Rheumatology, 2024, **00**, 1–9
https://doi.org/10.1093/rheumatology/keae532
Advance access publication 30 September 2024
Original Article

Clinical sience

Long-term retention rate, adverse event temporal patterns and rescue treatment strategies of mycophenolate mofetil in systemic sclerosis: insights from real-life

Enrico De Lorenzis [1,2], Gerlando Natalello [1,*], Greta Pellegrino [3], Lucrezia Verardi [1], Veronica Batani [4], Gemma Lepri [5], Stefano Stano [6], Giuseppe Armentano [7], Marco De Pinto [8], Francesca Motta [9,10], Stefano Di Donato [2], Vishal Kakkar [2], Silvia Fiore [1], Ilaria Bisconti [3], Corrado Campochiaro [4], Laura Cometi [5], Antonio Tonutti [9], Amalia Spinella [8], Simona Truglia [3], Silvia Cavalli [7], Maria De Santis [9,10], Dilia Giuggioli [8], Nicoletta Del Papa [7], Serena Guiducci [5], Fabio Cacciapaglia [6], Giacomo De Luca [4], Fiorenzo Iannone [6], Valeria Ricceri [3], Marco Matucci Cerinic [4], Maria Antonietta D'Agostino [1], Francesco Del Galdo [2], Silvia Laura Bosello [1]

[1]Unit of Rheumatology, Catholic University of the Sacred Heart, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy
[2]Scleroderma Program, Leeds Institute of Rheumatic and Musculoskeletal Diseases, University of Leeds, Leeds, UK
[3]Rheumatology Unit, Department of Clinical Internal, Anesthesiological and Cardiovascular Sciences, Sapienza University of Rome, Rome, Italy
[4]Unit of Immunology, Rheumatology, Allergy and Rare Diseases, IRCCS San Raffaele Hospital, Milan, Italy
[5]Rheumatology Unit, Department of Clinical and Experimental Medicine, University of Florence, Florence, Italy
[6]Rheumatology Unit, Department of Emergency and Organs Transplantation, Università degli Studi di Bari Aldo Moro, Bari, Italy
[7]Scleroderma Clinic, Dip. Reumatologia, ASST G. Pini-CTO, Università degli Studi di Milano, Milano, Italy
[8]Department of Rheumatology, University of Modena and Reggio Emilia, Modena, Italy
[9]Rheumatology and Clinical Immunology, IRCCS Humanitas Research Hospital, Rozzano, Italy
[10]Department of Biomedical Sciences, Humanitas University, Pieve Emanuele, Italy

*Correspondence to: Gerlando Natalello, Division of Rheumatology, Università Cattolica del Sacro Cuore, Policlinico Universitario Agostino Gemelli IRCSS, Largo Francesco Vito, 1—00168 Rome, Italy. E-mail: gerlando.natalello1@guest.policlinicogemelli.it

Abstract

Objectives: MMF is a mainstay for the treatment of SSc. The occurrence and implications of MMF-related adverse events (AEs) on drug retention rates in real life remain poorly defined. We aimed to determine the MMF retention rate and to investigate the causes and patterns of discontinuation, AEs and treatment options used after discontinuation.

Methods: SSc patients who started MMF treatment underwent a retrospective longitudinal assessment for up to 5 years. We documented the incidence, predictors and impacts of MMF treatment on gastrointestinal intolerance, infections, laboratory abnormalities and cancer. Rescue strategies implemented after MMF discontinuation were recorded.

Results: The 5-year MMF retention rate of 554 patients stood at 70.7%, and 19.6% of them stopped MMF due to AEs. One out of every four patients experienced a dose reduction or discontinuation of MMF due to AEs, with gastrointestinal intolerance being the predominant cause. The 5-year cumulative incidence rates for gastrointestinal intolerance, cancer, severe infections and laboratory toxicity leading to MMF discontinuation were 6.4%, 4.1%, 3.1% and 2.1%, respectively. Lower respiratory tract was the most affected, with bacteria being the predominant causative agent. Intestinal and pulmonary circulation involvement were tied to elevated AE rates and MMF discontinuation. The most common approaches post-MMF cessation were 'watch and wait' and switch to rituximab.

Conclusions: : MMF use in SSc appears to be limited by the occurrence of AEs, both in terms of persistence and dosing of the drug. Rescue options after MMF discontinuation are limited and many patients remain without immunosuppressant.

Keywords: SSc, mycophenolate mofetil, safety, persistence, infections, cancer, rescue strategy.

Received: 3 July 2024. **Accepted:** 17 September 2024

Rheumatology key messages

- One in five SSc patients has to discontinue MMF due to adverse events (AEs).
- Gastrointestinal intolerance, cancer, severe infections and laboratory toxicity are leading causes of discontinuation, each presenting with a peculiar temporal pattern.
- Involvement of the intestinal and pulmonary circulation are the main risk factors for AEs leading to MMF discontinuation.

Introduction

MMF is a first-line treatment for SSc-related interstitial lung disease (SSc-ILD) [1]. In clinical practice, its use is commonly extended to the treatment of diffuse skin involvement and associated myositis [2]. Backed by recent clinical data, MMF has been increasingly used as part of combination therapies together with rituximab (RTX) and nintedanib (NTD) [3, 4]. The safety and potential efficacy of MMF in the limited cutaneous subset are also being investigated, irrespective of other established indications (https://classic.clinicaltrials.gov/ct2/show/NCT04927390).

Among possible adverse events (AEs) associated with MMF, gastrointestinal intolerance symptoms are common but reversible upon discontinuation of the drug, while infections could have a negative impact on lung function, symptoms, overall health and survival [5, 6]. The evidence regarding an increased risk of cancer in patients on MMF remains elusive [7].

The retention rate of MMF depends on its efficacy, emergence of AEs, anticipated risk of relapse after discontinuation and availability of alternative treatments. Real-life data on MMF use in SSc, which also considers long-term follow-up and potential interactions with other treatments and comorbidities commonly unaddressed in controlled trials, are lacking. Therefore, the majority of the data published on MMF are derived from cohorts of solid organ transplanted patients [8].

The primary objective of the study was to determine the retention rate of MMF in a multicentre cohort of SSc patients and characterize the discontinuation patterns in relation to AEs. Second, AEs of specific interest, such as infections, laboratory abnormalities and newly diagnosed cancer, were analysed regardless of their impact on MMF treatment. Finally, we performed an exploratory analysis to identify clinical characteristics associated with a higher risk of AE-related discontinuation and the rescue strategies implemented following MMF discontinuation in clinical practice.

