An Open-label, Phase II Study of the Safety and Tolerability of Pirfenidone in Patients with Scleroderma-associated Interstitial Lung Disease: the LOTUSS Trial

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ABSTRACT. *Objective.* Systemic sclerosis-associated interstitial lung disease (SSc-ILD) shares a number of clinical features and pathogenic mechanisms with idiopathic pulmonary fibrosis (IPF). This study was designed to evaluate the tolerability of the IPF treatment pirfenidone in SSc-ILD. The known gastrointestinal, skin, and liver adverse events (AE) of pirfenidone are of importance given the involvement of these organs in SSc.

Methods. All patients received pirfenidone and were randomized 1:1 to either a 2- or 4-week titration starting at 801 mg/day and finishing at a maintenance dose of 2403 mg/day. Patients received pirfenidone for 16 weeks in total. Assessments included treatment-emergent AE (TEAE) and exploratory disease outcomes.

Results. Sixty-three patients were randomized; 96.8% experienced a TEAE and more patients reported TEAE during the titration versus the maintenance period. The most commonly reported TEAE were consistent with those observed for pirfenidone in IPF (nausea, headache, fatigue) and were similar regardless of titration schedule. More patients discontinued treatment because of TEAE in the 2- versus 4-week titration group (5 vs 1, respectively); all discontinuation events occurred > 3 weeks after reaching the full dose of pirfenidone. Mycophenolate mofetil (MMF), taken by 63.5% of patients in addition to pirfenidone, did not appear to affect tolerability. Exploratory disease outcomes remained largely unchanged.

Conclusion. Pirfenidone showed an acceptable tolerability profile in SSc-ILD, although a longer titration may be associated with better tolerability. Tolerability was not affected by concomitant MMF. The present findings support further investigation of pirfenidone in future clinical trials in patients with SSc-ILD. Trial registration: ClinicalTrials.gov; www.clinicaltrials.gov NCT01933334. (J Rheumatol First Release July 1 2016; doi:10.3899/jrheum.151322)

Key Indexing Terms:
SYSTEMIC SCLEROSIS   SCLERODERMA   INTERSTITIAL LUNG DISEASES
PIRFENIDONE   SAFETY   TOLERABILITY

Interstitial lung disease (ILD) is a frequent complication of systemic sclerosis (SSc), a rare heterogeneous systemic autoimmune disease, characterized by excessive collagen production and tissue fibrosis of the skin and internal organs[1,2]. Up to 90% of patients with SSc show evidence of ILD on high-resolution computed tomography (HRCT) and 40%–75% show impairment in pulmonary function tests[2]. Further, ILD and pulmonary arterial hypertension (PAH) are the 2 main causes of death in SSc[2,3]. SSc-ILD is characterized by interstitial and alveolar inflammation and fibrosis,

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typically manifesting on radiographic imaging and histology as a nonspecific interstitial pneumonia pattern[4,5,6].

To date, there are no approved treatments for SSc-ILD. Treatment with cyclophosphamide (CYC) has been recommended[7]; however, improvements in lung function are generally modest[8,9] and concerns exist regarding its safety profile[2,7,10]. Mycophenolate mofetil (MMF) is frequently used with the intention to stabilize lung function in SSc-ILD[2,10,11], particularly in patients who cannot tolerate CYC. A study comparing MMF and CYC in patients with SSc is currently under way, with interim results showing a similar but minimal improvement for both treatments of about 4%–4.5% in percent-predicted forced vital capacity (FVC) at 24 months (Scleroderma Lung Study II, NCT00883129)[2,10,12].

Pirfenidone is an antifibrotic agent[13] with antiinflammatory properties, including inhibition of proinflammatory cytokines[14] and inhibition of inflammatory cell proliferation[15]. Pirfenidone was approved by European and US regulatory agencies in 2011 and 2014, respectively, for the treatment of patients with idiopathic pulmonary fibrosis (IPF)[16,17,18,19], a chronic, progressive, and almost invariably fatal disease[20]. Unlike SSc-ILD, however, IPF is limited to the lungs and is defined by a pattern of usual interstitial pneumonia[5]. Despite differences in their clinical presentation[5], IPF and SSc-ILD share some overlapping pathogenic mechanisms, including injury to structural cells, fibroblast activation, myofibroblast accumulation, expression of fibrogenic cytokines and growth factors, and progressive ILD[2,5,21].

