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Mycophenolate versus Placebo for Systemic Sclerosis-Related Interstitial Lung Disease: An Analysis of Scleroderma Lung Studies I and II

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Abstract

Objective—To compare mycophenolate (MMF) with placebo for the treatment of systemic sclerosis-related interstitial lung disease (SSc-ILD).

Methods—Participants enrolled in the placebo arm of Scleroderma Lung Study (SLS) I and the MMF arm of SLS II were included. SLS I randomized participants to oral cyclophosphamide (CYC) versus placebo for 1 year, while SLS II randomized participants to MMF for 2 years versus oral CYC for 1 year followed by 1 year of placebo. Eligibility criteria for SLS I and II were nearly identical. The primary outcome was FVC%-predicted and key secondary outcomes included the DLCO%-predicted, skin score, and dyspnea. Joint models were created to evaluate the treatment effect on the course of these outcomes over 2 years.

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Results—SLS II-MMF (N=61) and SLS I-placebo (N=61) participants had similar baseline characteristics for gender, disease duration, SSc subtype, extent of skin disease and FVC%-predicted. SLS II-MMF patients were slightly older (mean[SD] years: 52.6[9.7] vs. 48.1[12.4]; P=0.015) and had a higher DLCO%-predicted (mean[SD]: 54.0[11.1] vs. 46.2[13.3]; P=0.0002) than SLS I-placebo participants. After adjusting for baseline disease severity, treatment with MMF in comparison with placebo was associated with an improved course of FVC%-predicted (P<0.0001), DLCO%-predicted (P<0.001), skin score (P<0.0001), and dyspnea (P=0.0112) over 2 years.

Conclusions—Although there are inherent limitations in comparing participants from different trials, treatment with MMF was associated with improvements in physiologic outcomes and dyspnea compared with placebo, even after accounting for baseline disease severity. These results further substantiate the use of MMF for the treatment of SSc-ILD.

Interstitial lung disease (ILD) accounts for the majority of deaths in patients with systemic sclerosis (SSc).[1, 2] Historically, randomized controlled trials have favored the use of cyclophosphamide (CYC) for treating SSc-ILD. [3, 4] Given concerns regarding the potential long-term toxicity associated with CYC use, mycophenolate mofetil (MMF) has emerged as an alternative treatment agent for SSc-ILD.[5] Uncontrolled studies have demonstrated that MMF may prevent progression of SSc-ILD.[6–12]

To further explore the safety and efficacy of MMF in SSc-ILD, Tashkin and colleagues designed the Scleroderma Lung Study (SLS) II to directly compare CYC with MMF for the treatment of SSc-ILD.[13] The study demonstrated that the majority of participants in the MMF (72%) arm showed improvements in the forced vital capacity (FVC%)-predicted.[13] However, as the study design lacked a placebo arm, it has been difficult to interpret the absolute magnitude of the treatment effect for MMF when compared to the natural history of SSc-ILD. A proportion of patients with SSc-ILD exhibit intrinsically stable ILD that fails to progress even in the absence of treatment.[14]

To address this shortcoming, the present study compared outcomes for patients assigned to the MMF arm of SLS II with patients assigned to the placebo arm of SLS I. The primary objective was to determine whether patients assigned to MMF experienced an improvement in the course of the FVC%-predicted over 24 months compared with patients assigned to placebo. This study also aimed to compare secondary efficacy outcomes and the safety profiles for patients in these two groups.

PATIENTS AND METHODS

Study participants

All participants enrolled in the MMF arm of SLS II [13] and the placebo arm of SLS I [3] were included in this analysis. Participating centers and investigators were similar for both trials. Eligibility criteria for both studies were also similar. Common inclusion criteria included age ≥18 years, duration of disease ≤7 years from onset of the first non-Raynaud's symptom of SSc, FVC 40–85% predicted (SLS I) or 40–80% predicted (SLS II), hemoglobin-adjusted single-breath diffusing capacity for carbon monoxide (DLCO) ≥40% predicted (or 30–39% predicted if no evidence of clinically significant pulmonary

hypertension), and evidence of *any* ground glass opacity (GGO), i.e., hazy parenchymal opacity, on high resolution computed tomography (HRCT) of the chest in the presence or absence of reticular opacity or architectural distortion, as an indication of "active" disease.