Methods

Study design, participants, and data collection

The STROBE checklist was utilized to outline the longitudinal retrospective cohort study design [9]. Consecutive patients evaluated in nine academic centres between 1 January 2012 and 31 December 2021 were included in the final analysis if they (i) met the SSc ACR/EULAR classification criteria [10] and (ii) had started MMF treatment for the first time within the specified period. Ethical approval was obtained from the following local Ethics Committees: Comitato Etico Policlinico A. Gemelli, English Health Research Authority, Comitato Etico Sapienza University of Rome, Comitato Etico IRCCS San Raffaele Hospital protocol, Comitato Etico Poclinico di Bari, Comitato Etico ASST Gaetano Pini CTO, Comitato Etico Università di Modena e Reggio Emilia and Comitato Etico Humanitas Research Hospital (Supplementary Table S1, available at *Rheumatology* online).

Clinical data were extracted through an electronic health records review process [11] based on a standard workflow agreed in two preliminary meetings among authors, carried out by clinicians directly involved in SSc management. Disease duration was calculated from the first non-Raynaud symptom. Definitions of SSc-related organ involvement, comorbidities, treatments and outcomes were standardized to ensure reproducibility and consistency across centres, and were based on definitions reported in the literature or consensually agreed (Supplementary Table S2, available at *Rheumatology* online). The starting dosage was defined as the initial MMF dosage following the commonly adopted 4–6-week titration period. While subsequent dosage changes were reported, the initial dosage was used as the outcome predictor. A mid-term central quality check was performed.

Outcome measures

The primary outcome was the permanent discontinuation of MMF due to AEs (i.e. those that lasted for at least 12 weeks). MMF discontinuation was further classified according to the primary reason of interruption: (i) gastrointestinal intolerance, (ii) severe infection, (iii) recurrent infection, (iv) laboratory toxicity, (v) cancer (newly diagnosed or recurrence) and (vi) other intolerance. The secondary end point included the occurrence of AEs of specific interest, irrespective of their impact on therapeutic decisions (severe infections, laboratory abnormalities and cancer). Rescue therapies adopted within the 6 months following AE-related MMF discontinuation were also detailed.

Characterization of infective episodes

Only data on severe infections were collected to minimize potential patient recall biases. We relied on the classification systems developed for immunosuppressed patients post-bone marrow transplant [12]. They included bacteraemia and sepsis, lower respiratory tract infections, any bacterial foci requiring inpatient management, symptomatic CMV infection, Herpes Zoster virus infection, *Candida* infections with candidemia or deep organ involvement, aspergillosis and toxoplasmosis (Supplementary Table S3, available at *Rheumatology* online).

We categorized infectious episodes based on the required intervention, drawing on the Common Terminology Criteria for Adverse Events (CTCAE) used in oncology (https://ctep.cancer.gov). Infections presenting mild or no symptoms, requiring only observation (grade 1), were excluded. Remaining infections were characterized as those needing oral treatment at home or other non-invasive interventions (grade 2), those that required hospital admission for intravenous treatment, surgery, or unstable disease (grade 3) and finally, the most severe infections that necessitated admission to the intensive care unit or led to death due to critical

complications like shock, hypotension, acidosis or tissue necrosis (grade 4).

Statistical analysis

Statistical plan and sample size determination are reported as supplementary material, available at *Rheumatology* online. Notably, a competing risk analysis with sub Hazard Ration (sHR) with 95% CI calculation was performed to explore the clinical variables linked to AEs. This approach was selected over the cause-specific hazard model Cox regression since competing events could not be regarded as censored upon their occurrence. This choice was influenced by the expected high incidence of competing events and the possible associations between the clinical variables and both the outcomes and competing events [13, 14].

Data on mycophenolate retention rates in SSc are limited, so a single hypothesis-driven analysis was considered inadequate for the purposes of the study. We anticipated that clinical predictors of discontinuation due to AEs, inefficacy or clinical stability would differ and impact the analysis in various ways. Consequently, we included all the principal demographic and disease-related variables as potential predictors. Statistical analysis was adjusted for multiple comparisons using Benjamini–Hochberg correction.

Results

Overall drug retention rate and impact of AEs on MMF treatment

A total of 545 patients fulfilling the inclusion criteria were included in the analysis after the screening of medical records from 3595 patients. The median (interquartile range) follow-up duration was 3.1 (1.3–4.9) years. The starting dose of MMF ranged from 2.0 to 2.5 g/day for 69.9% of patients, was <2 g/day for 23.7%, and was 3 g/day for 6.4% of patients. A combination of RTX and MMF was recorded in 11.4% of patients.

The clinical characteristics of the cohort are presented in Table 1 and detailed in Supplementary Table S4, available at *Rheumatology* online for single centre. Notably, only 12 patients were treated with azathioprine and 17 with methotrexate prior to the initiation of MMF.

We reported 106 discontinuation events. The MMF retention rates (95% CI) were 91.6% (89.2–94.0%), 88.6% (85.9–91.5%), 83.7% (80.3–87.2%), 79.6% (75.7–83.7%) and 70.7% (65.7–76.1%) at the end of the 1, 2-, 3-, 4-, and 5-year periods, respectively. The MMF discontinuation rate stood at 6.5 (5.3–7.9) per 100 patient-years (Fig. 1). Out of these, 71 MMF cessations were due to AEs, corresponding to a 5-year cumulative incidence (95% CI) of 19.6% (15.3–24.3%) and to an AE-related discontinuation rate of 4.4 (3.4–5.5) per 100 patient-years. The primary cause for MMF cessation at the 5-year mark was the occurrence of gastrointestinal symptoms with a discontinuation cumulative incidence of 6.4% (4.2–9.3%) and a discontinuation rate of 1.6 (1.0–2.3) per 100 patient-years, followed by cancer with a 5-year discontinuation cumulative incidence of 4.1% (2.1–7.2%) and a discontinuation rate of 0.7 (0.3–1.2) per 100 patient-years. Severe infections produced a 5-year discontinuation cumulative incidence of 3.1% (1.5–5.8%) with a discontinuation rate of 0.6 (0.3–1.0) per 100 patient-years while for recurrent infections was observed a 5-year discontinuation cumulative incidence of 2.3% (1.1–4.2%) and a discontinuation rate of 0.6 (0.3–1.0) per 100 patient-years. Finally, laboratory abnormalities led to a discontinuation cumulative incidence at 5 years of 2.1% (1.1–3.6%) and a discontinuation rate of 0.6 (0.3–1.1) per 100 patient-years. Fig. 2 depicts the temporal patterns in MMF discontinuations. In the initial treatment year, the primary reasons for cessation were gastrointestinal intolerance and laboratory abnormalities. However, as the follow-up lengthened, discontinuations attributed to infections and cancer became more prevalent.