Pirfenidone is generally well tolerated in patients with IPF, and compared with placebo, pirfenidone significantly reduces disease progression (as measured by change in percent-predicted FVC) and increases progression-free survival[17,18,22]. Pirfenidone also significantly reduces the risk of mortality in patients with IPF compared with placebo and can benefit patient outcomes including the 6-min walking distance and dyspnea[17,23]. However, pirfenidone is known to be associated with adverse events (AE) of the liver, gastrointestinal (GI) system, and skin[17,18], which may overlap with the organ systems frequently affected in patients with SSc[1,24,25]. Therefore, in the setting of SSc-ILD, it is important to investigate the tolerability of pirfenidone before assessing its efficacy.

The LOTUSS study (An Open Label, RandOmized, Phase 2 STUdy of the Safety and Tolerability of Pirfenidone when Administered to Patients with Systemic Sclerosis-Related Interstitial Lung Disease) was designed to assess the safety and tolerability of pirfenidone in patients with SSc-ILD at the same therapeutic dose used in IPF, and using 2 dose-titration schedules, with or without stable background SSc-ILD therapy.

MATERIALS AND METHODS

Design and patients. The LOTUSS study (NCT01933334) was an international, multicenter, randomized, open-label, phase II study (Figure 1).

Eligible patients were men or women aged 18–75 years with a confirmed diagnosis of SSc based on the preliminary criteria of the American College of Rheumatology for the classification of SSc[26] and an HRCT scan with evidence of ILD within 2 years of the study start. Eligibility criteria included SSc disease duration of < 7 years from first non-Raynaud symptoms; percent-predicted FVC of ≥ 50%; DLCO of ≥ 40% (adjusted for hemoglobin); absence of clinically significant PAH, right atrial or ventricular enlargement or left ventricular dysfunction; absence of underlying liver disease; and absence of moderate to severe gastroesophageal reflux [as assessed by the University of California Los Angeles Scleroderma Clinical Trial Consortium Gastrointestinal Tract (UCLA SCTC GIT) 2.0 questionnaire reflux subscale score > 1.0][27]. Concomitant background SSc-ILD medication of oral CYC (≤ 2 mg/kg/day) or MMF (≤ 1.5 g twice daily) was permitted if patients had received a stable dose for ≥ 3 months prior to study start. Full inclusion and exclusion criteria are provided in the Supplementary Material 1 (available online at jrheum.org).

We conducted our study in accordance with the International Conference on Harmonisation guidelines, consistent with the Declaration of Helsinki, and applicable laws and regulations of the countries in which the research was conducted. Local institutional review boards and independent ethics committees approved the protocol (Supplementary Table 1, available online at jrheum.org). All patients provided written informed consent.

Randomization. Patients received pirfenidone (267 mg oral capsules with food) at a starting dose of 801 mg/day (1 capsule, 3× daily) titrated to a maintenance dose of 2403 mg/day (3 capsules, 3× daily). Patients were randomized 1:1 to a 2-week titration group (as standard for patients with IPF) or a 4-week titration group (Figure 1). Randomization occurred through a blocked scheme prospectively prepared by the study sponsor and was stratified by background SSc-ILD treatment.

Assessments. Safety assessments were treatment-emergent AE (TEAE) and treatment-emergent serious AE (TE SAE), and their relationship to pirfenidone. AE were collected from study start until 28 days after the last dose or the posttreatment visit, whichever occurred later. Changes in clinical laboratory variables or electrocardiogram results were recorded. The frequency of GI symptoms and their effect on patient quality of life were assessed using the UCLA SCTC GIT 2.0 questionnaire[27].

Exploratory disease outcomes included relevant lung function assessments [percent-predicted FVC, DLCO (adjusted for hemoglobin)], patient-reported outcomes [Mahler baseline and Transition Dyspnea Indices (TDI), Health Assessment Questionnaire-Disability Index (HAQ-DI), patient's global assessment of disease activity (PtGA)], and the modified Rodnan skin score (mRSS).

Statistical analyses. The study was designed to enroll about 50 patients (25 per titration group) to provide a ≥ 95% probability of observing a common AE with a true event rate of ≥ 6%. Analyses were summarized descriptively by titration group for all patients, for the entire treatment period, during the titration period (weeks 1–6) and during the maintenance period (weeks 7–16). Study endpoints were also summarized by subgroups, defined by background SSc-ILD treatment and type of cutaneous SSc. Fisher's exact test was used to provide p values for safety outcomes with numeric differences for descriptive purposes.

