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Treatment with mycophenolate and cyclophosphamide leads to clinically meaningful improvements in patient-reported outcomes in scleroderma lung disease: *Results of Scleroderma Lung Study II*

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ABSTRACT

Objective: To determine whether treatment with cyclophosphamide (CYC) and mycophenolate mofetil (MMF) improve patient reported outcomes (PROs) among SSc patients with ILD.

Methods: This study examined PROs in SSc-ILD patients (N=142) who participated in Scleroderma Lung Study (SLS) II, a randomized controlled trial comparing MMF for 2 years versus oral CYC for 1 year followed by 1 year of placebo. Joint models were created to evaluate the course of PROs over 2 years. The difference in PRO scores from baseline to 24 months were measured, and the percentage of patients meeting the minimum clinically important difference (MCID) were calculated. Correlations between PRO and SSc-ILD disease severity measures were also examined.

Results: Treatment with CYC and MMF led to improvements in several PRO outcomes, with no between-treatment differences. Scores for the Transitional Dyspnea index (TDI) and St. George's Respiratory Questionnaire (SGRQ) improved significantly over 2 years, and 29%/24% and 28%/25% of participants in the CYC/MMF groups met or exceeded the MCID estimates for TDI and SGRQ, respectively. At baseline, the forced vital capacity (FVC)%-predicted did not correlate with the Baseline dyspnea index (BDI) or SGRQ. However, improvements in the FVC%-predicted were weakly associated with improvements in dyspnea (assessed by the TDI) and SGRQ scores.

Conclusion: Treatment with CYC and MMF improved overall HRQOL in patients with SSc-ILD. The relationship between PRO measures and the FVC was relatively weak, suggesting that PROs provide complementary information about treatment efficacy not captured by changes in the FVC alone in this patient population.

Key words: Interstitial lung disease, systemic sclerosis, mycophenolate, cyclophosphamide, patient reported outcomes, outcome measures

INTRODUCTION

Patient-reported outcomes (PROs) directly assess how patients feel and function from their own perspective. For complex, systemic diseases, such as systemic sclerosis, PROs play a central role in providing insight into a patient's experience living with this disease [1-3]. Specifically, PROs measure symptoms, such as dyspnea, and health-related quality of life

(HRQOL), and they may reveal treatment effects that are not captured by other measures, such as pulmonary function.

In SSc-ILD therapeutic research trials, PROs have included dyspnea indexes [4-6] (cough questionnaires [7, 8], and HRQOL surveys [4]. While other outcomes, such as the forced vital capacity (FVC)% predicted shed light on treatment-related changes in pulmonary physiology, only the PROs provide information about how a particular treatment affects a patient's experience with the disease. In some SSc-ILD trials, improvements in PRO scores have paralleled improvements observed in the FVC% predicted [4], while in other trials, changes in PRO scores do not parallel changes in the FVC% predicted [5]. These conflicting results suggest that PROs may be measuring distinct treatment-related effects that are important to consider in caring for patients with SSc-ILD.

The present study sought to evaluate changes in PROs in the Scleroderma Lung Study (SLS) II, a randomized controlled trial comparing the safety and efficacy of mycophenolate mofetil (MMF) and oral cyclophosphamide (CYC) for SSc-ILD [9]. The results of SLS II demonstrated that the FVC% predicted improved significantly over 24 months in both treatment arms (average FVC% predicted improvement: MMF 3.3%, CYC 3.0%) [9]. The primary objective of this study was to investigate how specific PROs changed in response to therapy with CYC and MMF. A secondary goal was to determine whether changes in PROs correlate with changes in the FVC% predicted in SLS II.