Notably, 63 more patients had a reduction in their MMF dosage from the initially titrated dosage due to AEs. Globally, 134 patients, representing 24.6% of the population at risk at the index date, underwent either persistent MMF cessation or dosage reduction because of AEs over the monitored period (Fig. 3). Only 17 patients increased their dosage of MMF to 3 g/day during follow-up.

Lastly, 35 MMF cessation events were unrelated to AEs as a leading cause of decision. Nineteen were due to treatment

Table 1. Characteristics of the study cohort at baseline

	N = 545
Age (years), mean±SD	53.1 ± 14.2
Male gender, *n* (%)	97 (17.8%)
BMI, kg/m^2, mean ± SD	24.1 ± 4.4
Current or former smoker, *n* (%)	155 (28.5%)
Disease duration (years), median (IQR)	2.0 (0.0, 8.0)
Le Roy Diffuse cutaneous variant, *n* (%)	298 (54.7%)
ACA positive, *n* (%)	88 (16.1%)
Anti-Scl70 positive, *n* (%)	287 (52.7%)
Capillaroscopy pattern	
Nonspecific, *n* (%)	83 (16.3%)
Early scleroderma, *n* (%)	92 (18.0%)
Active scleroderma, *n* (%)	189 (37.1%)
Late scleroderma, *n* (%)	146 (28.6%)
mRSS, median (IQR)	6.0 (2.0, 12.0)
Digital ulcers, *n* (%)	253 (46.4%)
Skin calcinosis, *n* (%)	107 (19.6%)
Synovitis, *n* (%)	98 (18.0%)
Myositis, *n* (%)	51 (9.4%)
ILD on HRCT, *n* (%)	434 (79.6%)
FVC, % of predicted, mean ± SD	90.7 ± 21.5
DLco, % of predicted, mean ± SD	61.7 ± 20.4
Pulmonary hypertension, *n* (%)	81 (14.9%)
Severe gastro-oesophageal involvement, *n* (%)	388 (71.2%)
Severe intestinal involvement, *n* (%)	96 (17.6%)
MMF starting dose	
Low dose (0.5–1.5 g/die), *n* (%)	129 (23.7%)
Standard dose (2.0–2.5 g/die), *n* (%)	381 (69.9%)
Full dose (3.0 g/die), *n* (%)	35 (6.4%)
Previous CYC treatment, *n* (%)	122 (22.4%)
Combination of immunosuppressants, *n* (%)	80 (14.7%)
Combination of MMF and RTX, *n* (%)	62 (11.4%)
Combination of MMF and corticosteroids, *n* (%)	214 (39.3%)
Combination of MMF and NTD, *n* (%)	29 (5.3%)
Diabetes mellitus, *n* (%)	32 (5.9%)
COPD, *n* (%)	14 (2.6%)
CKD, *n* (%)	18 (3.3%)
Chronic viral hepatitis, *n* (%)	18 (3.3%)
Major cardiovascular events, *n* (%)	33 (6.1%)
Cancer at baseline, *n* (%)	35 (6.4%)

CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DLco, diffusion capacity of the lung for carbon monoxide; FVC, forced vital capacity; HRCT, high-resolution computed tomography; ILD, interstitial lung disease; IQR, interquartile range; mRSS, Modified Rodnan Skin Score; NTD, nintedanib; PH, pulmonary hypertension; RTX, rituximab.

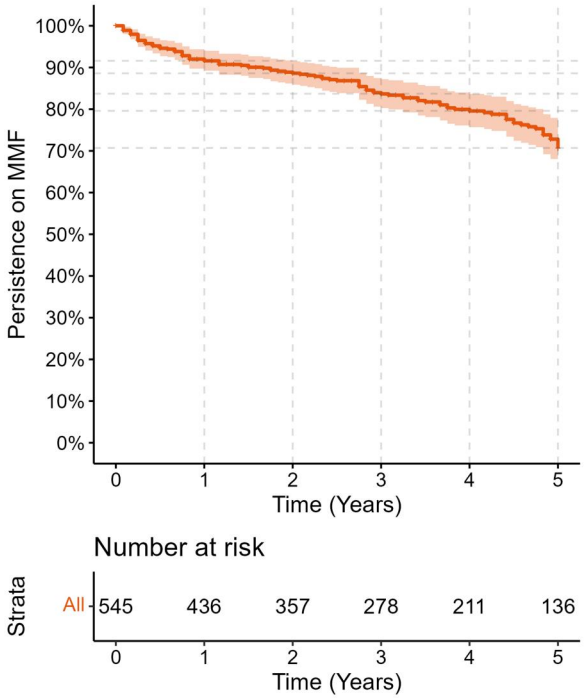

Figure 1. Drug persistence in SSc patients treated with MMF

failures, primarily leading to the initiation or switch to CYC. The remaining 16 patients discontinued MMF because of clinical stability, planning for pregnancy or personal preference.

Clinical risk factors for MMF discontinuations related to AEs

When considering all AEs leading to MMF discontinuation, patients at a higher risk of discontinuing this medication had a lower alveolar diffusion of carbon monoxide (DLco) at baseline (sHR 0.98, 95% CI 0.97–0.99), had a severe intestinal involvement related to SSc (sHR 2.16, 95% CI 1.31–3.56), a history of current or past smoke exposure (sHR 1.78, 95% CI 1.11–2.87), were anti-Scl70 negative (sHR 0.57, 95% CI 0.35–0.91), had pulmonary hypertension (PH) (sHR 1.81, 95% CI 1.08–3.05) and had associated chronic kidney disease (CKD) (sHR 2.84, 95% CI 1.16–6.95). Statistical significance was maintained for low DLco and severe intestinal involvement associated with SSc after adjusting for multiple comparisons. Additionally, patients experiencing AEs that led to MMF discontinuation were older and had a higher Modified Rodnan Skin Score (mRSS) at baseline, although these associations did not achieve statistical significance (Fig. 4).

As detailed above, gastrointestinal intolerance was the leading reason for discontinuing MMF. The clinical phenotype of these patients was marked by myositis (sHR 3.07, 95% CI 1.22–7.75), PH (sHR 2.43, 95% CI 1.06–5.57) and intestinal involvement (sHR 2.76, 95% CI 1.27–6.02). Moreover, these patients exhibited lower DLco values at baseline (sHR 0.98, 95% CI 0.95–0.99). Statistical significance was affected by multiple comparison adjustment. Additionally, patients who discontinued MMF during follow-up due to gastrointestinal intolerance were more likely to be anti-Scl70 negative, exhibit a late pattern on capillaroscopy, have a longer disease duration and show higher mRSS, without reaching statistically significant association (Supplementary Fig. S1, available at *Rheumatology* online).

