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Usefulness of monitoring mycophenolic acid exposure in systemic sclerosis-related interstitial lung disease: a retrospective cohort study

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Abstract

Background Systemic sclerosis-related interstitial lung disease (SSc-ILD) represents a significant cause of morbidity and mortality in Systemic Sclerosis (SSc). Mycophenolate mofetil (MMF) is currently the first line treatment for SSc-ILD. There is no recommendation on the dosage of mycophenolic acid (MPA) blood concentrations, so we aimed to study the correlation between MPA exposure and respiratory outcomes in this population.

Methods We conducted a retrospective cohort study of SSc-ILD patients treated with MMF in our center. According to our policy, a complete patient evaluation was performed approximately one year after MMF initiation, during which the mycophenolic acid (MPA) residual rate (RR) was measured. We analyzed the association between RR and changes in forced vital capacity (FVC) and diffusion capacity for carbon monoxide (DLCO) over time.

Results Forty-three SSc-ILD patients were included. Patients with higher RR levels (≥ 1.5 mg/L) had a significantly better FVC evolution with a higher proportion of stabilization and lower proportion of FVC decrease ($p = 0.024$). RR above 1.5 mg/L was a predictive factor of reduced FVC decline compared with lower RR levels adjusting for MMF dose and duration of MMF exposure ($p = 0.008$). There was no difference regarding DLCO outcome.

Conclusion Our study suggests that optimal MPA exposure, as indicated by RR levels, may better protect against FVC decline in SSc-ILD patients treated with MMF. Routine monitoring of MPA exposure could be beneficial in optimizing treatment outcomes. Prospective, multicenter studies are needed to further explore the relationship between MPA exposure and clinical outcomes in SSc-ILD.

Keywords Scleroderma, Connective tissue diseases, Interstitial lung disease, Mycophenolic acid, Pharmacology

Introduction

Systemic Sclerosis (SSc) is a rare connective tissue disease characterized by microvascular damage and remodeling with fibroblasts activation and extra-cellular matrix synthesis [1]. Organs involved can be the skin, heart, kidney, muscles, articulations and lungs [2]. Lung involvement is frequent in SSc, indeed, pulmonary fibrosis had been showed in 70 to 100% in autopsy series [3]. Furthermore, up to 50% of patients present significant clinical lung involvement making SSc related interstitial lung disease (SSc-ILD) a major determinant of prognosis and

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quality of life [4–6]. Currently, interstitial lung disease is the most common cause of death among these patients.

Immunosuppressive therapy (IS) for SSc-ILD is indicated for severe or worsening ILD based on international guidelines [7, 8]. In SSc-ILD, according to the Scleroderma lung study II, MMF can be used as first line-therapy or as maintenance therapy after Cyclophosphamide (CYC) [9]. MMF belongs to the anti-metabolite family and exhibits a complex pharmacokinetics. MMF is hydrolyzed by carboxylesterases in the active component, mycophenolic acid (MPA) in the stomach and absorbed [10, 11]. It is used in several diseases such as Solid Organ Transplantation (SOT), Systemic Lupus erythematous (SLE) or chronic graft versus host disease (GvHD) [12–15]. Plasma concentration has already been investigated in these diseases but not in SSc whereas MMF is now an established therapy. Plasma concentrations should range between 30–60 mg/h/L in SOT [16] and at least 35 and 30 mg/h/L respectively in SLE [17] and GvHD [18]. In SSc, the target dose of 3 grammes of MMF has shown equivalent efficacy as CYC against ILD [9, 19]. Furthermore, in SSc there are considerable MMF inter-individual variations in drug exposure and concentration: higher concentrations are found in female patients, patients with poor renal function, low body weight, whereas lower concentrations are observed in proton pump inhibitor (PPI) users [20] or overweight patient. Gastro-intestinal disorders, frequently observed in SSc patients may also cause a variation of the MMF concentration [21].

To our knowledge, only one retrospective monocentric study tried and failed to demonstrate a relationship between MMF area under the concentration–time curve (AUC) and outcomes in skin involvement using Rodnan skin score or Pulmonary Function Tests (PFTs) evolution [22]**.** Unfortunately, no data concerning radiologic or clinical evolution was reported which are two key prognostic determinants for SSc progression. Despite of this, through their study, Legendre et al. showed large inter-individual variability in MPA AUC in SSc patients for a daily dosing of 1000 mg twice daily. This result suggests that monitoring MMF could be required in SSc. However, as there is no evidence supporting measurement of MPA exposure in SSc, such dosage is not routinely recommended in current guidelines. When practitioners do use it, they generally consider that the target of MPA should be the same as in SOT. The recommended target ranges include an AUC between 30–60 mg/h/L or an estimation with residual rate (RR) (concentration level just before the next intake of medication) ranging between 1.5–5 mg/L depending on the indication of treatment. [23–25].