PATIENTS AND METHODS

Patient population

Participants of SLS II were all adults with SSc-ILD (18-75 years) and either limited (lcSSc) or diffuse (dcSSc) SSc [10] who had active ILD, defined as the presence of both a restrictive to borderline restrictive ventilatory impairment (FVC<80-85% but ≥ 45% predicted) AND the presence of any ground glass opacity (GGO; hazy opacity through which normal lung markings can be discerned) on high-resolution computed tomography (HRCT). Participants also had to have exertional dyspnea based on the Mahler Baseline Dyspnea Index (BDI) [11] and a disease duration of less than or equal to 7 years from the onset of the first non-Raynaud's symptom of SSc. Key exclusion criteria included pulmonary hypertension, clinically significant

abnormalities on HRCT not attributable to SSc, smoking within the past 6 months, and evidence of significant airflow obstruction, defined as a ratio of the forced expired volume in 1 second (FEV_1) to the FVC% predicted of ≤65%. The study was approved by the Office of Human Research Protection Program at UCLA (IRB#11-002659-CR-00005) and by the IRBs of all 14 participating centers.

SLS II Study Design

Participants in SLS II were randomized to either oral CYC for one year followed by one year of placebo or MMF for 2 years [9]. The primary endpoint for the study was the course of the FVC% predicted measured every 3 months over 2 years. Thoracic HRCT imaging was obtained at baseline and 2 years, and a Computer Aided Design (CAD) scoring system was employed to provide quantitative measures of different patterns of ILD as previously described [12]. Quantitative ILD (QILD) score was the sum of all abnormally classified scores, including scores for quantitative lung fibrosis (QLF, linear reticular markings with architectural distortion), GGO and honeycomb changes (clustered air-filled cysts with dense walls). Scores were calculated as a percentage of total counted voxels for both the whole lung (WL), including both lungs, and for the zone of maximal involvement (ZM). The complete details of the SLS II protocol appear in the supplementary web appendix accompanying the main SLS II publication [9].

Patient reported outcomes

The following PROs were examined in SLS II: Short Form 36 (SF-36) [13], Health Assessment Questionnaire (HAQ) disability index (DI) [14], Baseline and Transitional Dyspnea Index (BDI) [11] and TDI [15], the Leicester Cough Questionnaire (LCQ) [16], St. George's Respiratory Questionnaire (SGRQ) [17], and the UCLA Scleroderma Clinical Trials Consortium Gastrointestinal Tract (GIT) 2.0 [18]. Each PRO aimed to address a unique aspect of the disease experience of SSc-ILD. For instance, the SF-36 measures HRQOL and consists of 8 scales with both physical and mental components of HRQOL [13]. For this analysis, we focused on the summary scores for the physical components (PCS) and mental components (MCS). The HAQ-DI measures functional ability in patients with musculoskeletal conditions [14] and has been studied extensively in patients with SSc [19, 20].

The PROs targeting respiratory symptoms included the BDI, TDI, LCQ and SGRQ. The BDI assesses patients' perception of their breathlessness at baseline based on 3 categories (e.g., functional impairment, magnitude of task and magnitude of effort); whereas, the TDI measures the change in dyspnea from baseline in each of these categories, the results of which are summed into a total score [11, 15]. The LCQ is a 19-item HRQOL measure of chronic cough that is highly responsive to change [16]. It is a patient-derived questionnaire; therefore, it contains items, domains and response scales that are clinically meaningful to the patient. The SGRQ is a 50-item questionnaire that was originally designed to measure the impact of overall health, daily life and perceived well-being in patients with obstructive airway disease [21]. However, prior studies have demonstrated that it correlates well with other measures of disease activity in patients with SSc-ILD [17] and is responsive to change in patients with dcSSc [22].

The UCLA SCTC GIT 2.0 is an instrument that measures gastrointestinal tract involvement in SSc and contains 34 items from 7 scales (e.g. reflux, distention/bloating, diarrhea, fecal soilage, constipation, emotional well-being and social functioning) [18]. It has been translated into several languages and has also been found to discriminate between patients with and without objective evidence of gastrointestinal tract involvement [23]. A recent study from 6 international SSc centers demonstrated that the reflux scale is sensitive to change in SSc patients with active GERD [24].