RESULTS

Patients. Overall, 63 patients were recruited at 18 sites across 3 countries (Canada, Italy, and the United States) and were randomized to the 2-week or 4-week pirfenidone titration groups (Figure 2). An additional 26 patients did not satisfy the eligibility criteria and were not randomized. The first patient was enrolled on October 31, 2013, and the last patient completed the study on September 16, 2014. All randomized patients received ≥ 1 dose of study medication.

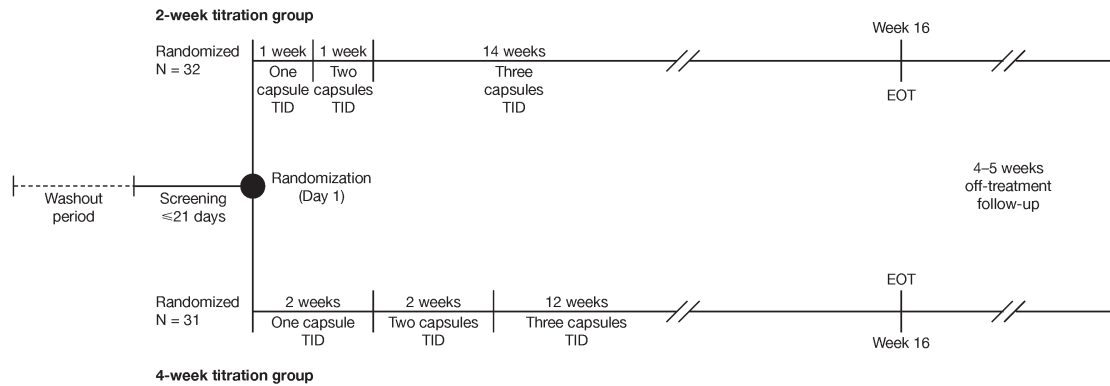Baseline demographics and clinical characteristics were

Figure 1. LOTUSS study design. Analysis periods were defined as follows: titration period, weeks 1–6; maintenance period, weeks 7–16. LOTUSS: An Open Label, RandOmized, Phase 2 STUdy of the Safety and Tolerability of Pirfenidone when Administered to Patients with Systemic Sclerosis-Related Interstitial Lung Disease; TID: 3× daily; EOT: end of treatment.

Table 1. Summary of baseline demographic characteristics. Values are n (%) unless otherwise specified.

| Demographic Variables | Pirfenidone, 2403 mg/day | | |
	2-week Titration Group, n = 32	4-week Titration Group, n = 31	Total, n = 63
Age, yrs, mean (SD)	49.3 (12.08)	51.9 (12.52)	50.6 (12.27)
Female	26 (81.3)	26 (83.9)	52 (82.5)
Primary race/ethnicity			
White	21 (65.6)	27 (87.1)	48 (76.2)
Black or African American	5 (15.6)	2 (6.5)	7 (11.1)
Other	6 (18.8)	2 (6.5)	8 (12.7)
Hispanic or Latino ethnicity	4 (12.5)	3 (9.7)	7 (11.1)
Weight, kg, mean (SD)	74.6 (19.79)	70.8 (14.62)	72.7 (17.40)
Background SSc-ILD treatment			
None	12 (37.5)	11 (35.5)	23 (36.5)
MMF	20 (62.5)	20 (64.5)	40 (63.5)
SSc type			
Limited	20 (62.5)	12 (38.7)	32 (50.8)
Diffuse	12 (37.5)	19 (61.3)	31 (49.2)
SSc duration, mos, mean (SD)	36.4 (25.84)	40.3 (26.53)	38.3 (26.04)
SSc-ILD duration, mos, mean (SD)	25.3 (20.01)	28.1 (25.36)	26.7 (22.66)
Predicted FVC, %, mean (SD)	72.8 (14.39)	79.4 (13.32)	76.0 (14.15)
≥ 70%	16 (50.0)	23 (74.2)	39 (61.9)
< 70%	16 (50.0)	8 (25.8)	24 (38.1)
DLCO, %, mean (SD)*	59.3 (14.36)	60.1 (18.64)	59.7 (16.47)
Concomitant medication taken by > 20% of patients in either titration group			
Drugs for acid-related disorders	26 (81.3)	24 (77.4)	50 (79.4)
Immunosuppressants	20 (62.5)	21 (67.7)	41 (65.1)
Vitamins	12 (37.5)	17 (54.8)	29 (46.0)
Calcium channel blockers	11 (34.4)	11 (35.5)	22 (34.9)
Antithrombotics	6 (18.8)	10 (32.3)	16 (25.4)
Lipid-modifying agents	9 (28.1)	6 (19.4)	15 (23.8)
Analgesics	9 (28.1)	5 (16.1)	14 (22.2)
Agents acting on renin-angiotensin system	8 (25.0)	6 (19.4)	14 (22.2)
Antianemic preparations	8 (25.0)	5 (16.1)	13 (20.6)
Antiinflammatory and antirheumatics	8 (25.0)	4 (12.9)	12 (19.0)
Mineral supplements	7 (21.9)	5 (16.1)	12 (19.0)
Systemic corticosteroids**	7 (21.9)	5 (16.1)	12(19.0)