The only difference between SLS I and SLS II entry criteria related to bronchoscopy. In SLS I, patients were encouraged to undergo a screening bronchoscopy and considered eligible if they had ≥3% neutrophils and/or ≥2% eosinophils in bronchoalveolar lavage fluid even if they had a HRCT scan that did not show any GGO. Sixteen out of the 162 randomized participants (9.2%) in SLS I were included based on these criteria. Although they did not have GGO, all of these patients did exhibit evidence of fibrosis on HRCT. Bronchoscopy was not performed in SLS II and all patients were required to have GGO on HRCT. Exclusion criteria for both studies were nearly identical.[3,13]

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 one year, followed by an additional year of observation off-treatment as previously published.[15] 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 gm/day in divided doses) for 2 years or oral CYC (titrated as tolerated to 2 mg/kg one daily) for 1 year followed by an additional year on placebo using a double-dummy design to maintain the blinding.[13]

SLS I and II Assessment Measurement

Baseline measurements included the following physiological variables: spirometry (forced vital capacity [FVC], forced expired volume in 1 second [FEV_1]), lung volumes (functional residual capacity [FRC], residual volume [RV] and total lung capacity [TLC] by whole-body plethysmography or helium dilution), diffusing capacity for carbon monoxide (DLCO) and the ratio of DLCO to alveolar volume (DL/VA).

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).[16,17] In SLS I, an interview-administered paper version of the BDI/TDI was used,[16] while in SLS II a self-administered computer-assisted version of the BDI/TDI was used.[17] The Modified Rodnan Skin Score (MRSS),[18] was used to assess cutaneous sclerosis. The MRSS [18] was performed every 3 months in SLS II and every 6 months in SLS I.

HRCT thoracic imaging was obtained at baseline and at 24 months in SLS II and at baseline and at 12 months in SLS I. Both studies used similar HRCT acquisition and analysis methods,[19] except that, in SLS I, non-volumetric CT scans of 1–2 mm slice thickness were acquired at 10 mm increments, while in SLS II volumetric CT scans of 1–1.5mm slice thickness were acquired contiguously. For both studies, scans were reconstructed with sharp or manufacturer-recommended over-enhancing filters. After semi-automated lung segmentation, the images were entered into a quantitative image workstation to produce quantitative scores automatically as described previously.[20] For the present study, we

report the quantitative lung fibrosis (QLF) score, which represents the percentage of counts with reticular opacity with architectural distortion, and the Quantitative ILD (QILD) score, which represents the sum of all abnormally classified scores, including scores for fibrosis, ground glass opacity and honeycombing defined as clustered air-filled cysts with dense walls. In both studies, scores were summated for both the whole lung (WL), including both lungs, and for the zone of maximal involvement (ZM) using the same methods.

Statistical Analysis

Baseline characteristics—Summary statistics were generated for baseline characteristics from the two cohorts. Group comparisons were performed using a two-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 (i.e. likely related to disease or treatment and therefore not random).[21,22] 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. The complete-case analysis was not felt to be a valid approach in this scenario since it assumes data are missing completely at random. 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 outcome monitoring up until 24-months for both studies.

Repeated measurements of the FVC %-predicted were characterized by a linear mixed effects sub-model in the joint model, and intra-subject data correlation among multiple measurements over time was accounted for by random intercept and random time trend. Fixed effects were pre-specified 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 placebo as the reference by convention. Thus, the model estimates three piece-wise linear trends for the placebo group in 3 – 12 months, 12 – 21 months, and 21 – 24 months, and change in these time trends in the MMF group when compared to placebo.

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 (AEs) and serious adverse events (SAEs) between treatment arms. The definitions of specific AEs (i.e. leukopenia, anemia, etc.) were identical between SLS I and SLS II.[3,13]

All tests were 2-sided. Group comparisons of baseline characteristics were performed using SAS 9.4 (SAS Institute; Cary, NC). The joint modeling analysis was implemented in C.