Severe infections

Severe infections were the most common AEs recorded during MMF treatment, even if they did not represent the leading cause of MMF discontinuation or dose reduction. Within the 5-year follow-up, 26.2% (95% CI 21.6–30.9%) of patients reported at least one severe infection, leading to an incidence rate of 7.1 (95% CI 5.8–8.6) per 100 patient-years (Fig. 2B).

The characteristics of the infections according to the year of follow-up are comprehensively illustrated in Fig. 5. The annual absolute risk of severe or life-threatening infections ranged from 5.9% to 12.7% of the at-risk population, peaking during the final year of observation. A progressive increase in the annual risk of life-threatening infections over the years was also observed, starting from 0.4% in the first year to 3.3% in the last year. Similarly, the highest annual absolute risk of hospitalization occurred in the last year of observation, peaking at 9.9%. Of these patients, 22 (21.6%) experienced multiple infective episodes during MMF treatment: 15 experienced two episodes, 4 experienced three episodes and 3 experienced four episodes. Notably, more than half of the patients who experienced severe infections each year encountered their first episode of severe infection at that time. Respiratory tract infections were predominant. Even when excluding those associated with SARS-CoV-2, they represented at least two-thirds of the severe infections each year. Similarly, bacteria were by far the most common responsible agent, accounting for more than three out of every four severe infections each year.

The risk of encountering at least one severe or life-threatening infection during MMF treatment was higher in males (sHR 1.98, 95% CI 1.30–3.03), in patients with ACA positivity (sHR 1.82, 95% CI 1.16–2.86) and anti-Scl70 negativity (sHR 0.64, 95% CI 0.43–0.95), in those with a late capillaroscopy pattern (sHR 1.54, 95% CI 1.03–2.31), PH (sHR 2.03, 95% CI 1.29–3.18) and associated chronic obstructive pulmonary disease (sHR 3.17, 95% CI 1.38–7.30). Statistical significance was maintained for male gender and PH after adjusting for multiple comparisons. The risk also seemed elevated, though without statistical significance, in older patients, current and past smokers, those who had CYC induction prior to starting MMF, those concurrently on corticosteroids and those diagnosed with CKD or diabetes mellitus (Fig. 3). No association emerged with the presence of SSC-ILD.

Laboratory abnormalities

During the 5-year follow-up, 8.8% (95% CI 6.2–11.8%) of the population experienced laboratory abnormalities, which resulted in an incidence rate of 2.5 (95% CI 1.8–3.4) per 100 patient-years (Fig. 2B). Out of the 39 recorded toxicity episodes, 21 (53.8%) were attributed to cytopenia, 14 (35.9%) to elevated transaminase levels and 4 (10.3%) to increased pancreatic enzymes. Laboratory abnormalities led to a persistent dose reduction in 13 cases (33.3%) and to the MMF discontinuation in 10 cases (25.6%). Patients with intestinal involvement related to SSc exhibited a heightened risk of laboratory abnormalities (sHR 2.04, 95% CI 1.03–4.05). Statistical significance was affected by multiple comparison adjustment. Though not reaching statistical significance, there was a trend towards patients who encountered laboratory abnormalities having lower mRSS and DLco values at baseline (Supplementary Fig. S2, available at *Rheumatology* online).

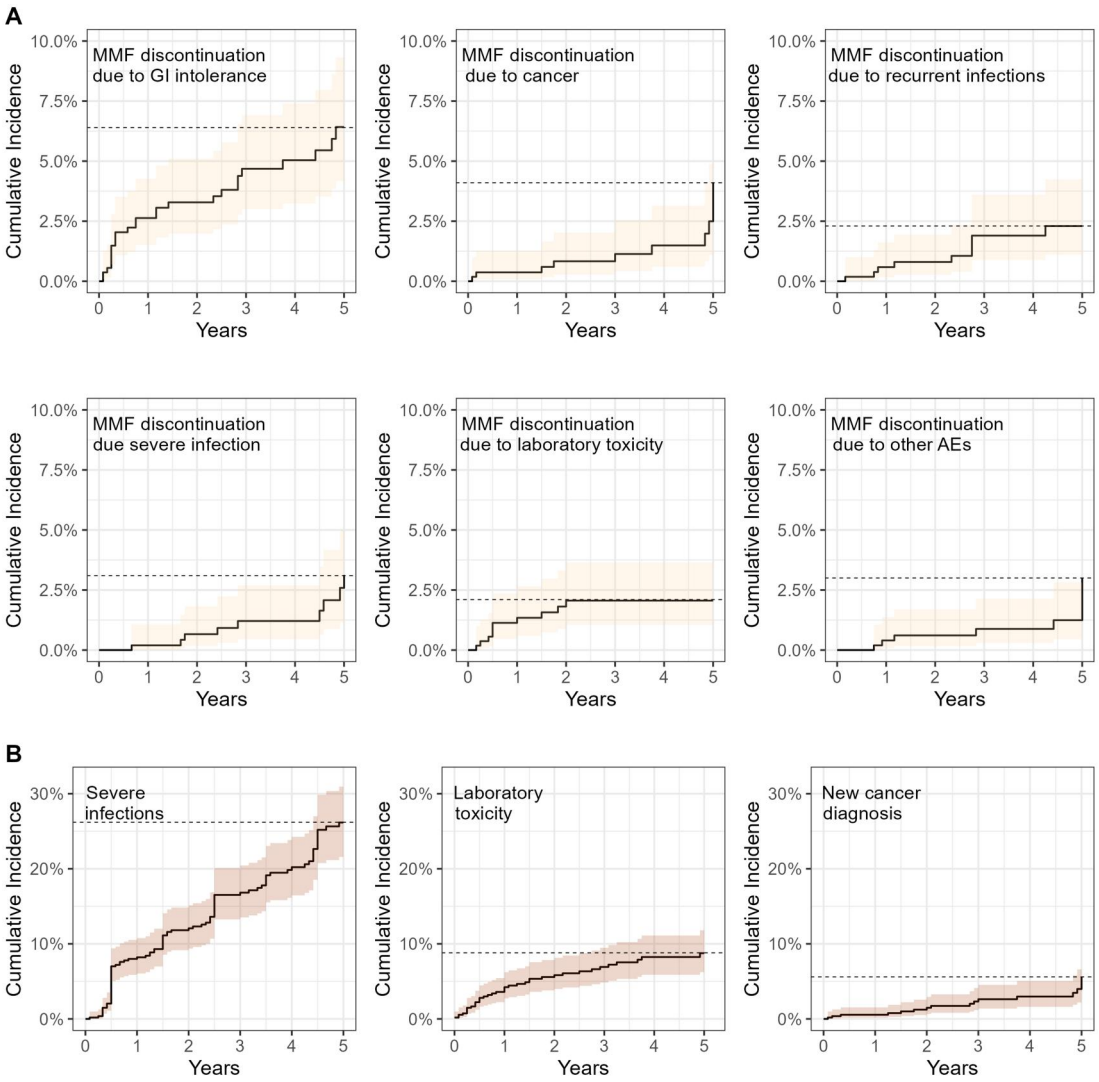

Figure 2. Cumulative incidence outcome measures. **A**) Comparison of AE-related discontinuation cumulative incidence curves, **B**) comparison of severe infection, laboratory toxicity and cancer cumulative incidence curves. AE, adverse event; GI, gastrointestinal