*Adjusted for hemoglobin. ** Oral corticosteroids for systemic use were permitted at a dose ≤ 10 mg/day prednisone equivalent. SSc: systemic sclerosis; ILD: interstitial lung disease; MMF: mycophenolate mofetil; FVC: forced vital capacity.
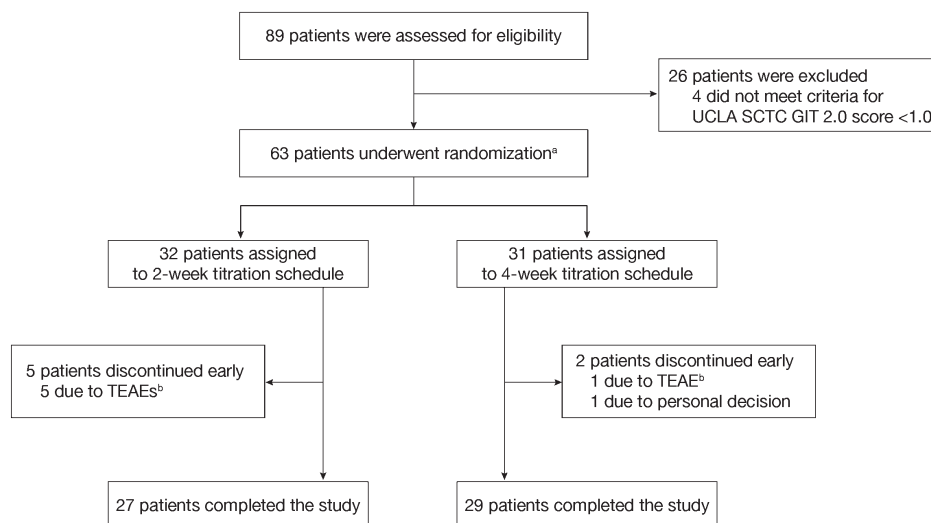
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│ 89 patients were assessed for eligibility │
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              ├─────────▶│ 26 patients were excluded       │
              │          │ 4 did not meet criteria for     │
              │          │ UCLA SCTC GIT 2.0 score <1.0    │
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│ 63 patients underwent randomizationᵃ │
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Figure 2. Summary of patient disposition. ᵃ Following initiation of study medication, 3 patients were discovered to not meet all eligibility criteria [DLCO < 40% (n = 2) and systemic sclerosis disease duration > 7 yrs (n = 1)], but were permitted to continue. ᵇ All TEAE leading to discontinuation started > 3 weeks after completion of the 2- or 4-week titration. TEAE: treatment-emergent adverse event; UCLA SCTC GIT: University of California Los Angeles Scleroderma Clinical Trial Consortium Gastrointestinal Tract.

comparable in the 2 titration groups with the exception that more patients in the 2-week titration group had limited SSc and that the 4-week titration group had slightly better lung function (Table 1). Background SSc-ILD medication was used by 63.5% of patients, all of whom were receiving MMF (Table 1). No patients were receiving CYC. Prednisone was used by 17.5% of patients.

Most patients (88.9%) completed our study; 7 patients (11.1%) withdrew early, 6 (9.5%) because of AE (5 in the 2-week group and 1 in the 4-week group; Figure 2). All patients reached the target dose of pirfenidone 2403 mg/day, except 1 patient in the 2-week group owing to a site dosing error.

Overall, 57.1% of patients had a dose adjustment; in both titration groups, the majority of dose adjustments occurred during the maintenance versus titration period (dose reductions: 48.4% vs 12.7%, respectively; dose interruptions: 22.6% vs 6.3%, respectively). Patients in the 2-week titration group had more dose adjustments overall compared with the 4-week group; the difference between the 2 titration groups was most striking during the titration period (dose reductions: 21.9% vs 3.2%, difference 18.7%, p = 0.0534; dose interruptions: 12.5% vs 0%, difference 12.5%, p = 0.1132, for the 2- vs 4-week group, respectively).