In this context, we conducted a retrospective study to explore the relationship between clinical, radiological, and functional ILD evolution in SSc patients and MPA-RR measured at one year of MMF treatment.

Methods

Study design and population

We conducted a retrospective monocentric study in the department of respiratory medicine of hospital Nord in Marseille, France between January 2010 and February 2024. In our hospital, SSc-ILD patients treated with MMF are monitored by RR in routine clinical practice. To be eligible, patients had to fulfill ACR/EULAR criteria [26] for SSc with ILD assessed by an expert radiologist in Multidisciplinary Discussion (MDD), to receive MMF (Cellcept® or Myfortic®) and to have a measurement of MPA-RR. All patients included in the analysis underwent PFTs and High-resolution computed tomography (HRCT) of the lungs after MMF initiation.

The Institutional Review Board of the French learned society for respiratory medicine -Société de Pneumologie de Langue Française- approved the protocol (CEPRO 2023–014), and a written information and non-objection notice was given to all participants according to French law.

Parameters analyzed

The aim of our study was to explore the relationship between the MPA-RR at steady state and the progression of the respiratory disease. For this purpose, we analyzed the variation of forced vital capacity (FVC), diffusing lung capacity for carbon monoxide (DLCO) and evolution of HRCT and dyspnea after one year of MMF treatment. Baseline was defined as the time of initiation of MMF. The evaluation time was defined as the closest time point to one year from MMF initiation, and included clinical, functional, radiological respiratory parameters and MPA-RR dosage.

For all the subjects, we collected the following data carried out in clinical routine, before MMF initiation and at the time of RR: age, sex, BMI, smoking status, dyspnea according to the mMRC (modified Medical Research Council) scale, 6-min walk test (6MWT), oxygen supplementation, co-morbidities, blood cell count, treatments used such as corticosteroids or immunosuppressants, HRCT patterns and evolution. Pulmonary hypertension, from any cause, was defined as a mean pulmonary arterial pressure above 20 mmHg, measured via right heart catheterization. All participants benefited from spirometry, plethysmography, and diffusion analysis when available (Ilmeter 1,304; Masterlab Jaeger, Wurzberg, Germany).

Variations of FVC, DLCO and HRCT patterns between MMF introduction and MPA-RR measurement were pooled in three groups: improved, stable or worsened.

Regarding PFTs, an absolute increase of more than 10% of FVC was considered as an improvement whereas an absolute decrease of more than 10% was considered as worsened. All other variations were considered as stable. An absolute increase of more than 15% in DLCO was classified as improved, whereas an absolute decrease of 15% of more was considered as worsened. All other variations were classified as stable [27]. Concerning radiologic evolution, progression, stability or amelioration was assessed in MDD with an expert radiologist in accordance with current international guidelines. The composite criterion for SSc-ILD evolution was based on the progressive pulmonary fibrosis (PPF) guidelines: meeting two of the three following criteria indicating progression: an absolute decline of 5% in FVC and/or 10% in DLCO, clinical deterioration, or radiological progression [28].

Pharmacokinetics

Residual rate samplings were performed after MPA plasma concentration has reached steady state (i.e. 5 half-lives) that mean at least 5 days after the first intake of MMF. We performed the samplings into 5 mL EDTA heparinized vacutainer tubes.

MPA RR was defined as the concentration at 12 h ± 2 h after the last drug intake. Analysis of MPA in plasma was performed by liquid chromatography-tandem mass spectrometry (LC–MS/MS). LC–MS/MS is the gold standard method with High analytical selectivity and sensitivity. A Waters XEVO TQ-S Micro Mass spectrometer coupled to a Waters Acquity liquid chromatography system was used in positive electrospray ionization mode as previously described [29]. MPA quantification was achieved using multiple reaction monitoring. MPA quantification was achieved through multiple reaction monitoring. Deuterated Mycophenolic acid was used as an internal standard. The method is linear from 0.20 to 30 µg/mL, with both accuracy and precision within 10%.

The MPA RR threshold of 1.5 mg/L was chosen in our study based on the reference value provided by our institution's pharmacologist and our center's experience, reflecting the limited evidence available regarding MMF target concentration ranges for residual rate in both SOT and SSc [24]. Accordingly, patient management at our center followed this threshold, with MMF dosing adjusted as part of routine clinical practice.

Statistical analysis

A descriptive analysis was performed on our population. Continuous variables were expressed in median and interquartile or mean and standard deviation, depending on the distribution (Shapiro–Wilk test), and qualitative variables were expressed in numbers and percentages. Qualitative parameters were compared using Chi-square tests. Quantitative parameters were compared using a student's test or a Mann–Whitney-Wilcoxon non-parametric test depending on the distribution. The association between MPA-RR and MMF dose was analyzed using Pearson correlation. Predictive factors for worsened FVC in SSc-ILD patients, in relation to the MPA-RR, were analyzed using logistic regression in both univariate and multivariate models.