RESULTS

Baseline Characteristics

Patients assigned to MMF in SLS II and placebo in SLS I exhibited similar baseline demographic features except for a slight difference in age (Table 1). The extent of lung disease, as measured by the FVC%-predicted, and skin involvement, as measured by the MRSS, were also similar. Patients assigned to placebo had a lower DLCO%-predicted than those in the MMF arm and more extensive QILD. Patients assigned to placebo reported more dyspnea at baseline than those assigned to MMF, although as mentioned above, different versions of the BDI were used in SLS I and II.

Disposition of Study Participants

In SLS II, 20 (28.9%) patients in the MMF arm prematurely stopped study drug treatment (1 death, 0 treatment failures, 19 other withdrawals) over 24 months. There were an additional 4 deaths in the MMF arm that occurred in subjects who had already withdrawn for other reasons. In SLS I, during the initial 12 months, 24 patients (30.4%) in the placebo arm prematurely stopped study drug treatment (3 deaths, 5 treatment failures, 16 other withdrawals). Of the 55 placebo arm patients remaining at the conclusion of the 12-month treatment period, 45 patients completed visits up to and including the 24-month visit. An additional 11 placebo arm patients returned for the 24-month visit after having withdrawn or failed treatment at earlier time points in the study. Among the 56 placebo arm patients followed for the entire 24 months, there were an additional 10 study withdrawals during the second year of follow up (1 death, 3 treatment failures, 6 study withdrawals). Please see Supplementary Figure 1 for patient disposition details.

Use of Potential Disease Modifying Therapy in the Placebo Arm

Of the 56 placebo arm patients followed during year two of SLS I, 14 began treatment with immunosuppressant therapy during this year “off study drug.” Therapies included: prednisone >10 mg daily (N= 12; Mean dose 11.6 mg daily), and oral CYC (N=2; Mean dose 72.5 mg daily). No patients received mycophenolate or azathioprine during this time. Our prior publication found that neither prednisone nor the oral CYC had an independent effect on any of the outcome measures at 24 months in SLS I.[15]

Treatment with MMF is Associated with Improved Course of FVC

After controlling for baseline FVC%-predicted and baseline QILD-WL, treatment with MMF was associated with an improved course of FVC%-predicted over 24 months (Table 2; Figure 1). The test of the overall treatment group effect for the entire model was highly significant ($P<0.0001$). From 3 to 12 months, patients in the MMF arm experienced a significant improvement in the FVC%-predicted compared with those in the placebo arm (Figure 1). There was continued improvement in the course of the FVC%-predicted from 12 to 24 months in the MMF arm. In contrast, in the placebo arm, there was a significant decline in the FVC%-predicted from 3 to 12 months, with a subsequent improvement from 12–21 months. From 12 to 21 months and from 21 to 24 months, there was no significant difference in the course of the FVC%-predicted between the two groups (Figure 1; Table 2);

however, as depicted in Supplementary Figures 2 and 3, substantially more patients assigned to MMF in SLS II experienced an improvement in FVC at both 12- and 24-months compared with patients assigned to placebo. Using the intention-to-treat population, 64.4% and 71.7% of MMF patients had any improvement in FVC%-predicted at 12 and 24 months, respectively, and the majority of patients who experienced an improvement in FVC%-predicted at 24 months had an absolute improvement of >5% (Supplementary Figures 2, 3). Among study completers, the percentage of MMF patients who had any improvement in FVC%-predicted at 24 months was even higher (75.5%).[13] By contrast, only 28.8% of placebo patients had any improvement in FVC%-predicted at 12 months, and 37.5% had any improvement in FVC%-predicted at 24 months (Supplementary Figures 2, 3).

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). The absolute change in the FVC%-predicted (unadjusted) over 24 months by treatment arm appears in Supplementary Table 1A.

Treatment with MMF is Associated with Improved Course of DCLO

After controlling for baseline DLCO%-predicted and baseline QILD-WL, treatment with MMF was associated with an improved course of DLCO%-predicted over 24 months (P <0.0001) (Figure 2). From 3 to 12 months, patients in the MMF arm experienced a significant improvement in the DLCO%-predicted compared with those in the placebo arm (P=0.0063; Figure 2); whereas, patients in the placebo arm experienced a significant decline in the DLCO%-predicted (P=0.0060; Figure 2). From 12 to 21 months (P = 0.38) and 21 to 24 months (P=0.99), there was no significant difference in the course of the DLCO%-predicted between groups (Figure 2). While statistically significant, the improvement in the DLCO%-predicted in the MMF arm relative to the placebo arm is of uncertain clinical significance.