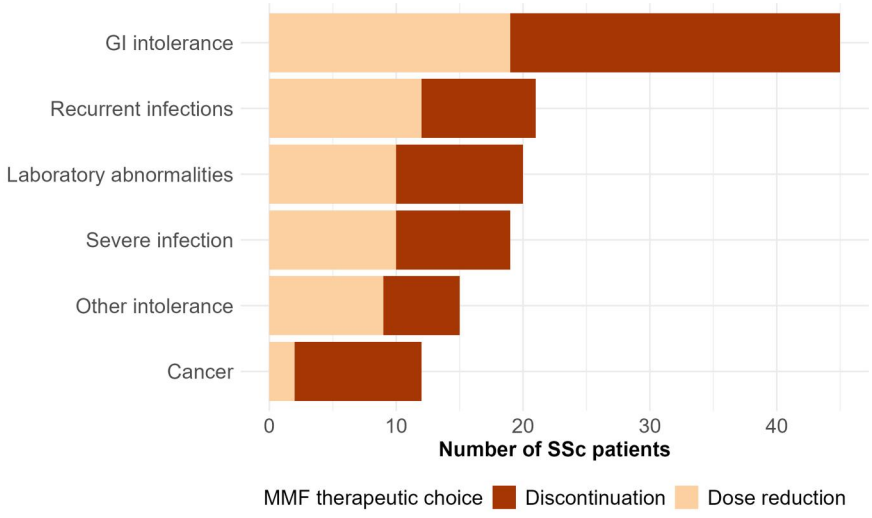

Figure 3. MMF permanent discontinuations or dose reductions by the end of the follow-up, categorized by different AEs. AE, adverse event; GI, gastrointestinal

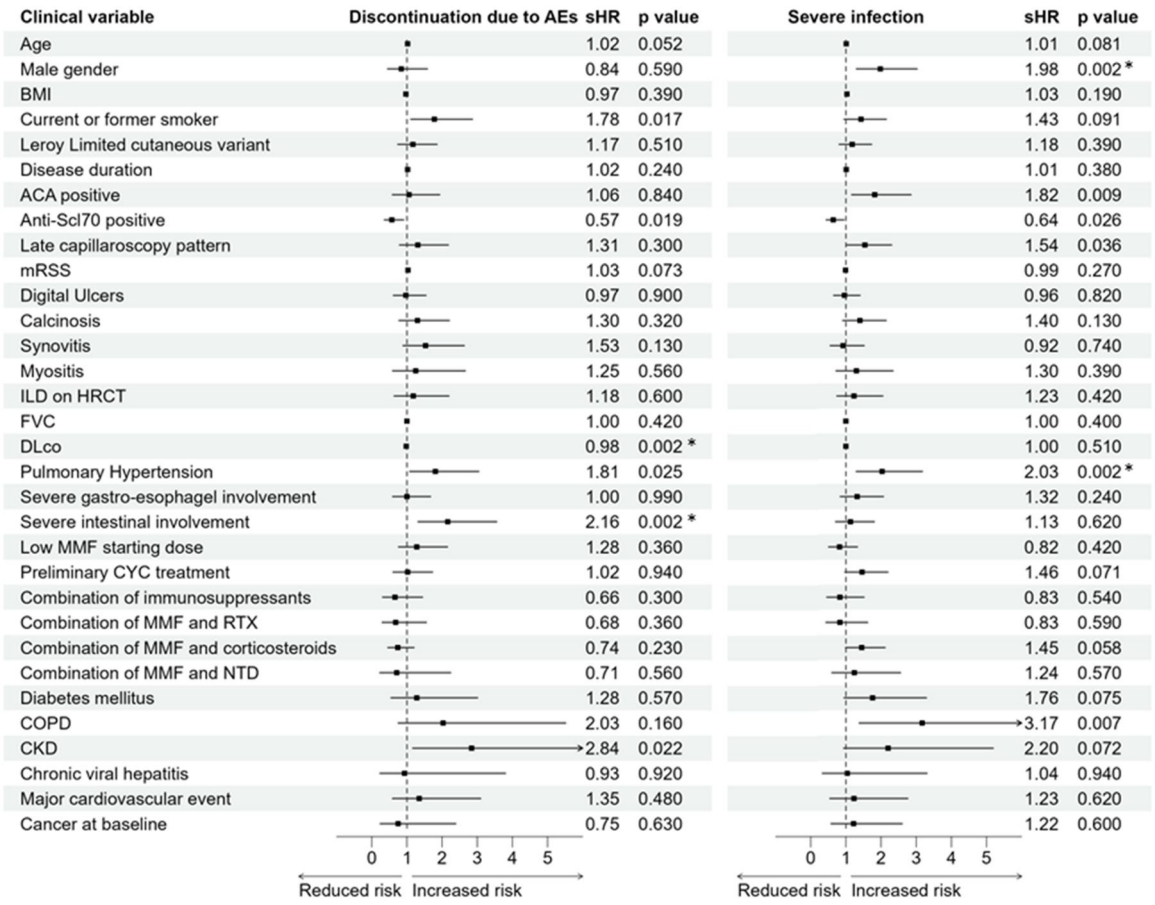

Figure 4. Association of baseline clinical characteristics and risk of MMF discontinuation due to AEs and risk of severe infections. CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DLco, diffusion capacity of the lung for carbon monoxide; FVC, forced vital capacity; HRCT, high-resolution computed tomography; ILD, interstitial lung disease; NTD, nintedanib; mRSS, Modified Rodnan Skin Score; PH, pulmonary hypertension; RTX, rituximab; sHR, sub hazard ratio. *Statistically significant, with a formal *P*-value threshold of 0.003, after adjustment for multiple comparisons

Cancer

During the follow-up, 17 new cancer diagnoses were recorded, resulting in a cumulative incidence of 5.6% (3.2–8.9%) within 5 years of initiating MMF treatment and in an incidence rate of 1.0 (95% CI 0.6–1.7) per 100 patient-years. Of note, the cumulative incidence curve indicates cancer as a late event during the available follow-up (Fig. 2B). All these patients were diagnosed with cancer for the first time, as none of them had a prior history of oncological conditions. Conversely, none of the 35 patients with a history of cancer at the time of MMF initiation experienced a relapse during the follow-up. Among the newly diagnosed cancers, five were haematological, three were pulmonary, three were breast, two were non-melanoma skin cancers and the remaining four were cases of ovarian, pancreatic, melanoma and thyroid cancers, respectively. Following the diagnosis, 11 patients (64.7%) discontinued MMF, while the treatment remained unchanged for 5 patients (29.4%). Finally, 1 patient underwent a permanent dose reduction after cancer diagnosis.