All tests were two-sided. A p-value < 0.05 was considered significant. The analysis was performed using version 4.3.2 (2022–06-23) of the R software (R Core Team (2022). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/).

Results

Patient characteristics

Over the studied period (January 2010 and February 2024), we identified 54 patients who fulfilled the ACR/EULAR criteria for SSc and treated with MMF. Eleven patients did not undergo measurement of MPA-RR. Finally, 43 patients were included in the analysis. Main population characteristics at the time of MMF treatment onset are detailed in Table 1**.** Mean age was 54 years (± 14), with 34 (79%) women. Seventeen (40%) presented with diffuse cutaneous disease, 24 (56%) with limited cutaneous disease, and 2 (4,7%) with *sine scleroderma* SSc. Gastrointestinal tract involvement and PPI use was reported in 38 (88%) patients. Autoimmune diseases were associated with SSc in 10 (23%) patients, mostly Sjogren disease or SLE. Six (14%) patients died during the follow-up.

Patients presented SSc-ILD with non-specific interstitial pneumoniae (NSIP) pattern in 31 (72%) of cases. Other patterns were usual interstitial pneumoniae (UIP), unclassifiable and Pleuroparenchymal fibroelastosis in 9 (21%), 2 (4.7%) and 1 (2.3%) case, respectively. At time of treatment introduction, median FVC was 73% (range 27–109), and median DLCO was 41% (8–69) of predicted values. Fifteen patients had pulmonary hypertension (36%) and 17 patients needed supplemental oxygen (40%).

We created two groups of patients based on their MPA-RR levels at evaluation time: 19 (44%) with RR < 1.5 mg/L and 24 (56%) with RR ≥ 1.5 mg/L. A comparison of baseline characteristics between the two groups is summarized in Table 1. The MMF dose was the only variable with a significant difference between these groups (p-value 0.032), with a higher MMF dose in the ≥ 1.5 mg/L group. Seventeen (40%) patients presented adverse event, mainly digestive, without significant difference between the two groups. Treatments such as CYC, rituximab or antifibrotic drugs, as well as PFTs

Table 1 Baseline characteristics of 43 systemic sclerosis treated with mycophenolate mofetil

Characteristics	Total patients ($N=43$)[1]	T0 < 1,5, $N=19$[1]	T0 > 1,5, $N=24$[1]	*p*-value[2]
Female	34 (79%)	16 (84%)	18 (75%)	0.7
Diagnostic age (y)	50 (± 16)	46 (± 19)	54 (± 12)	0.3
Time from SSc diagnosis (months)	117 (20–464)	130 (22–464)	91 (20–337)	0.11
Age at ILD diagnostic (y)	54 (± 14)	51 (± 17)	56 (± 11)	0.4
Time from SSc-ILD diagnosis (months)	86 (20–337)	103 (22–193)	68 (20–337)	0.12
BMI (kg/m^2)	24.2 (18.0–35.7)	23.0 (18.0–32.6)	25.3 (21.6–35.7)	0.2
Comorbidities	30 (70%)	14 (74%)	16 (67%)	0.6
Other AID	10 (23%)	6 (32%)	4 (17%)	0.3
Tobacco	17 (40%)	8 (42%)	9 (38%)	0.8
mMRC				0.11
0–1	15 (36%)	4 (22%)	11 (46%)	
> 1	27 (64%)	14 (78%)	13 (54%)	
SSc type				0.3
Diffuse	17 (40%)	6 (32%)	11 (46%)	
Limitée	24 (56%)	13 (68%)	11 (46%)	
Sine scleroderma	2 (4.7%)	0 (0%)	2 (8.3%)	
Gastrointestinal tract involvment	38 (88%)	16 (84%)	22 (92%)	0.6
Anti-scl70	33 (77%)	12 (63%)	21 (88%)	0.079
Anti-centromere	1 (2.3%)	1 (5.3%)	0 (0%)	0.4
HRCT Pattern				0.2
PPFE	1 (2.3%)	1 (5.3%)	0 (0%)	
Unclassifiable	2 (4.7%)	1 (5.3%)	1 (4.2%)	
UIP	9 (21%)	6 (32%)	3 (13%)	
NSIP	31 (72%)	11 (58%)	20 (83%)	
FVC (L)	2.02 (0.93–4.38)	1.91 (1.00–4.38)	2.12 (0.93–3.34)	0.2
FVC (%)	73 (27–109)	66 (27–107)	74 (37–109)	0.2
DLCO (%)	41 (8–69)	41 (8–54)	43 (20–69)	0.3
PH (from any causes)	15 (36%)	8 (44%)	7 (29%)	0.3
Oxygen	17 (40%)	9 (47%)	8 (33%)	0.3
Steroids	19 (44%)	8 (42%)	11 (46%)	0.8
Time before MMF onset (months)	59 (0–396)	80 (0–396)	39 (0–312)	0.085
Time between MMF and residual rate (months)	12 (0–112)	13 (3–50)	12 (0–112)	0.7
MMF dose (g)				**0.032**
< 1	8 (19%)	6 (32%)	2 (8.3%)	
1–2	23 (53%)	11 (58%)	12 (50%)	
> 2	12 (28%)	2 (11%)	10 (42%)	
Residual rate MMF	1.70 (0.50–6.20)	0.70 (0.50–1.30)	2.05 (1.50–6.20)	< 0.001
Adverse event	17 (40%)	8 (42%)	9 (38%)	0.8
CYC	4 (9.3%)	1 (5.3%)	3 (13%)	0.6
Rituximab	7 (16%)	4 (21%)	3 (13%)	0.7
Antifibrosant	3 (7.0%)	1 (5.3%)	2 (8.3%)	> 0.9
Deaths	6 (14%)	4 (21%)	2 (8.3%)	0.4

