with the online version of this article). Unlike the lung variables, the mRSS continued to decline in both CYC groups during the second year of the study while not taking treatment, an observation that is consistent with the natural history of cutaneous sclerosis in SSc[14]. Taken together, these findings suggest that continued immunosuppression (beyond 1 yr) among patients with SSc-ILD may be beneficial for ILD outcomes but may not be necessary for skin disease.

From a safety and tolerability standpoint, we observed differences in the rates of specific AE in the CYC arms from both studies. For example, hematuria occurred in numerically more CYC patients in SLS I compared with SLS II, while leukopenia and anemia occurred in numerically more CYC patients in SLS II compared with SLS I. The reasons for these disparities are unclear because the dosages of CYC used in both studies were similar. However, the number of patients who experienced these AE was relatively small in both studies; thus, these differences may be due to chance alone.

One striking observation was that over twice as many patients in the SLS I–CYC arm experienced an SAE compared with the SLS II–CYC arm. The definitions for SAE were identical for both studies. A possible explanation for this observation is that more patients withdrew from the study drug in the CYC arm of SLS II compared with SLS I, and perhaps these SLS II–CYC withdrawals occurred in patients who may have developed an SAE had they not withdrawn.

Interestingly, substantially more deaths occurred in the SLS II–CYC arm compared with the SLS I–CYC arm. Age may have contributed to the difference in death rates because patients in SLS II were older than patients in SLS I. However, given that this is an analysis of patients enrolled in 2 different

studies, it is impossible to discern the exact reason for the observed differences in SAE and death rates. Overall, the safety and tolerability results from these 2 trials suggest that CYC does not appear to be well tolerated and is associated with a high number of SAE, including death.

There are important limitations. First, comparing cohorts from 2 different trials can introduce bias. Time period bias is one potential source of bias because enrollment for SLS I and II concluded in 2004 and 2012, respectively. Further, without a randomization process, one cannot adequately control for differences in those unknown baseline features, which may affect ILD progression. Fortunately, the CYC arms from these 2 studies appeared relatively similar in terms of their key baseline features. Moreover, the patients for these 2 studies were recruited from similar academic centers (9 centers were the same for both trials) and were often treated by the same principal investigators[3,5].

A survival bias may also contribute to the diminished CYC-treatment effect in months 12 to 24. However, as stated, our joint model analysis specifically adjusts for non-ignorable missing data due to study dropout, treatment failure, or death.

Our study also has important strengths. First, the sample size is relatively large for an SSc-ILD interventional trial. Second, unlike many prior studies in this area, we did not evaluate an outcome measure at a single timepoint, but instead examined outcomes measured at many timepoints. Measuring ILD-related outcomes at multiple timepoints is likely a more meaningful reflection of ILD progression than a single outcome measurement.

In patients with symptomatic SSc-ILD, treatment with 1 year of oral CYC is associated with short-term improvements in the FVC%-predicted and the mRSS, but not the DLCO%-predicted. Following treatment cessation, the FVC-related treatment effect diminished in the SLS I–CYC arm, and to a lesser degree, in the SLS II–CYC arm. As described previously, CYC use in both studies was associated with a number of treatment-related AE and SAE, including a high death rate in SLS II. These findings suggest that alternate safe and effective therapy is still needed for SSc-ILD and that continued immunosuppression beyond 1 year may be necessary to achieve a sustained treatment response in patients with SSc-ILD.

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ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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