The joint model also revealed that baseline DLCO%-predicted (Estimate effect 0.95; Std Err 0.03; P-value <0.0001) and the QILD-WL (Estimate effect 0.08; Std Err 0.03; P-value 0.0077) were independently associated with the course of the DLCO%-predicted over 24 months (Supplementary Table 2). The absolute change in the DLCO%-predicted (unadjusted) over 24 months by treatment arm appears in Supplementary Table 1B.

Treatment with MMF is Associated with Improved Course of MRSS

In all patients (those with diffuse and limited cutaneous SSc combined), after adjusting for baseline MRSS, treatment with MMF was associated with an improved course of MRSS over 24 months (P<0.0001). From 3 to 12 months, patients in the MMF arm experienced a significant improvement (decrease) in the MRSS compared with those in the placebo arm (P=0.0018; Figure 3). There was continued improvement in the course of the MRSS from 12 to 21 and 21 to 24 months in the MMF arm. Patients in the placebo arm experienced an increase (worsening) in the MRSS from 3 to 12 months, followed by a decline in MRSS from 12 to 21 and 21 to 24 months. There was a similar rate of improvement in the course of the MRSS from 12 to 21 months (P=0.95) and from 21 to 24 months (P=0.90) between treatment arms (Figure 3; Supplementary Table 3).

In patients with diffuse cutaneous disease (N= 41 for MMF; N= 45 for placebo), treatment with MMF was associated a stronger treatment effect on the course of MRSS than in all patients (diffuse and limited combined). From 3 to 12 months, the MRSS improved (declined) at a faster rate in the MMF arm compared with the placebo arm (P=0.0017; Supplementary Figure 4; Supplementary Table 4).

In patients with limited cutaneous disease (N= 25 for MMF; N= 45 for placebo), there was no significant difference between MMF and placebo in the course of the MRSS over the 24-month period at any of the aforementioned time intervals (all P>0.2).

The absolute change in the MRSS (unadjusted) over 24 months by treatment arm appears in Supplementary Tables 1C and 1D.

Treatment with MMF is Associated with Improved Course of TDI

After adjusting for baseline BDI, treatment with MMF was associated an improved course of dyspnea as measured by the TDI compared with placebo (P=0.0112). From 3 to 12 months, patients in the MMF arm experienced a trend for an improved course of dyspnea compared with those in the placebo arm (P=0.0906; Figure 4). The observed improvement in the TDI in the MMF arm exceeded that minimal clinically important difference in the TDI for SSc-ILD [23]. The TDI progressively worsened in the placebo arm during the first 12 months, but over the second year trended toward progressive improvement relative to the change over the first year of the study (Supplementary Table 5). The absolute change in the TDI (unadjusted) over 24 months by treatment arm appears in Supplementary Table 1E.

Safety Analysis

In terms of pre-defined AEs that would warrant clinical intervention and a change in therapy, leukopenia (MMF: 4; Placebo: 0), neutropenia (MMF: 3; Placebo: 0), anemia (MMF: 8 Placebo: 1), and pneumonia (MMF: 5; Placebo: 1) occurred in more patients in the SLS II-MMF arm than in the SLS I-placebo arm (Table 3). However, more patients in the SLS I-placebo arm experienced SAEs (N=38) compared with patients with the MMF arm of SLS II (N=27). Seven of the SAEs occurring in the placebo arm were judged by the Morbidity and Mortality Committee to be related to treatment compared with 3 in the MMF arm. The number of deaths was similar between the two groups (MMF: 5; Placebo: 6).

DISCUSSION

The present study describes the first analysis comparing MMF with placebo for the treatment of SSc-ILD, albeit using data from two independent studies with nearly identical study designs and similar patient populations. The results reported herein demonstrate that treatment with MMF is associated with improvements in physiologic outcomes and dyspnea, as well as with reductions in the extent of cutaneous sclerosis, in comparison with placebo.