RR Residual rate, *ILD* Interstitial Lung disease, *BMI* Body mass index, *AID* Auto-immune disease, *mMRC* modified Medical Research council, *SSc* Systemic sclerosis, *HRCT* High-resolution computed tomography, *PPFE* Pleuroparenchymal Fibroelastosis, *FVC* Forced vital capacity, *DLCO* Diffusing lung capacity for carbon monoxide, *PH* Pulmonary Hypertension, *MMF* Mycophenolate mofetil, *CYC* Cyclophosphamide

[1] n (%); Mean (± SD); Median (Minimum–Maximum)

[2] Fisher's exact test; Wilcoxon rank sum test; Pearson's Chi-squared test

or duration between MMF introduction and RR measurement, were not statistically different between the two groups.

MMF dose and MPA-RR relationship

The median duration between MMF introduction and RR measurement was 12 months (range 0–112). The median MMF dose and MPA-RR were 1000 mg/day (0.5–3) and 1.7 mg/L (0.5–6.2), respectively. There was a significant positive correlation between MMF dose and MPA-RR using Pearson model (rho: 0.47, *p*-value 0.002) (Fig. 1).

Patients' evolution

Table 2 compares the evolution of the PFTs, HRCT and clinical outcomes between these two groups. Concerning PFTs, the absolute evolution of FVC was significantly better in RR ≥ 1.5 mg/L group than in lower RR group (*p*-value 0.024). Indeed, a stabilization of FVC was observed in a higher proportion of patients (*n* = 17; 74%) in RR ≥ 1.5 mg/L group compared with the RR < 1.5 mg/L group (*n* = 5; 33%). In addition, a lower proportion of patients experienced a decrease of FVC in the RR ≥ 1.5 mg/L group (*n* = 3; 13%) *versus* the RR < 1.5 mg/L group (*n* = 7; 47%). Figure 2 represents the evolution of mean FVC in patients depending on MPA-RR upper or lower 1.5 mg/L.

Conversely, no significant results were found with DLCO between the 2 groups (*p*-value 0.6). Of note, data on DLCO were missing in 15 (35%) patients. Regarding HRCT, dyspnea evolution and SSc-ILD evolution based on international PPF criteria, no differences were observed between the two groups. As for missing data, 5 patients (11%) had missing FVC measurements, and 3 patients (7%) had missing HRCT data.

Table 3 summarizes predictive factors for worsened FVC evolution using logistic regression in univariate and multivariate analysis. The only protective factor was MPA-RR at evaluation time in both univariate and multivariate analyses, adjusting for MMF dose, time of MMF exposure, and patient age at diagnosis. In our cohort, a MPA-RR over 1.5 mg/L independently reduced the risk of worsened FVC evolution by