The SF-36, HAQ-DI, LCQ and SGRQ were assessed at baseline and every 3 months during the study, while the TDI was assessed at baseline and every 6 months during the study. The GIT 2.0 was assessed at baseline and at 12 and 24 months.

Statistical Analysis

Summary statistics were generated for the SF-36, HAQ-DI, BDI, LCQ, SGRQ, and GIT 2.0 at baseline. Between group comparisons in baseline PRO scores were performed using the Student's *t*-test.

The percentage of participants who met or exceeded the threshold for the minimum clinically important difference (MCID) for each of the PROs was analyzed using the Chi-square test. The MCID is the smallest improvement in the PRO score necessary for the patients to perceive an improvement that is meaningful to them [25]. MCID estimates are captured at a group level. The MCID for each PRO is summarized in Table 1 [26-31].

We used Pearson's correlation coefficient was used to examine the relationship between baseline PROs scores and extent of physiologic impairment (baseline FVC% predicted and diffusing capacity for carbon monoxide [DL_{CO}]), structural lung disease (QLF and QILD), modified Rodnan skin score (mRSS), as well as the relationship between the change in PRO scores and the change in FVC% predicted, DLCO% predicted, mRSS, QLF and QILD scores. We included all of the radiographic imaging scores because we wanted to understand whether changes in certain structural parameters correlated better with PROs (i.e. improvement in the total lung versus improvement in the zone of maximum involvement). Pearson correlation coefficients were interpreted as proposed by Cohen [32]: 0.1, small correlation; 0.3, medium correlation; 0.5, large correlation. We did not correct for multiple hypothesis testing.

For the SGRQ, TDI, and HAQ-DI, an inferential joint model was used to examine the course of the PRO score over the course of the study. The joint model consisted 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 (i.e. likely related to disease or treatment and therefore not random) [33]. Fixed effects for the longitudinal portion of the joint model included treatment assignment, a time trend, the PRO at baseline and a treatment group by time trend interaction. The time trend was modeled by linear splines with knots at 12 and 21 months, except for TDI which only included a knot at 12 months since TDI was only collected every 6 months.

Statistical analyses were performed using SAS version 9.4 except for the joint modeling which was conducted in R. P-values less than 0.05 were considered statistically significant.

RESULTS

Main SLS II study findings

In SLS II, 73 patients with SSc-ILD were randomized to CYC and 69 to MMF. Participants were predominantly women (74%) with an average age of 52 years, an average disease duration of 2.6 years, and a moderate degree of restriction on pulmonary function testing [9]. Both treatment arms had similar scores for PROs at baseline (Please see Supplementary Table S1 for a complete list of baseline characteristics). Moreover, both treatment arms experienced a significant improvement in the course of the FVC% predicted over 24 months with

an average absolute improvement of 3.0 and 3.3 in the CYC and MMF arms, respectively [9]. In addition to improvement in the FVC% predicted from baseline, treatment with MMF and CYC also led to significant improvements in the course of the mRSS, as well as the QILD-WL scores, with no between-treatment differences [9, 34].

Treatment with CYC and MMF improves breathlessness and respiratory HRQOL

Supporting the results of the primary SLS II manuscript, the present analysis found significant improvements in overall HRQOL in patients who participated in SLS II. Participants randomized to CYC and MMF experienced significant improvements in self-reported dyspnea and respiratory-related HRQOL based on the TDI and SGRQ, respectively. Figure 1 demonstrates the course of the TDI in SLS II based on the joint model analysis. At 12, 18 and 24 months, both the CYC and MMF arms experienced significant improvements in breathlessness relative to baseline as measured by the TDI (Figure 1; Supplementary Table S2). There was no difference in the course of the TDI between participants randomized to CYC versus MMF (Supplementary Table S2).