The observed treatment effects were greatest within the first 12 months of therapy and diminished with time. Possible explanations for this observation include the use of potential disease modifying therapy in the placebo arm during months 12 to 24. As mentioned above, 12 patients received prednisone and 2 patients received CYC in the placebo arm during this

period. Given the paucity of patients on CYC and the lack of substantial evidence that prednisone prevents SSc-ILD progression, additional explanations for the loss of treatment effect after 12 months may relate to the natural history of SSc-ILD. Steen and colleagues [24] demonstrated that the greatest decline in FVC occurs within the first year among patients with severe SSc-ILD; therefore, it is plausible that lung function, as well as dyspnea as measured by the TDI, stabilized/improved in both groups after 12 months regardless of treatment. Similarly, the MRSS also improved in the placebo arm in the second year of the study, which again likely reflects the natural of history of cutaneous sclerosis progression in SSc.[25] A survival bias may also contribute to the diminished MMF-treatment effect in months 12 to 24, although our joint model analysis specifically adjusts for non-ignorable missing data due to study dropout, treatment failure or death.

Notably, when compared with placebo, the MMF-treatment effect persisted at 24 months in contrast to the CYC-treatment effect observed in SLS I.[3, 15] In SLS I, less than half of patients assigned to CYC had any improvement in FVC%-predicted at 12 months,[3] and by 24 months there was no difference in the FVC%-predicted between patients assigned to placebo versus CYC.[15] By contrast, the percentage of patients with any improvement in FVC%-predicted at 24 months was substantially higher in patients receiving MMF (71.7%; nearly 3 times more than those assigned to placebo). Furthermore, even though the course of the FVC%-predicted in the second year improved in both study arms, there was still an MMF advantage at 24 months.

From a safety and tolerability standpoint, MMF appears to be well tolerated. There were 8 pre-defined treatment failures in the placebo arm and none in the MMF arm over 24 months. Furthermore, 30 patients in the placebo arm experienced treatment failures/drug withdrawals compared with only 19 patients in the MMF arm during this time frame. As a reference point, there were 30 treatment failures/drug withdrawals in the CYC arm of SLS I and 34 treatment failures/drug withdrawals in the CYC arm of SLS II over 24 months.

The present analysis found that numerically more patients experienced AEs in the MMF arm than in the placebo arm; however, patients in the placebo arm experienced more SAEs. It is unclear why more SAEs occurred in the placebo arm; however, it is possibly related to progression of the SSc disease state in the absence of disease-modifying therapy as most of the SAEs were not attributed to study drug in both groups. When compared with placebo, CYC use in SLS I was associated with more AEs, SAEs, and deaths.[3] Taken together, these observations seem to suggest that MMF introduction may pose less serious risk to the patient.

The results of our analyses should be interpreted within the context of certain limitations. Namely, comparing cohorts from two different trials can introduce bias. Time-period bias is one concern as enrollment for SLS I concluded in 2004 and enrollment for SLS II concluded in 2012. However, this time difference is unlikely to contribute significantly to the phenotypic expression SSc-ILD in each cohort as no new major therapeutic discoveries were made during this time period.

Of greater concern are potential differences in the baseline features of these two groups, which may affect SSc-ILD progression. Patients assigned to the placebo arm had greater radiographic extent of ILD and a lower DLCO compared with patients assigned to the MMF arm. While we attempted to control for baseline ILD disease severity in our analyses (i.e. FVC, DLCO, QILD-WL), without a randomization process, one cannot adequately control for those “unknown” variables, which may be different in the two groups and which may affect the study outcome.

Reassuringly, the MMF and placebo groups appeared relatively similar in terms of their baseline features. Moreover, the participants in SLS I and II were recruited from similar academic centers. Nine of the 13 centers for recruitment in SLS I were used in SLS II. In addition, these 9 centers recruited the majority of patients for both SLS I and SLS II. The principal investigators from these centers were also similar for SLS I and II, suggesting that practice management styles were likely consistent between the two trials.