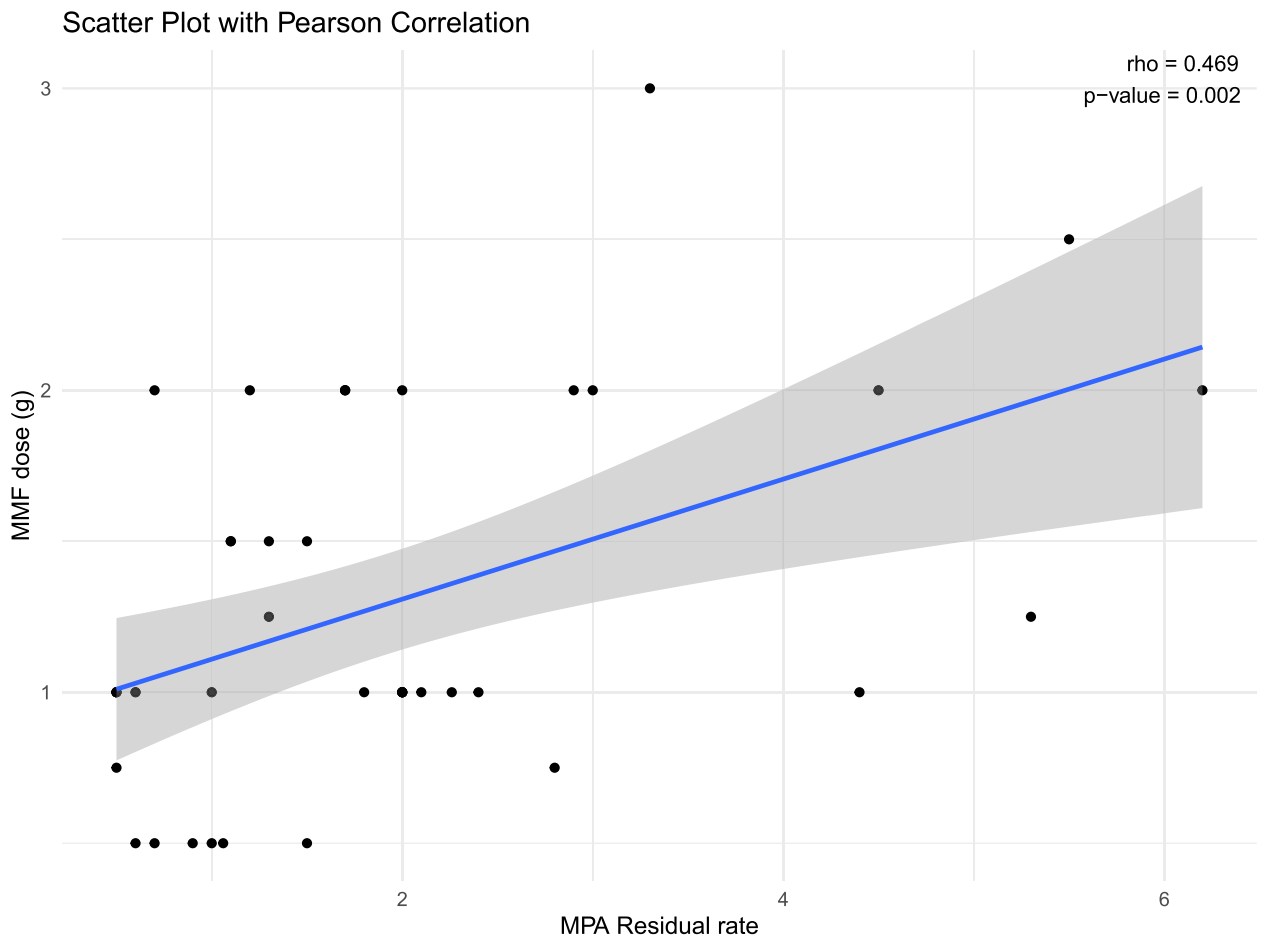

Fig. 1 Pearson correlation between mycophenolic acid residual (MPA) rate and Mycophenolate Mofetil (MMF) dose

Table 2 Clinical, functional and radiologic evolution of patients based on mycophenolic acid residual rate

Characteristics	RR < 1,5, *N* = 19[1]	RR > 1,5, *N* = 24[1]	*p*-value[2]
FVC absolute evolution			**0.024**
Decrease	7 (47%)	3 (13%)	
Increase	3 (20%)	3 (13%)	
Stable	5 (33%)	17 (74%)	
DLCO absolute evolution			0.6
Worsened	1 (9.1%)	3 (18%)	
Stable	9 (82%)	14 (82%)	
Improved	1 (9.1%)	0 (0%)	
HRCT evolution			0.4
Worsened	2 (11%)	3 (14%)	
Improved	2 (11%)	0 (0%)	
Stable	14 (78%)	19 (86%)	
mMRC evolution			0.4
Worsened	5 (29%)	5 (22%)	
Stable	10 (59%)	11 (48%)	
Improved	2 (12%)	7 (30%)	
SSc-ILD Evolution			> 0.9
Progression	3 (16%)	3 (13%)	
Stable	16 (84%)	21 (88%)	

RR Residual rate, *FVC* Forced vital capacity, *DLCO* Diffusing lung capacity for carbon monoxide, *HRCT* High-resolution computed tomography, *mMRC* modified Medical Research council, *SSc-ILD* Systemic sclerosis related interstitial lung disease

FVC = absolute increase of more than 10% was considered as an improvement whereas an absolute decrease of more than 10% was considered as worsened. All other variations were considered as stable

DLCO = absolute increase of more than 15% was considered as an improvement whereas an absolute decrease of more than 15% was considered as worsened. All other variations were considered as stable

[1] Median (Minimum–Maximum); n (%)

[2] Wilcoxon rank sum test; Fisher's exact test

95% (*p*-value 0.008) compared to a MPA-RR lower than 1.5 mg/L.