The risk of developing cancer during MMF treatment was higher in patients with a reduced BMI (sHR 0.87, 95% CI 0.77–0.98), in those exhibiting intestinal involvement related to SSc (sHR 2.90, 95% CI 1.10–7.63), shorter disease duration (sHR 0.84, 95% CI 0.71–1.00), concurrent CKD (sHR 8.22, 95% CI 2.46–27.48) and reduced exposure to corticosteroids (sHR 0.28, 95% CI 0.08–0.95). Statistical significance was affected by multiple comparison adjustment (Supplementary Fig. S3, available at *Rheumatology* online).

Rescue strategies implemented after MMF discontinuations due to AEs

The clinical decision flow following 71 MMF discontinuation episodes is illustrated in Supplementary Fig. S4, available at *Rheumatology* online. In 33 cases (46.5%), patients who discontinued MMF due to AEs did not initiate any alternative treatment. The primary reasons for MMF discontinuation were heterogeneous: 11 patients experienced severe gastrointestinal intolerance, 5 had a severe infection, 5 had recurrent infections, 4 presented laboratory abnormalities, 5 were diagnosed with cancer and 2 had other forms of intolerance. RTX emerged as the primary alternative treatment choice post-discontinuation, selected for 14 (19.7%) patients. Other significant alternatives included azathioprine for 6 patients, NTD for 5 patients and CYC for 3 patients. Importantly, 6 patients passed away post-MMF discontinuation due to causes directly or indirectly related to SSc or MMF treatment. Excluding those who passed away, patients who did not commence any active immunosuppressive or antifibrotic treatment typically had lower forced vital capacity values at the outset, a longer disease duration and were more inclined to take RTX in combination with MMF, but they did not continue RTX after MMF discontinuation. Additionally, these

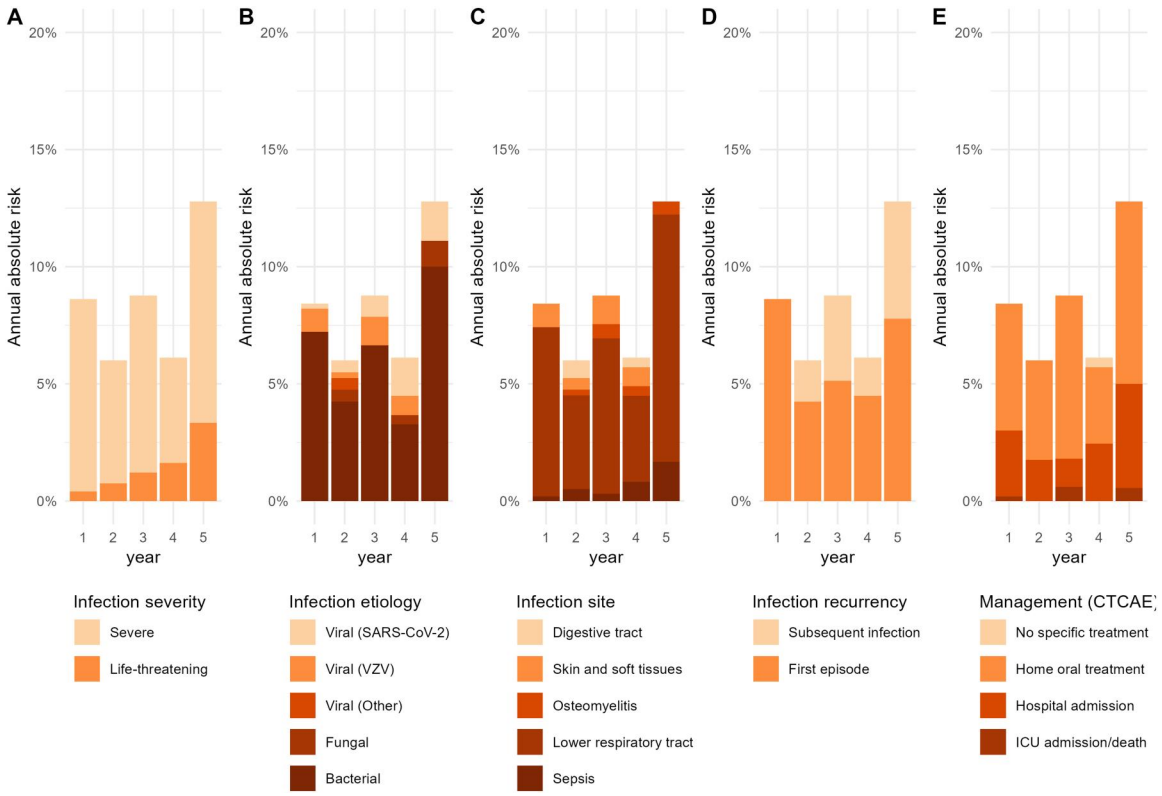

Figure 5. Characterization of severe infections during MMF treatment according to the year of follow-up. **A**) Infection severity, **B**) microbiologically demonstrated or clinically presumed aetiology, **C**) infection site, **D**) Temporal relationship with other severe infections, **E**) required intervention according to CTCAE system. CTCAE, Common Terminology Criteria for Adverse Events; ICU, intensive care unit; VZV, varicella zoster virus

individuals often had a lower BMI at baseline, though this difference was not statistically significant. The individual causes of discontinuation were distributed similarly (Supplementary Table S4, available at *Rheumatology* online).

Discussion

In this retrospective longitudinal study, we performed a comprehensive evaluation of the 5-year retention rate and discontinuation patterns of MMF treatment for SSc. AEs emerged as a primary reason for MMF discontinuation in a large real-life cohort of SSc patients. Additionally, a substantial number of patients required a reduction of the initially prescribed dose due to AEs. In figures, one in five patients had to discontinue MMF and one in four patients could not maintain the desired dose due to AEs.