Aside from the inherent limitations associated with comparing groups from different trials, our study also has important strengths. First, the number of patients is relatively large for an SSc-ILD intervention study in both trials. Second, unlike many prior studies in this area, we did not evaluate an outcome measure at a single follow-up time point. Instead, we employed sophisticated statistical techniques to examine outcomes measured at multiple time points (i.e. FVC measured at 3-month intervals over 24 months), which likely embodies a more clinically meaningful characterization of SSc-ILD progression. Third, our analysis adjusted for missing data due to drop-outs, treatment failures, and deaths and thus represents a novel approach for dealing with non-ignorable missing data in clinical trials.

To conclude, in patients with symptomatic SSc-ILD, treatment with MMF is associated with improvements in FVC%-predicted, DLCO%-predicted, TDI, and MRSS, compared with placebo using data from a historical study. The MMF-treatment effect was greatest within the first 12 months, but persisted throughout the 2-year trial. These findings support the use of MMF for the treatment of SSc-ILD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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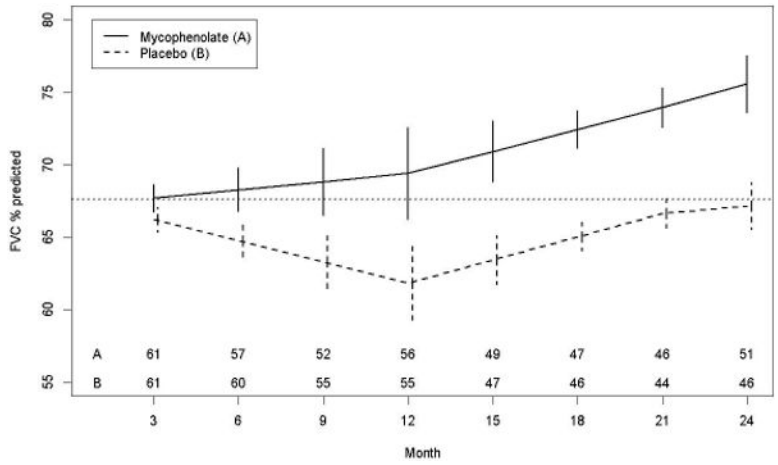

Figure 1. Course of the FVC% from 3 to 24 Months in SLS II Patients Assigned to MMF versus SLS I Patients Assigned to Placebo Using Joint Model Analysis

The test of the overall treatment group effect is significant at P<0.0001. Pre-specified 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.

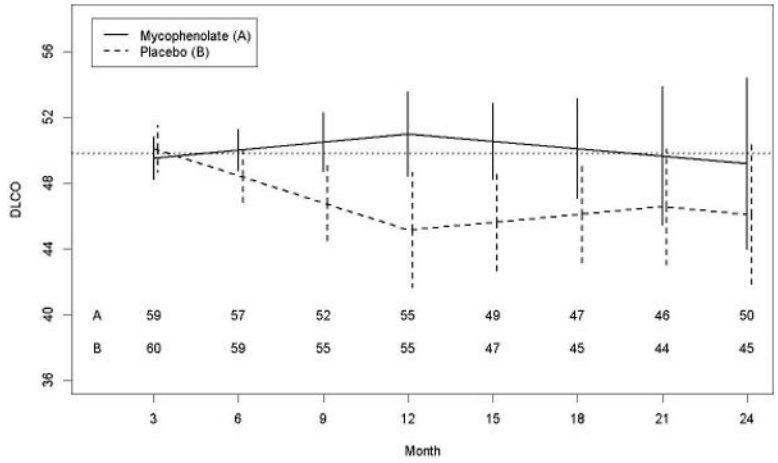

Figure 2. Course of the DLCO% from 3 to 24 Months in SLS II Patients Assigned to MMF versus SLS I Patients Assigned to Placebo Using Joint Model Analysis

The test of the overall treatment group effect is significant at P<0.0001. Pre-specified 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.