Discussion

In this study, we observed that patients with MPA-RR above 1.5 mg/L had a preserved FVC overtime compared to patients with MPA-RR under 1.5 mg/L. Additionally, our findings failed to reveal significant associations between DLCO, HRCT or SSc-ILD evolution using PPF criteria and the MPA-RR values. However, approximately 80% of patients in both groups showed stability concerning these three criteria. Without a placebo control group, we cannot definitively conclude that MMF allowed for stability in our cohort. Nonetheless, these findings are in accordance with previous multicentric studies demonstrating the efficacy of MMF in improving both FVC and DLCO in SSc-ILD patients [9, 30–32]. Indeed, MMF is established as a first-line therapy for SSc-ILD with fibrosis extent exceeding 20% [7, 8]. We believe that the lack of power in our study may have contributed to the non-significant results for DLCO, HRCT, or PPF criteria. This suggests that our sample size or the duration of MMF exposure might have been insufficient to detect significant differences. Moreover, as approximately 35% of our patients had missing DLCO data, we did not conduct further analyses comparing DLCO and MPA-RR to avoid the risk of misinterpretation of our data.

Of note, our patient cohort exhibited more severe disease manifestations with compromised PFTs compared to previous studies. Specifically, our median FVC and DLCO values were lower (73% and 41%, respectively) compared to those reported by Legendre et al. [22]. Consequently, the rate of FVC improvement in our cohort (21%) was lower than that reported in other studies [9, 33–35]. Tashkin et al. demonstrated FVC improvement in 71% of cases in Scleroderma Lung Study (SLS) II. It is noteworthy that our patients received lower MMF doses compared to those received in previous trials. Indeed, the median MMF dose in our study was 1000 mg/day, whereas patients in controlled studies such as SLS II received 3000 mg/day [9] or 2000 mg/day for most patients in Legendre et al. study [22]. This discrepancy in MMF dosage may suggest an undertreatment in our cohort, especially considering that only 56% of subjects had MPA-RR levels above 1.5 mg/L. All these differences may have contributed to the absence of a significant association between DLCO, HRCT and SSc-ILD evolution and RR measurements in our cohort.

In clinical practice, we advocate for the necessity of measuring MPA exposure and emphasize the importance of further investigation in this area. Our findings revealed that a MPA-RR level above 1.5 mg/L was the only protective factor against FVC worsening in multivariate analysis, with a remarkable 95% reduction in the risk of progression. Interestingly, this analysis was adjusted on MMF dose and time of exposure, underscoring the significance of inter- and intra-individual variability in MMF pharmacokinetics. This variability is also highlighted by the moderate correlation of MMF dose and MPA-RR observed in our study. However, it is worth mentioning that we employed MPA target ranges established in other conditions, and optimal ranges specific to SSc may differ.

Prior research has demonstrated a correlation between MPA exposure and disease activity with recommended target ranges for MPA plasma exposure typically expressed as AUC values ranging from 30 to 60 mg/L.h or residual rate concentrations between 1.5 to 4 mg/L [23]. Moreover, considerable inter-individual variability in MPA plasma exposure has been observed [36, 37], which may also be extended to SSc due to factors such as