Gastrointestinal intolerance emerged as the leading cause for MMF discontinuation and was associated with SSc intestinal involvement, myositis and aspects of impaired pulmonary circulation, as indicated by the lower DLco and elevated pulmonary pressure.

Predictably, SSc gastrointestinal involvement is linked to a higher chance of symptoms, such as nausea, dyspepsia, bloating and diarrhoea that could also favour MMF intolerance. Furthermore, it could also be associated with MMF-altered bioavailability due to malabsorption with reduced serum albumin levels, weight loss with decreased volume of distribution and changes in the drug's enterohepatic circulation, which can be attributed to alterations in gut microbiota [15]. From this perspective, preliminary data indicate a weak relationship between the serum concentration of mycophenolic acid, the MMF metabolite and clinical response in SSc [16]. However, it is not yet established whether its concentration could predict the risk of side effects and guide dose titration.

Notably, the risk of discontinuing MMF due to AEs isn't confined to either the initial or advanced stages of the disease or medication use. Previous small, monocentric studies largely concur with these findings [17–19]. However, different types of AEs seem to have different incidence patterns throughout the treatment period. In our cohort, gastrointestinal intolerance and laboratory toxicity appeared earlier, while infections and cancer were more frequently observed later during the treatment. This finding suggests distinct mechanisms of toxicity for the early and long-term phases of MMF treatment, with a predominance of aspects of cellular toxicity in the early period and more profound functional alteration of the immune system in the long term. The discontinuation of MMF in the presence of recurrent infections later in treatment could be related to a medical decision that balances the benefits and risks of continuing MMF.

Taking such a pattern into account could be useful for a fine titration strategy based on pharmacokinetic parameters could provide a personalized therapeutic window for the patient [20, 21], reducing acute AEs related to cellular toxicity and aligning drug bioavailability according to the clinical phenotype. On the other hand, the introduction of strategies of MMF interruptions or reductions in therapy in case of clinical stability could help to balance the negative effects related to immunosuppression and infections.

Notably, two out of three patients started with an MMF dose ranging from 2 to 2.5 g/day, which is lower than the dose tested in clinical randomized trials. Only 6.4% of

patients received the full dose of 3 g/day. Using a lower dose, <2 g/day, did not appear to reduce the risk of AEs overall or specific AEs, such as gastrointestinal intolerance, infections, laboratory abnormalities or cancer.

Similarly, MMF was combined with RTX in 11.4% of patients, but no increased risk of AEs, specifically severe infections, was reported in SSc patients treated with this combination in this real-life cohort. It should be considered that the use of RTX in combination may be less common in patients with higher infection risk factors [22]. Patients with both limited and diffuse cutaneous variants face a similar risk of AE-related MMF discontinuation. This risk seems at least partially independent of the presence of other major complications of the disease, such as digital ulcers, lung fibrosis and involvement of the upper digestive tract. Anti-Scl70 positivity appeared to be a protective factor for MMF discontinuation. However, it is likely that patients who are anti-Scl70 positive are likely perceived as being at high risk for a more severe disease course. This perception may result in a higher threshold for drug discontinuation and a strong indication to continue medication. Additionally, anti-Scl70-positive patients might experience reduced MMF bioavailability, which could lower their risk of adverse effects [23].

Severe infections, predominantly bacterial lower respiratory tract infections, were a common AE during MMF treatment while complications from varicella zoster virus, CMV or fungal infections were relatively rare, as were complicated skin infections resulting from skin ulcerations. The impact of severe infections on MMF discontinuation appears to be limited, indicating that most patients who experienced severe infections or related hospitalizations continued MMF treatment once the acute infection was resolved.

New cancer diagnoses were among the least common AEs considered, while none of the patients with a history of cancer experienced a relapse during MMF treatment. This aligns with existing data suggesting there is no heightened risk of neoplastic transformation with MMF, although, in this regard, the limitation related to the length of the observation period must be kept in mind. Still, cancer was the second leading cause of MMF discontinuation among considered AEs. Clinicians showed uncertainty in pursuing immunosuppressant therapy in the context of a concomitant neoplastic disease, possibly due to expected interactions with cancer therapies or uncontrolled infective risk, leading to the discontinuation of MMF in almost all cancer findings. More robust data on the safety of MMF in this situation are desirable, as they might better help to balance the treatment schedule according to specific situations. The correlation with a shorter baseline disease duration might suggest the presence of some paraneoplastic form of SSc; meanwhile, the association with clinically evident intestinal involvement could potentially be a misclassification, influenced by a reduced BMI or symptoms related to cancer.

A notable observation pertains to rescue strategies. Our data indicate that active rescue treatment is typically reserved for patients with severe functional pulmonary involvement and those with a longer disease duration to avoid potential disease reactivation upon stopping MMF, while decision-making report highlights the use of RTX as the most common rescue therapy [24], and it is important to mention that many of these patients were observed before NTD was licensed for treating rapidly progressive ILD. This context might, at least in part, account for the identified therapeutic gaps revealed by the analysis. The 'wait and see' decision could be related also to the scarcity of controlled data for rescue therapies and to the delay in starting alternative drugs due to local regulations for off-label therapies.

Some limitations of this study should to be taken into account. The first is its retrospective design. While measures were taken to minimize recall biases, the study design is not suited to establish a causative relationship between clinical variables and outcome measures. The limited number of events prevented a sufficiently powered multivariate analysis to examine all the potential confounders. Despite the retrospective study design, our data about the discontinuation of MMF go in the same direction as what was previously shown in the two main controlled trials using MMF [1–25], and the observations about the discontinuation and distribution of AEs are in line with a systematic review on MMF in SSc [2] and with other previous studies with a lower number of patients and with a shorter follow-up [26, 27].

Moreover, gastrointestinal involvement did not rely on a standard conventional definition, which is not available for SSc patients. We used a comprehensive definition that included symptoms, instrumental and laboratory evidence or the need for symptomatic treatments in an attempt of methodological standardization.

Finally, we did not provide any real-life data on the efficacy of MMF in controlling clinical manifestations in SSc patients, as this was beyond the aims of our data collection.

In conclusion, MMF use in SSc appears to be limited, both in terms of persistence on therapy and dosing of drug, by the occurrence of AEs. MMF-based treatment strategies and schemes other than those used under the controlled conditions of clinical trials are advisable in real life to optimize the management of SSc. Our data, derived from a large cohort of well-characterized patients in a specialty care setting, may be useful in informing forthcoming pre-clinical and clinical studies on the topic.

Supplementary material

Supplementary material is available at *Rheumatology* online.