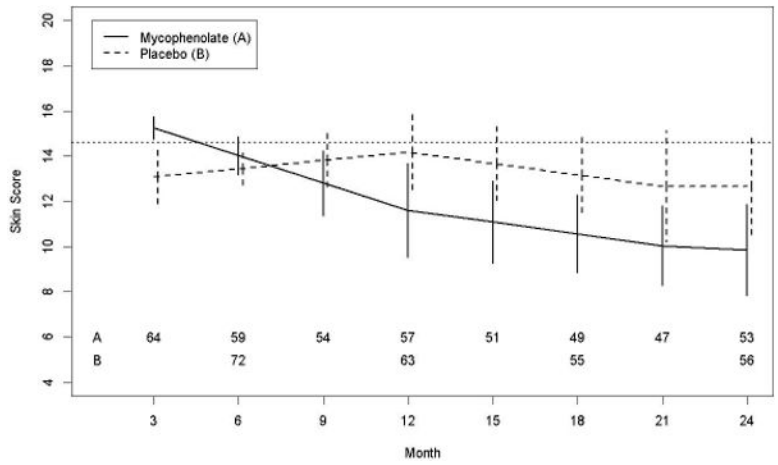

Figure 3. Course of the MRSS from 3 to 24 Months in SLS II Patients Assigned to MMF versus SLS I Patients Assigned to Placebo Using Joint Model Analysis

The test of the overall treatment group effect is significant at P<0.0001. The dotted line represents the mean baseline value for the entire cohort.

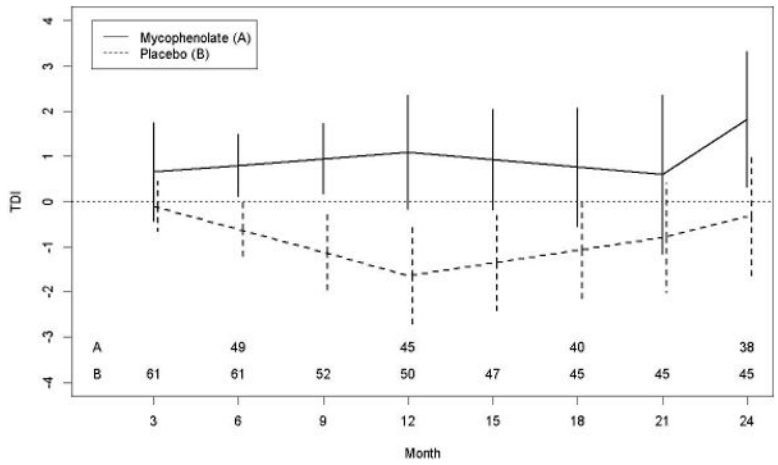

Figure 4. Course of the TDI from 3 to 24 Months in SLS II Patients Assigned to MMF versus SLS I Patients Assigned to Placebo Using Joint Model Analysis

The test of the overall treatment group effect is significant at P=0.0112. The dotted line represents the mean baseline value for the entire cohort.

Table 1

Baseline characteristics of participants assigned to placebo in SLS I and mycophenolate in SLS II*

Characteristics	N	Placebo Arm (N=79)	Mycophenolate Arm (N=69)	P-value
Age (yr)	148			0.0152δ
Mean		48.1±12.4	52.6±9.7	
Range		19–83	34–79	
Female sex (%)	148	64.6	69.6	0.5184 σ
Duration of scleroderma (yr) †	146			0.0742 Ψ
Median (IQR)		3.0 (1.7 – 4.7)	2.1 (1.3 – 4.2)	
Range		0.2–6.8	0.3–6.5	
Limited/Diffuse (%)	148	43.0/57.0	37.7/62.3	0.5079σ
FVC (% of predicted)	148	68.6±13.0	66.5±8.3	0.2510δ
DLCO (% of predicted)	148	46.2±13.3	54.0±11.1	0.0002 δ
Mahler Dyspnea Index (Focal score)	144	5.7±2.0	7.3±2.1	<0.0001δ
SF-36 score				
Physical component	148	34.3±10.7	36.0±10.0	0.3326δ
Mental component	148	50.7±10.6	49.1±7.9	0.2847δ
Skin-thickness score (MRSS)				
All patients	148			0.3776 Ψ
Median (IQR)		11 (4 – 21)	13 (6 – 24)	
Range		0–40	1–41	
Patients with dcSSc	88			0.8351 Ψ
Median (IQR)		19 (13 – 28)	20 (13 – 26)	
Range		6–40	4–41	
Patients with lcSSc	60			0.4677 Ψ
Median (IQR)		4 (3 – 7)	6 (4 – 7)	
Range		0–14	1–14	
HAQ disability index (0–3), Median (IQR)	148	0.5 (0.1 – 1.1)	0.6 (0.1 – 1.1)	0.7110 Ψ
QLF-WL, Median (IQR)	131	8.0 (2.6 – 13.0)	7.1 (2.9 – 11.8)	0.5309 Ψ
QLF-ZM, Median (IQR)	131	21.4 (8.7 – 36.5)	18.6 (5.7 – 34.0)	0.5249 Ψ
QILD-WL	131	35.3±16.9	27.2±13.2	0.0027δ
QILD-ZM	131	58.0±21.3	50.0±20.9	0.0321δ