Similar to the TDI, the course of the SGRQ improved over the course of SLS II based on the joint model analysis (Figure 2; Supplementary Table S3). At 15, 18 and 24 months, participants randomized to CYC experienced statistically significant improvements in the SGRQ relative to baseline, while at 18 and 24 months, participants randomized to MMF experienced significant improvements in the SGRQ relative to baseline. There was a slight increase in SGRQ scores (worsening) from 21 to 24 months when participants who had prematurely stopped study drug were invited to return for the final study visit. There was no difference in the course of the SGRQ between participants randomized to CYC versus MMF (Supplementary Table S3).

The course of the HAQ-DI also improved over the course of the study, although the change was not statistically significant within or between treatment arms (Supplementary Figure S1; Supplementary Table S4). For a summary of the change scores for each PRO, please see Supplementary Table S5).

Proportion of participants treated with MMF and CYC whose PRO scores improved more than the MCID

For each PRO, a number of participants in the CYC and MMF arms met or exceeded the MCID estimates at both 12 and 24 months (Table 2). There were no between treatment arm differences in the proportion of participants whose PRO scores improved more than the MCID at either time point. For the SGRQ, 28% and 24% of participants randomized to CYC and MMF, respectively met or exceeded the MCID for this outcome at 24 months. For the TDI, 29% and 24% of participants randomized to CYC and MMF, respectively met or exceeded the MCID for this outcome at 24 months. For the HAQ-DI, 17% and 14% of participants randomized to CYC and MMF, respectively met or exceeded the MCID for this outcome at 24 months.

Overall generic health status also improved for a number of participants based on the results of the SF-36 (Table 2). In participants randomized to both CYC and MMF, 17% of participants met or exceeded the MCID for the SF-36 PCS at 24 months. For the SF-36 MCS, 20% and 21% of participants randomized to CYC and MMF, respectively met or exceeded the MCID for this outcome at 24 months. A relatively smaller percentage of participants met or exceeded the MCID for the total GIT 2.0 score at 24 months (CYC 13%; MMF 10%) (Table 2).

Relationship between PRO measures and objective SSc-ILD disease severity measures

At baseline, the FVC% predicted did not correlate with any of the PRO measures, except for a weak correlation with the LCQ (Table 3). There were medium correlations between the DLCO% predicted and the LCQ and SGRQ (Table 3). The BDI, SGRQ, and LCQ all correlated with the extent of quantitative radiographic fibrosis and ILD, demonstrating that patients with more self-reported dyspnea at baseline had worse diffusing capacity and increased extent of radiographic fibrosis. The HAQ-DI did not correlate with any of the objective measures of SSc-ILD disease severity, nor did the SF-36 MCS, GIT 2.0 total score, or GIT 2.0 reflux score (Table 3).

The change in the FVC% predicted significantly correlated with the change in the SF-36, HAQ-DI, TDI, and SGRQ at 24 months, indicating that patients who experienced an improvement in their FVC% predicted experienced parallel improvements in their dyspnea and HRQOL (Table 4). Of all of the PRO measures, the change in breathlessness (assessed by the TDI) correlated significantly with changes in the most objective measures of SSc-ILD severity (e.g., FVC% predicted, DLCO% predicted, QLF-WL, QILD-LM, QILD-WL), whereas the change in SGRQ correlated only with the change in the FVC% predicted, DLCO% predicted and

the QILD-LM, but not with changes in the other radiographic ILD and fibrosis scores. Similarly, the change in the HAQ-DI only modestly correlated with the change in the FVC% predicted and DLCO% predicted (Table 4).

The relationship between cutaneous sclerosis and PROs in SSc-ILD patients

The baseline mRSS correlated significantly with the baseline HAQ-DI and LCQ in all patients and in patients with dcSSc, but not in patients with lcSSc (Table 3). At 24 months, 42% and 49% of patients randomized to the CYC and MMF arms, respectively, met or exceeded the MCID for mRSS (defined as a decline of 5 points). An improvement in the mRSS from baseline to 24 months correlated significantly with an improvement in the SF-36, HAQ-DI, and the TDI in all patients (Table 4). Improvements in the mRSS correlated significantly with improvements in the SF-36 PCS, HAQ-DI and TDI in patients with dcSSc, but only an improvement in the HAQ-DI was associated with an improvement in the mRSS in patients with lcSSc (Table 4).