Safety. Overall, 96.8% of patients experienced at least 1 TEAE (Table 2A). The most commonly reported TEAE were nausea, headache, and fatigue. The frequency and type of TEAE were similar for both the 2- and 4-week titration groups (Table 2A).

A greater proportion of patients experienced TEAE during the titration versus the maintenance period (92.1% vs 79.0%).

Of the TEAE reported by > 10% of patients during the entire treatment period (Table 2B), nausea (44.4% vs 8.1%), gastroesophageal reflux disease (19.0% vs 4.8%), fatigue (31.7% vs 9.7%), and headache (30.2% vs 19.4%) were reported in more patients during the titration versus the maintenance period. Rash was reported in more patients during the maintenance period (17.7% vs 4.8% during the titration period).

The majority of TEAE were mild or moderate in intensity[28]. Sixteen severe TEAE were reported by 12 patients, 9 (28.1%) and 3 (9.7%) of whom were in the 2- and 4-week titration groups, respectively (difference 18.4%, p = 0.1069; Table 2A). Overall, most severe TEAE were reported after the completion of the titration periods (13/16 TEAE) and when the patients had been receiving the full dose of pirfenidone for > 2 weeks (11/16 TEAE). Severe TEAE reported by > 1 patient were fatigue (4.8%), diarrhea (3.2%), and nausea (3.2%; Table 2B).

Three patients reported 4 TE SAE; all events were new in onset and occurred in the 2-week titration group during the maintenance period. TE SAE were bronchitis (not related to study medication, per site investigator), intestinal obstruction (possibly related to study medication), and PAH (associated with SSc and diagnosed by right heart catheterization) alongside worsening ILD (neither of which were related to the study medication). The patient with PAH/ILD also discontinued the study because of PAH. A further 5 patients discontinued the study (Table 2A): 3 because of skin-related TEAE (2 in the 2-week group and 1 in the 4-week group); 1 patient owing to drug hypersensitivity to pirfenidone (with vomiting, 2-week group); and 1 patient after an exacerbation

Table 2A. Summary of TEAE. Values are n (%).

| TEAE* | Pirfenidone, 2403 mg/day | | |
	2-week Titration Group, n = 32	4-week Titration Group, n = 31	Total, n = 63
At least 1 TEAE	31 (96.9)	30 (96.8)	61 (96.8)
Maximal intensity of TEAE**			
Mild***	7 (21.9)	12 (38.7)	19 (30.2)
Moderate	15 (46.9)	15 (48.4)	30 (47.6)
Severe***	9 (28.1)	3 (9.7)	12 (19.0)
Life-threatening	0	0	0
Relationship of TEAE to study treatment[†‡]			
Not related	3 (9.4)	2 (6.5)	5 (7.9)
Possibly related	7 (21.9)	6 (19.4)	13 (20.6)
Related	21 (65.6)	22 (71.0)	43 (68.3)
At least 1 TE SAE	3 (9.4)	0	3 (4.8)
At least 1 treatment-related TE SAE[††]	1 (3.1)	0	1 (1.6)
Discontinuation of study treatment due to TEAE***	5 (15.6)	1 (3.2)	6 (9.5)
Death as an outcome of a TEAE	0	0	0

* AE were classified according to Medical Dictionary for Regulatory Activities, version 11.0, using preferred terms within each system organ class, and the severity of AE was recorded according to the Common Terminology Criteria for AE, version 4.0[28]. ** Each patient was counted only once as the maximal intensity of any event for that patient. *** Events with treatment differences ≥ 10%; p values by the Fisher's exact test all > 0.1. [†] Each patient was counted only once as the strongest relationship of any event for that patient. [‡] As assigned by the investigator. [††] An AE was considered serious if it resulted in death, required hospitalization, resulted in persistent or significant disability, resulted in a congenital anomaly or birth defect, or was an important medical effect, defined as an event that may have jeopardized the patient and may have required intervention to prevent death, an immediate threat to life, or hospitalization. AE: adverse event; TEAE: treatment-emergent AE; TE SAE: treatment-emergent serious AE.

of existing fibromyalgia (2-week group). All TEAE leading to discontinuation occurred > 3 weeks after reaching the full dose of pirfenidone. No life-threatening TEAE or deaths occurred.