*Values are mean ± standard deviation, unless otherwise noted.

†Disease duration based on the onset of the first non-Raynaud's symptom attributable to SSc.

δt-test

σChi-square test

ΨWilcoxon rank-sum test

Definitions of abbreviations: FVC = forced vital capacity; DLCO = diffusing capacity of the lung for carbon monoxide; QLF = quantitative extent of lung fibrosis on HRCT; QILD = quantitative extent of total interstitial lung disease (including fibrosis, honeycomb and ground glass opacity); WL = whole lung; ZM = zone of maximal involvement. Scores for the Mahler Baseline Dyspnea Index (BDI) can range from 0 to 12, with lower scores indicating worse dyspnea. Scores for skin thickening (Modified Rodnan Skin Scores, MRSS) can range from 0 to 51, with higher scores indicating more severe thickening. dcSSc = diffuse cutaneous systemic sclerosis; lcSSc = limited cutaneous systemic sclerosis. Scores for HAQ Disability Index can range from 1 to 3, with higher numbers indicating greater disability.

Table 2

Treatment with MMF is associated with an improved overall course of the FVC%-predicted over 24 months using a joint model analysis (N=125).

Covariate	Estimated Effect	Std Err	P-value
Time (3–12 months) *	−0.49	0.13	0.0002
Time (12–21 months) *	0.54	0.16	0.0007
Time (21–24 months) *	0.17	0.36	0.64
Baseline FVC%-Predicted	0.97	0.02	<0.0001
Baseline QILD-WL	0.01	0.02	0.62
Treatment Arm Assignment †	0.002	1.21	0.999
Treatment Arm Assignment × Time Interaction (3–12 months) δ	0.68	0.19	0.0003
Treatment Arm Assignment × Time Interaction (12–21 months) δ	−0.03	0.24	0.90
Treatment Arm Assignment × Time Interaction (21–24 months) δ	0.38	0.56	0.50
Treatment Arm Assignment × Baseline QILD-WL	−0.02	0.03	0.50

* The reference group is the placebo arm; therefore, these time trends represent the trends observed in the placebo arm. From 3–12 months, there was a significant decline in the FVC%-predicted in the placebo arm (Estimated effect −0.49).

† This represents the estimate for baseline differences in FVC%-predicted by treatment arm.

δ These time trends represent the trends observed in the MMF arm compared with the placebo arm. From 3–12 months, there was a significant improvement in the course of the FVC%-predicted in the MMF arm compared with the placebo arm (Estimated effect +0.68).

Table 3

Number of patients with adverse events and serious adverse events from baseline to 24 months.

	Placebo (N=79)	MMF (N=69)
Adverse event (AE) *		
Leukopenia	0	4
Neutropenia	0	3
Anemia	1	8
Thrombocytopenia	0	0
Hematuria	5	3
Pneumonia	1	5
Serious adverse event (SAE)		
Number of patients with SAEs	38	27
Related to treatment †	7	3
Not related to treatment †	31	23
Death	6	5

* Pre-defined by protocol as likely to be related to study drug and to warrant protocol-defined management (except for pneumonia): anemia = Hgb <10 gm/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 more than one urinalysis) in absence of urinary tract infection or menses

† According to consensus classification by Morbidity and Mortality Committee