Of note, there were no significant correlations between baseline mRSS and FVC% predicted in all patients, or in patients with dcSSc or lcSSc. There was a significant correlation between improvement in the mRSS and an improvement in the FVC% predicted in all patients (r= -0.24) and in patients with dcSSc (r= -0.28), but not in patients with lcSSc.

DISCUSSION

Treatment with immunosuppression is typically the first line therapeutic approach for patients with SSc-ILD [35]. The results of this study affirm that this approach improves PRO measures in patients with this condition, in addition to lung function and radiographic measures of ILD. Specifically, this study found that treatment with MMF and CYC led to significant and clinically meaningful improvements in self-reported dyspnea, health status and physical function in patients with SSc-ILD.

While the FVC is frequently used as the primary outcome measure in SSc-ILD clinical trials, changes in the FVC may not consistently translate into clinically meaningful improvements from a patient's perspective. For example, in the SENSCIS trial, SSc-ILD patients treated with nintedanib had a lower rate of annual FVC decline than those receiving placebo

(treatment difference of 41 mL); however, there was no significant difference in PROs (based on the SGRQ, or HAQ-DI) between treatment groups [5]. In contrast, both SLS I [6] and our current analyses showed clinically meaningful improvements in PROs with treatment for SSc-ILD. Both SLS II [9] and SENSCIS [5] had similar baseline characteristics (FVC% predicted, DLCO% predicted, disease duration, mRSS, and SGRQ); however, there are several plausible explanations for these discrepancies. First, in SLS II [9], there was an overall trend for improvement in the FVC% predicted, whereas in the SENSCIS [5], there was an overall trend for a decline in the FVC. Second, PROs capture the overall impact of an intervention on the whole person. Treatment with mycophenolate and cyclophosphamide favourably affects extra-pulmonary manifestations of SSc, including cutaneous sclerosis, and this may in turn affect PRO outcomes [36]. Our findings indicate that improvements in cutaneous sclerosis, particularly among patients with dcSSc, are associated with improvements in PROs (e.g., HAQ-DI, TDI and SF-36 PCS).

The present results found no significant correlation at baseline between the FVC % predicted and dyspnea (BDI) or HRQOL, with the exception of a weak correlation with the LCQ. On the other hand, at baseline, the DLCO % predicted and quantitative extent of ILD and fibrosis scores significantly correlated with the BDI and SGRQ. These findings suggest that when evaluating disease severity of SSc-ILD, these additional assessment measures may provide a more comprehensive understanding of a patient's experience with the disease and could help inform treatment decisions.

We did find that an improvement in the FVC% predicted and DLCO% predicted was significantly associated with an improvement in HRQOL (SF-36, HAQ-DI, SGRQ) and dyspnea (TDI). These results illustrate that underlying changes in lung function and physiology may lead to meaningful changes in how a patient feels and functions. Consistent with this hypothesis, our prior analysis of SLS-I and II demonstrated that clinically meaningful improvements in the FVC% predicted were associated with improvements in PCS, TDI, and HAQ-DI [37].

We also examined the course of the TDI and SGRQ using a joint model approach to adjust for non-ignorable missing data and baseline disease severity and demonstrated significant improvements in these measures over the two year trial. For the TDI, there was a steady increase (improvement) in TDI scores during the trial in both treatment groups. Similarly, there was a steady decrease (improvement) in SGRQ scores during the trial in both treatment groups. Both

the TDI and SGRQ continued to improve in year two, even in patients randomized to one year of CYC followed by one year of placebo. Of note, 10 participants in CYC arm began treatment with potentially disease-modifying immunosuppressant therapy during year two of the study (Azathioprine [N=2], MMF [N=7], CYC [N=1]) [38], raising the possibility that the improvements that occurred during this time period could have been influenced by this additional therapy. In SLS I, we also appreciated significant improvements in the course of the TDI beyond the 12-month treatment period (persisted until 18 months), suggesting that the effects of CYC persist even after the treatment is stopped for at least 6 months [39].