The incidence of TEAE was generally comparable in the predefined subgroups. However, the incidence of infections was higher in the no-MMF versus MMF subgroup (n = 13, 56.5% vs n = 10, 25.0%, respectively, difference 31.5%, p = 0.0161). A greater proportion of patients reported severe TEAE in the no-MMF versus MMF subgroup (n = 8, 34.8% vs n = 4, 10.0%, respectively, difference 24.8%, p = 0.0223) and in the diffuse versus limited cutaneous SSc subgroup (n = 8, 25.8% vs n = 4, 12.5%, respectively, difference 13.3%, p = 0.2132). Similarly, more patients discontinued treatment because of a TEAE in the no-MMF versus MMF subgroup (n = 4, 17.4% vs n = 2, 5.0%, respectively, difference 12.4%, p = 0.1794), as did patients with diffuse versus limited cutaneous SSc (n = 5, 16.1% vs n = 1, 3.1%, respectively, difference 13.0%, p = 0.1042).

Results for the patient assessment of GI symptoms using the UCLA SCTC GIT 2.0 questionnaire at Day 1 and Week 16 showed that mean total GIT scores and subscale scores remained stable throughout the study with no notable differences between the 2- and 4-week titration groups (Supplementary Table 2, available online at jrheum.org). Liver function tests showed that bilirubin values did not exceed the upper limit of normal (ULN) and aminotransferase levels remained below 3× the ULN. Minor elevations in liver function tests were sporadic and not considered clinically relevant. There were no abnormalities identified in other clinical laboratory data.

Exploratory disease outcomes. Percent-predicted FVC and DLCO values were basically unchanged throughout our study, and no clinically relevant differences were observed in lung function variables between the 2- and 4-week groups or in any of the subgroup analyses (Table 3). Mean change from baseline in percent-predicted FVC was 0.6% and –0.3% in the MMF and no-MMF subgroups at Week 16, respectively; mean change from baseline in percent-predicted DLCO was 3.2% and –0.2% in the MMF and no-MMF subgroups at Week 16, respectively (Table 3).

Relative to baseline at Week 16, dyspnea remained unchanged with a mean score of 1.0 on the Mahler TDI scale in all patients. Mean change from baseline in Mahler overall TDI score was greater in the 4- versus 2-week titration group (Table 3) and dyspnea was slightly more pronounced at baseline and more improved at Week 16 in the MMF versus no-MMF subgroup (Table 3).

Skin thickening, as measured by mean mRSS total score, remained unchanged from baseline to Week 16 (Table 3) and no clinically relevant differences were seen at Week 16 in the 2- versus 4-week titration groups or in the subgroup analyses.

Table 2B. TEAE reported in ≥ 10% of patients from both treatment groups overall. Values are n (%).

| TEAE | Pirfenidone, 2403 mg/day | | | | | |
| | 2-week Titration Group, n = 32 | | | 4-week Titration Group, n = 31 | | |
	Mild	Moderate	Severe	Mild	Moderate	Severe
Nausea	13 (40.6)	2 (6.3)	1 (3.1)	12 (38.7)	2 (6.5)	1 (3.2)
Headache	12 (37.5)	2 (6.3)	0	12 (38.7)	2 (6.5)	0
Fatigue	6 (18.8)	5 (15.6)	2 (6.3)	8 (25.8)	1 (3.2)	1 (3.2)
Diarrhea	7 (21.9)	0	2 (6.3)	8 (25.8)	2 (6.5)	0
Vomiting	5 (15.6)	3 (9.4)	1 (3.1)	7 (22.6)	2 (6.5)	0
Cough*	8 (25.0)	2 (6.3)	0	3 (9.7)	1 (3.2)	0
GERD, including worsening GERD	3 (9.4)	3 (9.4)	0	5 (16.1)	1 (3.2)	1 (3.2)
Rash	6 (18.8)	2 (6.3)	0	3 (9.7)	2 (6.5)	0
Dizziness	3 (9.4)	2 (6.3)	0	3 (9.7)	2 (6.5)	0
Arthralgia	3 (9.4)	2 (6.3)	0	2 (6.5)	2 (6.5)	0
Anorexia	3 (9.4)	2 (6.3)	0	1 (3.2)	1 (3.2)	0
Back pain	4 (12.5)	1 (3.1)	0	1 (3.2)	2 (6.5)	0
Dyspepsia	1 (3.1)	2 (6.3)	1 (3.1)	3 (9.7)	1 (3.2)	0
Pruritus	2 (6.3)	2 (6.3)	0	4 (12.9)	0	0
Asthenia*	0	1 (3.1)	1 (3.1)	3 (9.7)	2 (6.5)	0
Dyspnea	2 (6.3)	1 (3.1)	0	3 (9.7)	1 (3.2)	0
Insomnia*	0	2 (6.3)	0	5 (16.1)	0	0
Stomach discomfort	3 (9.4)	0	0	3 (9.7)	1 (3.2)	0
Constipation	5 (15.6)	0	0	1 (3.2)	0	0

* Events with treatment differences ≥ 10%; p values by the Fisher's exact test all > 0.1. TEAE: treatment-emergent adverse event; GERD: gastroesophageal reflux disease.