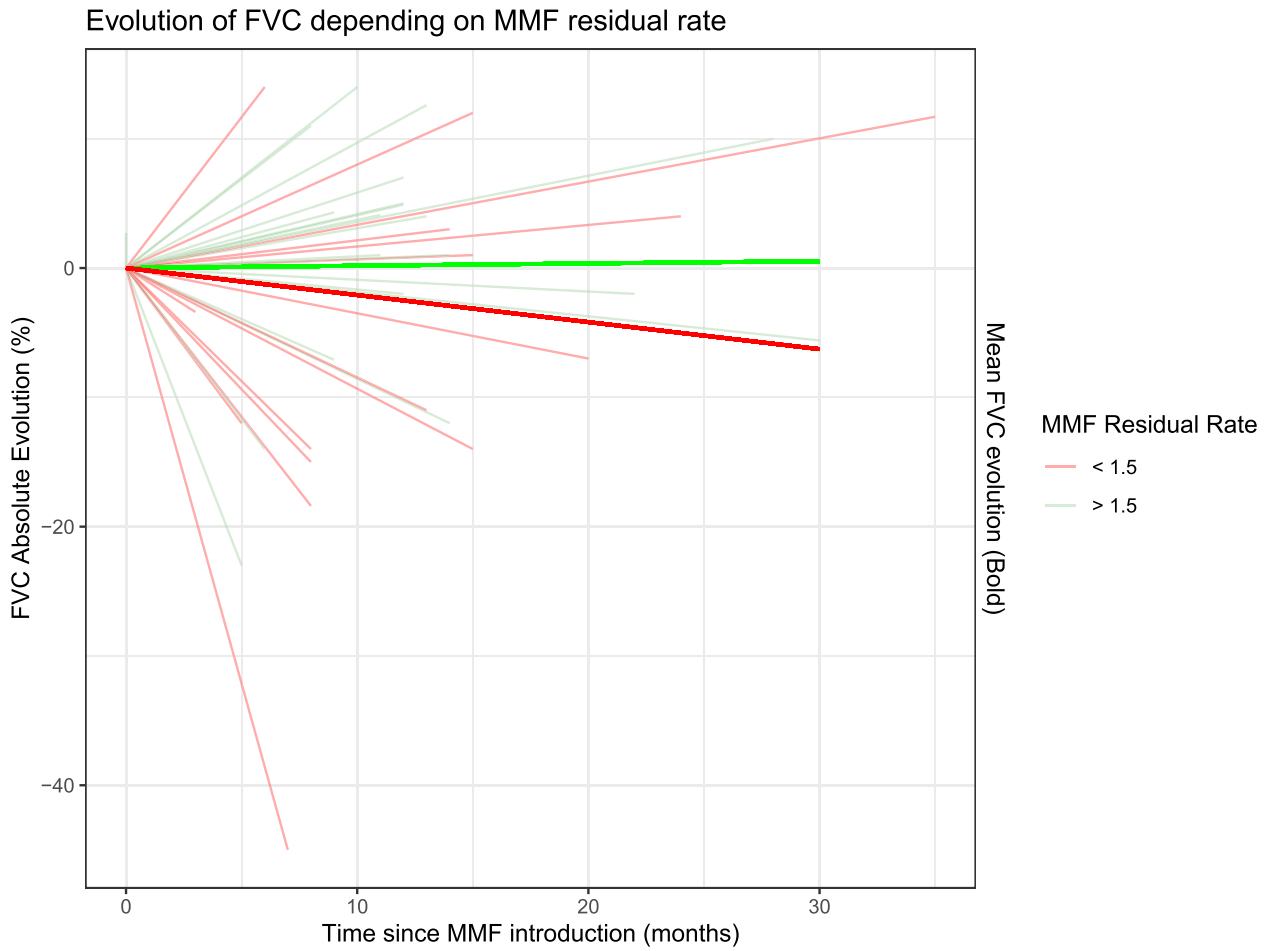

Fig. 2 Longitudinal Plot of mean FVC evolution depending on mycophenolic acid residual rate

PPI use or gastrointestinal tract involvement [21]. However to the best of our knowledge, Legendre et al. were the only investigators to explore the relationship between MMF treatment and skin or lung involvement, as assessed by Rodnan skin score and PFT variation, respectively [22]. Our findings are consistent with previous research indicating significant inter-individual variability in MPA plasma exposure, supporting the importance of documenting MPA plasma exposure in patients with SSc. MPA concentrations in our cohort ranged widely from 0.5 to 6.2 mg/L, with daily MMF doses varying from 500 to 3000 mg.

Our study boasts several strengths. We present the largest cohort of SSc-ILD investigating MPA exposure to date. Contrary to previous findings by Legendre et al., our study demonstrated the beneficial impact of RR measurements on FVC progression [22]. FVC has been identified as a critical determinant of mortality in ILD, underscoring the clinical relevance of this association [38]. Moreover, the simultaneous assessment of RR and PFTs is noteworthy, given the wide variability in MPA blood concentration. The comparable baseline characteristics of our two patient groups facilitated a more precise comparison of the effect of MMF exposure. The AUC is more difficult to measure in real life because of the need of multiple blood samples. Indeed, our results are easier to generalize in routine clinical practice as it only requires one sample for RR measurement.

Several limitations of our study should be acknowledged. First, due to the retrospective nature, we could only report RR of MPA, as there were significant missing data regarding AUC. Additionally, being monocentric with a relatively sample size, our study may be subject to inherent biases. Notably, skin involvement, a major outcome and an indication for MMF therapy in SSc patients, was not consistently reported. As a result, we could not assess usefulness of monitoring MPA on the skin progression of SSc. Furthermore, patients in our cohort could have been treated with either Cellcept® or Myfortic®, potentially introducing pharmacokinetic or

Table 3 Predictive factors of FVC worsening in univariate and multivariate analysis