We observed a slight worsening of SGRQ scores at month 24 compared with month 21 in both treatment groups. This was likely due to the fact that patients who withdrew from active treatment during the study were encouraged to return for the final 24-month study visit; therefore, this SGRQ assessment included participants who were not on active therapy.

The improvements appreciated in the joint model analysis of the SGRQ and TDI mirrored the improvements we observed in the joint model of analysis of the FVC% predicted in SLS II [9]. The peak improvement in the FVC% predicted in both treatment arms occurred at 21 months. In the present analysis, we also observed peak improvements in the SGRQ at this time point (the TDI was not obtained at 21 months). These findings further support the results of our correlation analyses demonstrating that improvements in lung function are accompanied by parallel improvements in patients' perception of their breathlessness.

Changes in quantitative radiographic scores for lung fibrosis and ILD correlated poorly with changes in all of the PROs with the exception of dyspnea as assessed by the TDI. These findings suggest that the relationship between the radiographic progression of ILD and how a patient feels and functions is likely influenced by other factors. These factors could include a patient's level of physical conditioning and the presence of comorbidities that limit mobility, such as arthritis. However, the participants in this trial did experience improvements in their overall health status (e.g. SF-35 MCS, SF-36 PCS, HAQ-DI). Taken together, these results may signify that treatment with CYC and MMF improves health outcomes in patients with SSc by also exerting beneficial effects on extra-pulmonary features of SSc (e.g., improvements in cutaneous sclerosis and arthritis).

The results of this study should be interpreted in the context of specific limitations. A substantial number of patients withdrew prematurely from active treatment during the study

(CYC: 44%; MMF: 30%). Although the joint model analysis adjusts for non-ignorable missing data from drop-outs [33], the high attrition rate in this trial could lead to biased estimates. We are reassured, however, that the improvements we observed in all of the PROs were robust and sustained over the course of the trial. Another limitation is that while most of the PROs were assessed every 3 months, the TDI was only assessed every 6 months. Additional data points for the TDI, especially earlier in the course of the trial, may have allowed us to further explore how breathlessness changes in response to treatment with CYC and MMF. Nonetheless, the joint model results clearly demonstrate an improvement in the course of the TDI with these therapies. Finally, the MCIDs estimates applied in the manuscript may be influenced by different aspects of the disease and other medical conditions. The data should be interpreted with this caveat in mind.

Strengths of this work include the scientific rigor of SLS II, a study which utilized the expertise of experienced SSc investigators at each study site and went to great lengths to ensure quality data collection and management. Another strength of this study is the use of a diverse array of PROs. Since SSc is a systemic disease affecting multiple organ systems, it is important to understand how various PROs change in response to particular treatments. As new treatment options for SSc emerge, understanding how these various treatment options affect different aspects of a patient's overall health may help guide treatment selection and continuation.

In summary, treatment with oral CYC and MMF led to clinically meaningful improvements in overall health status, function, and breathlessness in patients with SSc-ILD, bearing in mind the limitations noted above. Improvements in breathlessness paralleled improvements in lung function to a modest degree, despite the finding that the baseline level of restrictive ventilatory impairment did not correlate with how a patient felt. Above all, the findings of this study demonstrate that a comprehensive evaluation combining pulmonary physiology, radiographic extent of fibrosis and patient-reported outcomes is essential to understanding the impact of treatment on progression of ILD in SSc.