Table 3. Summary of exploratory disease outcomes.

| Variables | Pirfenidone, 2403 mg/day | | | | |
	2-week Titration Group, n = 32	4-week Titration Group, n = 31	No MMF, n = 23	MMF, n = 40	Total, n = 63
Predicted FVC, %, mean (SD)					
Baseline	72.8 (14.39)	79.4 (13.32)	78.7 (13.99)	74.5 (14.19)	76.0 (14.15)
Week 16	71.4 (15.14)	78.7 (13.60)	75.5 (14.26)	75.0 (15.13)	75.2 (14.71)
Change from baseline to Week 16*	–0.6 (8.91)*	–0.6 (5.90)	–0.3 (9.50)**	0.6 (5.82)***	–0.6 (7.44)*
Predicted DLCO, %, mean (SD)[†]					
Baseline	59.3 (14.36)	60.1 (18.64)	56.8 (14.92)	61.4 (17.26)	59.7 (16.47)
Week 16	60.6 (19.12)*	63.4 (18.12)	57.0 (14.96)**	64.7 (19.80)***	62.0 (18.51)
Change from baseline to Week 16*	0.7 (9.57)*	3.2 (10.00)	–0.2 (7.12)**	3.2 (10.85)***	2.0 (9.79)*
Mahler TDI overall score, mean (SD)[††]					
Baseline	7.7 (2.61)***	7.7 (3.41)***	8.4 (2.94)***	7.3 (3.01)***	7.7 (3.00)**
Change from baseline to Week 16	0.0 (3.16)	2.1 (3.40)	–0.3 (3.28)	1.8 (3.28)	1.0 (3.41)
mRSS total score, mean (SD)[†††]					
Baseline	9.6 (9.66)	13.3 (9.33)	11.1 (8.64)	11.6 (10.22)	11.4 (9.61)
Week 16	8.8 (9.18)	13.6 (10.15)	11.2 (8.94)	11.3 (10.55)	11.2 (9.90)
Change from baseline to Week 16	–1.1 (3.95)**	0.3 (3.40)	0.1 (4.32)	–0.7 (3.32)**	–0.4 (3.71)**
HAQ-DI score, mean (SD)[‡]					
Baseline	0.55 (0.624)	0.58 (0.854)	0.45 (0.606)	0.63 (0.807)	0.57 (0.740)
Week 16	0.61 (0.719)	0.53 (0.895)	0.51 (0.729)	0.61 (0.852)	0.57 (0.805)
Change from baseline to Week 16	0.06 (0.502)	–0.05 (0.310)	0.06 (0.503)	–0.03 (0.367)	0.00 (0.419)
PtGA score, mean (SD)[‡‡]					
Baseline	35.7 (27.13)	29.3 (28.16)	28.8 (26.67)	34.7 (28.24)	32.5 (27.61)
Week 16	41.7 (25.75)	31.5 (30.25)	39.7 (29.36)	35.0 (27.89)	36.7 (28.29)
Change from baseline to Week 16	6.0 (22.25)	2.3 (19.95)	11.0 (19.71)	0.3 (21.05)	4.2 (21.06)

* n = n – 3. ** n = n – 2. *** n = n – 1. [†] Adjusted for hemoglobin. [††] Measured using a scale from +9 to –9. Negative scores indicate more severe dyspnea. [†††] Higher values indicate greater skin thickness. [‡] Visual analog scale scores for HAQ-DI are provided in Supplementary Table 3 (available online at jrheum.org). [‡‡] Measured using a visual analog scale (0–100 mm). Higher values indicate more active or severe disease. MMF: mycophenolate mofetil; FVC: forced vital capacity; TDI: Transition Dyspnea Index; mRSS: modified Rodnan skin score; HAQ-DI: Health Assessment Questionnaire–Disability Index; PtGA: patient's global assessment of disease activity.