Characteristics	Univariate				Multivariate		
	N	OR[a]	95% CI[a]	*p*-value	OR[a]	95% CI[a]	*p*-value
Diagnostic age (y)	38	1.03	0.98, 1.09	0.2	1.05	0.99, 1.12	0.089
Female	38	0.51	0.10, 2.96	0.4			
BMI (kg/m2)	38	0.97	0.80, 1.17	0.8			
Comorbidities	38	1.30	0.29, 7.05	0.7			
Other AID	38	0.41	0.02, 2.89	0.4			
Tobacco	38	1.55	0.35, 6.82	0.6			
mMRC	38			0.8			
0–1		1.00	—				
> 1		0.83	0.19, 3.92	0.8			
SSc type	38			0.8			
Diffuse		1.00	—				
Limitée		1.00	0.22, 4.83	> 0.9			
Sine scleroderma		3.00	0.10, 89.1	0.5			
Gastrointestinal tract involvement	38	0.18	0.02, 1.28	0.085			
Anti-Scl70	38	0.64	0.13, 3.62	0.6			
Anti-centromere	38	0.00		0.4			
FVC (L)	38	2.00	0.78, 5.80	0.15			
FVC (%)	38	1.01	0.98, 1.06	0.4			
DLCO (%)	32	1.01	0.96, 1.07	0.6			
PH	38	0.53	0.07, 2.67	0.5			
Oxygen	38	0.66	0.12, 2.97	0.6			
Steroids	38	0.57	0.11, 2.54	0.5			
Time before MMF onset (months)	38	0.99	0.98, 1.00	0.2			
MMF dose (g)	38			0.7			0.8
< 1		1.00	—		1.00	—	
1–2		0.80	0.12, 6.88	0.8	0.51	0.02, 12.2	0.7
> 2		0.44	0.04, 4.80	0.5	1.00	0.03, 48.2	> 0.9
Time between MMF and residual rate (months)	38	0.89	0.75, 1.00	0.058	0.85	0.69, 1.00	0.053
MPA Residual rate	**38**			**0.022**			**0.008**
< 1.5		1.00	—		1.00	—	
> 1,5		0.17	0.03, 0.78	0.029	0.05	0.00, 0.49	0.021
CYC	38	0.00		0.2			
Rituximab	38	1.15	0.14, 6.62	0.9			
Antifibrotics	38	6.75	0.58, 157	0.12			

BMI Body mass index, *AID* Auto-immune disease, *mMRC* modified Medical Research council, *SSc* Systemic sclerosis, *FVC* Forced vital capacity, *DLCO* Diffusing lung capacity for carbon monoxide, *PH* Pulmonary Hypertension, *MMF* Mycophenolate mofetil, *CYC* Cyclophosphamide

[a] *OR* Odds Ratio, *CI* Confidence Interval

pharmacodynamic variations. Moreover, measurements of residual rate or AUC do not guarantee consistent MPA exposure throughout the follow-up period, as fluctuations in concentration may occur due to factors such as changes in medication or infections [21, 36, 37]. In clinical practice, poor compliance with mycophenolate dosing is not uncommon due to the large number of tablets required daily or the occurrence of side effects, which may lead patients to deviate from the indicated (and reported) dosage. However, as this is a real-life study, the significant difference observed between the groups can be considered a strength, as it reflects the clinical impact despite potential adherence issues. Despite its importance as a prognostic determinant in SSc-ILD, we were unable to draw conclusions regarding DLCO probably due to missing data. Although MPA-RR is routinely measured in our center, 11 patients did not undergo this assessment. This may be largely explained by the retrospective design of our study which contributed to the missing data. Even if these patients represent a small

portion of our cohort, their exclusion could introduce a bias.

Conclusion

We have identified for the first time, an association between MPA exposure and outcomes in SSc-ILD. Optimal MMF exposure, as indicated by MPA-RR above 1.5 mg/L appears to be a protective factor against FVC worsening. Thus, the routine monitoring of MPA exposure, for a better adaptation of MMF dose, may offer clinical benefits to patients. Future prospective, multicenter studies with larger sample sizes are warranted to further explore pharmacokinetic/pharmacodynamic relationships in SSc and to optimize methods for measuring MPA plasma exposure.

Abbreviations

SSc	Systemic sclerosis
SSc-ILD	SSc related interstitial lung disease
IS	Immunosuppressive therapy
ILD	Interstitial lung disease
MMF	Mycophenolate Mofetil
CYC	Cyclophosphamide
MPA	Mycophenolic acid
SOT	Solid Organ Transplantation
SLE	Systemic Lupus erythematous
GvHD	Chronic graft versus host disease
PPI	Proton pump inhibitor
AUC	Area under the concentration–time curve
PFTs	Pulmonary function tests
RR	MPA residual rate
MDD	Multidisciplinary Discussion
HRCT	High resolution computed-tomography
FVC	Forced vital capacity
DLCO	Diffusing lung capacity for carbon monoxide
mMRC	Modified Medical Research Council
PPF	Pulmonary Progressive Fibrosis
NSIP	Interstitial pneumoniae
UIP	Usual interstitial pneumoniae
SLS	Scleroderma Lung Study

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Authors' contributions

JM, JB, ES design the study and methods. Clinical data were provided by ES, JB, BC, AN, BG, MR. Statistical analyses were done by JM, SD. JM wrote the original draft. ES, JB, BG, MR reviewed and edited the manuscript. Figures were created by JM, SD, BC. Supervision by JB, AB, BG, MR. Guarantor of the study is JB. All authors read and approved the manuscript.

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Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The Institutional Review Board of the French learned society for respiratory medicine -Société de Pneumologie de Langue Française- approved the protocol (CEPRO 2023–014), and a written information and non-objection notice was given to all participants according to French law.

Consent for publication

A written information and non-objection notice was given to all participants according to French law.

Competing interest

The authors declare no competing interests.

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