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TABLES

Table 1. Minimum clinically important difference (MCID) scores for the PRO instruments examined in SLS II

Instrument	Description	MCID	Interpretation
SF-36 [26]	Measures health status	>=5	Increase in score indicates improvement

HAQ-DI [27]	Measures functional ability	<=-0.14	Decrease in score indicates improvement
TDI [29]	Measures dyspnea	>=1	Increase in score indicates improvement
LCQ [30]	Measures cough	>=1.5	Increase in score indicates improvement
SGRQ [31]	Measures health status and well-being	<=-4.0	Decrease in score indicates improvement
GIT 2.0 (total score) [28]	Measures gastrointestinal tract involvement	<-0.21	Decrease in score indicates improvement

Table 2. Number of participants meeting the minimum clinically important difference (MCID) scores for the PRO instruments examined in SLS II at 12 and 24 months

PRO	N (%) at 12 months		P-value*	N (%) at 24 months		P-value*
	CYC	MMF		CYC	MMF	
SF-36 PCS†	19 (16.9%)	17 (15.0%)	0.55	18 (17.0%)	18 (17.0%)	1
SF-36 MCS‡	23 (20.4%)	22 (19.5%)	0.67	21 (19.8%)	22 (20.8%)	0.84
HAQ-DI	20 (17.7%)	15 (13.3%)	0.23	18 (17.0%)	15 (14.2%)	0.53
TDI	21 (21.9%)	19 (19.8%)	0.56	23 (29.1%)	19 (24.1%)	0.31
LCQ	17 (15.6%)	11 (10.1%)	0.17	16 (15.4%)	13 (12.5%)	0.51
SGRQ	31 (27.7%)	28 (25.0%)	0.44	29 (27.6%)	25 (23.8%)	0.5
GIT 2.0 (total score)	16 (14.3%)	11 (9.8%)	0.23	14 (13.3%)	10 (9.52%)	0.38

* P-value for between treatment arm differences.

† Physical component summary of SF-36.

‡ Medical component summary of SF-36.

Table 3. Baseline correlations between PROs and objective measures of SSc-ILD disease severity in SLS II.

	FVC%	DLCO%	QLF-ZM	QLF-WL	QILD-ZM	QILD-WL	mRSS All	mRSS dcSSc	mRSS lcSSc
SF-36 PCS	0.05	0.18*	-0.02	-0.07	-0.13	-0.16	-0.14	-0.03	0.18
SF-36 MCS	0.1	0.06	-0.08	-0.12	-0.13	-0.12	-0.01	0.00	-0.09
HAQ-DI	0.07	0.01	-0.10	-0.07	0.01	0.04	**0.41***	**0.30***	-0.01
BDI	0.09	0.22*	-0.18*	-0.19*	-0.25*	-0.25*	0.11	0.18	0.07
LCQ	0.20*	**0.33***	-0.27*	**-0.32***	**-0.32***	**-0.33***	0.26*	0.29*	0.08
SGRQ	-0.14	**-0.30***	0.21*	0.29*	**0.30***	**0.33***	-0.11	-0.15	-0.07
GIT 2.0 (Total score)	-0.08	-0.06	-0.09	0.03	-0.02	0.06	-0.04	-0.11	-0.05
GIT 2.0 (Reflux)	-0.06	-0.09	-0.10	0.02	0.00	0.07	-0.04	-0.24*	0.08

* P<0.05 (Bold denotes medium correlation coefficients (*r*>=0.3)).

Table 4. Correlations between the change in PROs and the change in objective measures of SSc-ILD disease severity in SLS II from baseline to 24 months.