Data availability

The authors confirm that the data supporting the findings of this study are available within the article or its supplementary materials. The datasets generated and analysed during the current study are available from the corresponding author on reasonable request. All data have been anonymized to protect participant confidentiality and comply with ethical guidelines. For further inquiries, please contact gerlando.natalello1@guest.policlinicogemelli.it.

Funding

The authors declare that this research received no external funding. All aspects of the study, including design, data collection, analysis and manuscript preparation, were self-supported and undertaken without financial assistance from any institution, organization or grant provider.

Disclosure statement: The authors have declared no conflicts of interest.

References

1. Tashkin DP, Roth MD, Clements PJ *et al.*; Sclerodema Lung Study II Investigators.Mycophenolate mofetil versus oral cyclophosphamide in scleroderma-related interstitial lung disease (SLS II): a randomised controlled, double-blind, parallel group trial. Lancet Respir Med 2016;4:708–19.
2. Omair MA, Alahmadi A, Johnson SR. Safety and effectiveness of mycophenolate in systemic sclerosis. A systematic review. PLoS One 2015;10:e0124205.
3. Distler O, Highland KB, Gahlemann M *et al.*; SENSCIS Trial Investigators. Nintedanib for systemic sclerosis-associated interstitial lung disease. N Engl J Med 2019;380:2518–28.
4. Mankikian J, Caille A, Reynaud-Gaubert M *et al.*; EVER-ILD investigators and the OrphaLung Network. Rituximab and mycophenolate mofetil combination in patients with interstitial lung disease (EVER-ILD): a double-blind, randomised, placebo-controlled trial. Eur Respir J 2023;61:2202071.
5. Barahona-Correa JE, De La Hoz A, Lopez MJ *et al.* Infections and systemic sclerosis: an emerging challenge. Rev Colomb Reumatol 2020;27:62–84.
6. Tanaka M, Koike R, Sakai R *et al.* Pulmonary infections following immunosuppressive treatments during hospitalization worsen the short-term vital prognosis for patients with connective tissue disease-associated interstitial pneumonia. Mod Rheumatol 2015;25:609–14.
7. Hirunsatitpron P, Hanprasertpong N, Noppakun K *et al.* Mycophenolic acid and cancer risk in solid organ transplant recipients: systematic review and meta-analysis. Br J Clin Pharmacol 2022;88:476–89.
8. Bhat R, Tonutti A, Timilsina S, Selmi C, Gershwin ME. Perspectives on mycophenolate mofetil in the management of autoimmunity. Clin Rev Allergy Immunol 2023;65:86–100.
9. Von Elm E, Altman DG, Egger M *et al.*; STROBE Initiative. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. BMJ 2007;335:806–8.
10. Van den Hoogen F, Khanna D, Fransen J *et al.* 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/European League against Rheumatism collaborative initiative. Arthritis Rheum 2013;65:2737–47.
11. Vassar M, Holzmann M. The retrospective chart review: important methodological considerations. J Educ Eval Health Prof 2013;10:12.
12. Cordonnier C, Maury S, Ribaud P *et al.* A grading system based on severity of infection to predict mortality in allogeneic stem cell transplant recipients. Transplantation 2006;82:86–92.
13. Austin PC, Fine JP. Practical recommendations for reporting Fine-Gray model analyses for competing risk data. Stat Med 2017; 36:4391–400.
14. Latouche A, Porcher R, Chevret S. Sample size formula for proportional hazards modelling of competing risks. Stat Med 2004; 23:3263–74.
15. Bullingham RE, Nicholls AJ, Kamm BR. Clinical pharmacokinetics of mycophenolate mofetil. Clin Pharmacokinet 1998; 34:429–55.
16. Legendre P, Blanchet B, Porcher R *et al.* Mycophenolic acid drug monitoring in patients with systemic sclerosis associated with diffuse skin and/or pulmonary involvement: a monocentric and retrospective French study. J Scleroderma Relat Disord 2021;6:87–95.
17. Swigris JJ, Olson AL, Fischer A *et al.* Mycophenolate mofetil is safe, well tolerated, and preserves lung function in patients with connective tissue disease-related interstitial lung disease. Chest 2006;130:30–6.
18. Janardana R, Irodi A, Chebbi PP *et al.* Mycophenolate in scleroderma-associated interstitial lung disease: real-world data from rheumatology and pulmonology clinics in South Asia. J Scleroderma Relat Disord 2021;6:271–6.
19. Van Gelder T, Le Meur Y, Shaw LM *et al.* Therapeutic drug monitoring of mycophenolate mofetil in transplantation. Ther Drug Monit 2006;28:145–54.
20. Zahr N, Arnaud L, Marquet P *et al.* Mycophenolic acid area under the curve correlates with disease activity in lupus patients treated with mycophenolate mofetil. Arthritis Rheum 2010;62:2047–54.
21. Chaigne B, Gatault P, Darrouzain F *et al.* Mycophenolate mofetil in patients with anti-neutrophil cytoplasmic antibody-associated vasculitis: a prospective pharmacokinetics and clinical study. Clin Exp Immunol 2014;176:172–9.
22. De Luca G, De Lorenzis E, Campochiaro C *et al.* Rituximab retention rate in systemic sclerosis: a long term real-life multicenter study. Rheumatology (Oxford) 2024;15:keae280.
23. Andréasson K, Neringer K, Wuttge DM *et al.* Mycophenolate mofetil for systemic sclerosis: drug exposure exhibits considerable inter-individual variation-a prospective, observational study. Arthritis Res Ther 2020;22:230.
24. Narváez J, LLuch J, Molina-Molina M *et al.* Rituximab as a rescue treatment added on mycophenolate mofetil background therapy in progressive systemic sclerosis associated interstitial lung disease unresponsive to conventional immunosuppression. Semin Arthritis Rheum 2020;50:977–87.
25. Highland KB, Distler O, Kuwana M *et al.*; SENSCIS Trial Investigators. Efficacy and safety of nintedanib in patients with systemic sclerosis-associated interstitial lung disease treated with mycophenolate: a subgroup analysis of the SENSCIS trial. Lancet Respir Med 2021;9:96–106.
26. Mendoza FA, Nagle SJ, Lee JB, Jimenez SA. A prospective observational study of mycophenolate mofetil treatment in progressive diffuse cutaneous systemic sclerosis of recent onset. J Rheumatol 2012;39:1241–7.
27. Nihtyanova SI, Brough GM, Black CM, Denton CP. Mycophenolate mofetil in diffuse cutaneous systemic sclerosis—a retrospective analysis. Rheumatology (Oxford) 2007;46:442–5.

Rheumatology, 2024, 00, 1–9
https://doi.org/10.1093/rheumatology/keae532
Original Article