HAQ-DI score showed little change from baseline to Week 16, with results similar across the 2- and 4-week titration groups. Mean PtGA scores showed a slight worsening of disease status at study end, and a larger increase in mean PtGA score was seen at Week 16 in the 2- versus 4-week titration group (Table 3), although the data were highly variable. Similarly, a larger increase in PtGA score was seen in the no-MMF versus MMF subgroup.

DISCUSSION

Our present findings suggest that pirfenidone has an acceptable tolerability profile in patients with SSc-ILD. The TEAE reported during our study were consistent with those observed in 3 randomized, placebo-controlled phase III trials of pirfenidone in IPF (n = 1247)[17,18] and a longterm safety assessment of pirfenidone in IPF (n = 789)[29]. Common side effects included headache and fatigue, which were reported by 44.4% and 36.5% of patients, respectively. The high proportion of these events may warrant further investigation into their effect on the tolerability of pirfenidone in SSc-ILD. However, these events were all mild or moderate in severity and none were classified as serious or led to treatment discontinuation.

The known adverse effects of pirfenidone on the GI system, skin, and liver[17,18] were of interest in SSc-ILD because these organ systems are also affected in patients with SSc[1,24,25]. Although GI AE were common, this was not unexpected because of the high frequency of such events observed in clinical trials of pirfenidone in patients with IPF, although patients with moderate to severe gastroesophageal reflux disease (UCLA GIT reflux subscale score > 1.0) were excluded from our study. Patient assessment of GI side effects using the UCLA SCTC GIT 2.0 score suggested the GI effects were stable between baseline and Week 16. This tool has previously been shown to be sensitive to changes in GI symptoms in SSc[2,30,31]. However, because the UCLA SCTC GIT questionnaire only identified AE occurring within 7 days prior to its use at the baseline and final visits, it is possible that the symptoms reported as AE during our study may have resolved in the intervening weeks. More AE may have been identified if the questionnaire had been administered more frequently.

The frequency and type of TEAE reported during the standard 2-week and the longer 4-week titration schedule reflect the favorable tolerability profile of pirfenidone in SSc-ILD. Over the course of our study, severe TEAE, TE SAE, and TEAE leading to discontinuation were more common in patients who had undertaken the 2- rather than the 4-week titration. This was also the case for dose modifications; however, it should be noted that dose adjustments were made at the discretion of the investigator for safety or tolerability reasons; more specific information was not recorded. Overall, these findings suggest that the titration schedule may affect pirfenidone tolerability and it is possible

that patients who are susceptible to the AE commonly associated with pirfenidone may benefit from a longer titration period. Indeed, future studies investigating pirfenidone in SSc-ILD should use a 4-week titration schedule.

MMF is increasingly used in SSc-ILD and it is important that any new SSc-ILD therapy can be tolerated in conjunction with this medication. In our study, MMF was received by 63.5% of patients in addition to pirfenidone, with similar tolerability to pirfenidone alone; this is notable given the known GI toxicity of both treatments[17,18,32]. Further, patients who took pirfenidone and MMF, compared with pirfenidone alone, appeared to experience fewer severe TEAE and discontinuations and had a greater improvement in dyspnea scores (although this may be due to the small size of each subgroup or imbalances in patient characteristics or background disease at baseline). The reason for the lower rate of infections reported in patients receiving MMF versus no MMF remains unclear; however, it is reassuring that MMF did not increase the rate of infections in patients with SSc-ILD. Further research is required to support this finding and provide a rationale.

Given the overlapping pathogenic mechanisms between SSc-ILD and IPF[2,5,21], it may be possible that pirfenidone would slow the deterioration of lung function in patients with SSc-ILD[17,18]. Although stable results were reported in the exploratory disease outcomes, our study was not designed with sufficient duration to assess efficacy and the study population was not enriched for more advanced disease (which may explain why no patients received concomitant CYC). Future trials should consider enrichment of study populations to include patients with progressive disease to reduce the number of patients needed to detect a treatment effect[33,34]. A further limitation to be considered when reviewing the results from efficacy analyses is that ours was a small-scale exploratory study without a comparator group, and the dosing of MMF was also not uniform.

In our study, pirfenidone showed an acceptable tolerability profile in patients with SSc-ILD. While co-administration of MMF did not appear to affect overall tolerability, a longer dose titration may have a favorable effect on tolerability. Although these results have few immediate clinical implications, the findings from the LOTUSS study are encouraging and permit further investigation of the efficacy and longterm safety of pirfenidone in future clinical trials in patients with SSc-ILD.

ONLINE SUPPLEMENT

Supplementary data for this article are available online at jrheum.org.

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