	FVC%	DLCO%	QLF-ZM	QLF-WL	QILD-ZM	QILD-WL	mRSS All	mRSS dcSSc	mRSS lcSSc

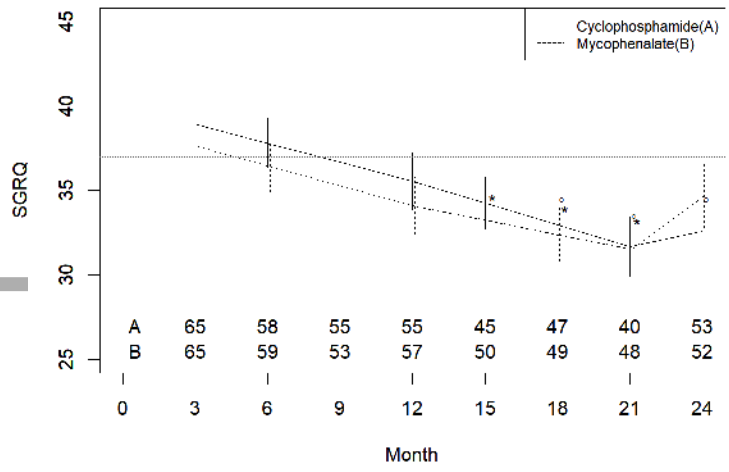
SF-36 PCS	**0.30***	0.29*	-0.14	-0.27*	-0.18	-0.20	**-0.30***	**-0.37***	-0.008
SF-36 MCS	0.08	0.15	0.08	-0.02	0.06	0.08	0.05	0.03	-0.04
HAQ-DI	**-0.32***	**-0.34***	0.02	0.04	0.07	0.00	**0.36***	**0.41***	**0.31***
TDI	**0.42***	0.28*	-0.14	-0.24*	-0.26*	-0.29*	**-0.35***	**-0.47***	0.05
LCQ	0.06	0.19	0.12	-0.04	-0.12	-0.15	-0.06	-0.09	0.04
SGRQ	-0.29*	**-0.32***	0.03	0.14	0.21*	0.15	0.14	0.2	0.08
GIT 2.0 (Total score)	-0.13	-0.12	-0.02	0.03	0.04	0.02	0.14	0.12	0.21
GIT 2.0 (Reflux)	-0.05	-0.09	-0.06	0.07	0.10	0.17	0.11	0.07	0.24

* P<0.05 (Bold denotes at least medium correlation coefficients [*r* >=0.3]).

FIGURE LEGENDS

Figure 1. Course of the SGRQ over 24 months by treatment arm. The solid line represents CYC and the dotted line represents MMF. The horizontal line represents the mean baseline SGRQ for the entire SLS II cohort. The * represents a significant change from baseline within the MMF arm at 15, 18, and 21 months. The º represents a significant change from baseline within the CYC arm at 18, 21, 24 months. Please see Supplemental Table S3 for complete summary of joint model results.

Figure 2. Course of the TDI over 24 months by treatment arm. The solid line represents CYC and the dotted line represents MMF. The horizontal line represents the mean baseline BDI for the entire SLS II cohort. The ***** represents a significant change from baseline within the MMF arm at 12, 18, and 24 months. The ^{o} represents a significant change from baseline within the CYC arm at 12, 18, 24 months. Please see Supplemental Table S2 for complete summary of joint model results.



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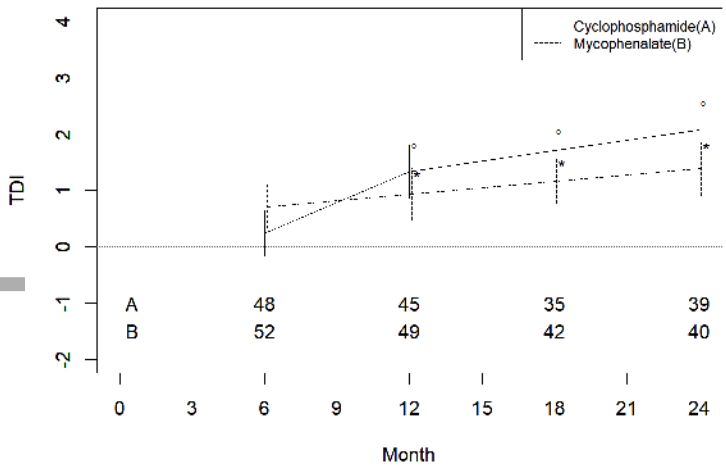

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