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

Form

Statistical plan and sample size determination

Categorical variables were presented as numbers and percentages and compared using the Chi-square or Fisher's tests. Continue variables were presented either as mean with standard deviation (SD) or as median with interquartile range (IQR) and compared using the T-test or Mann-Whitney test, as appropriate.

Patients were longitudinally monitored for up to 5 years, starting from the index date of MMF introduction. The follow-up ended upon treatment discontinuation, death from any cause, or the conclusion of the available follow-up, whichever came first. Follow-up ended on December 31, 2023, for all patients. The occurrence of outcomes was quantified in terms of incidence rate and 5-year cumulative incidence with 95% confidence interval (CI).

The Kaplan-Meier method was employed to compute the cumulative incidence in the at-risk population. Given the potential recurrence of the outcome, the annual absolute risk for the infection of interest was also calculated, with the at-risk population comprising those patients who completed at least six months of follow-up in each of the five years of observation. The pattern of censoring was compared based on the observation of the cumulative incidence plots.

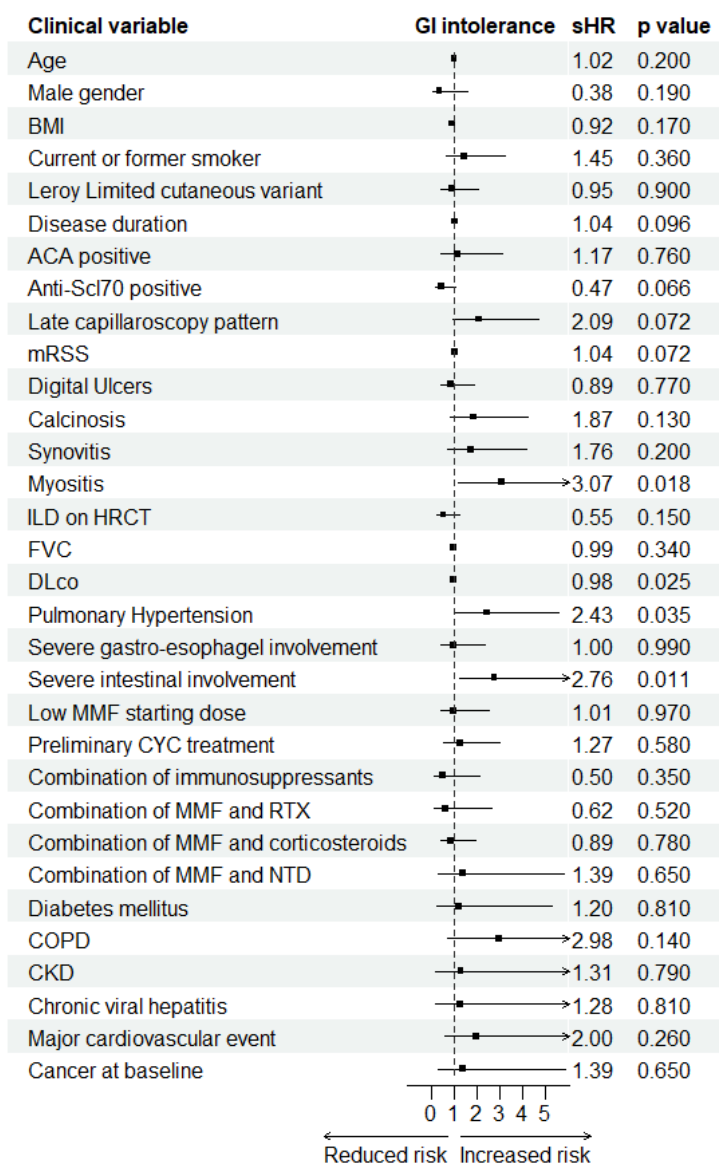
A competing risk analysis was performed to explore the clinical variables linked to MMF discontinuation due to AEs and the emergence of AEs of interest. This approach was selected over the cause-specific hazard model Cox regression since competing events could not be regarded as censored upon their occurrence. 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 events¹. MMF discontinuation for reasons other than AEs was considered the competing event to discontinue due to AEs. Similarly, MMF discontinuation for any reason was considered the competing event for occurrences such as gastrointestinal intolerance, severe or life-threatening infections, detection of laboratory abnormalities, and a new cancer diagnosis. The outcomes' sub-distribution hazard function was modeled using the Fine-Gray model. The association was expressed as a sub-Hazard Ratio (sHR) with 95% CI. For descriptive analysis, alluvial plots were utilized to illustrate treatment choice trajectories following MMF discontinuation based on the specific AE responsible.

All statistical analyses deemed a p-value of less than 0.05 as statistically significant, and all tests were two-tailed with Benjamini-Hochberg correction for multiple comparisons. The statistical analysis was conducted using RStudio, version 2023.06.1.

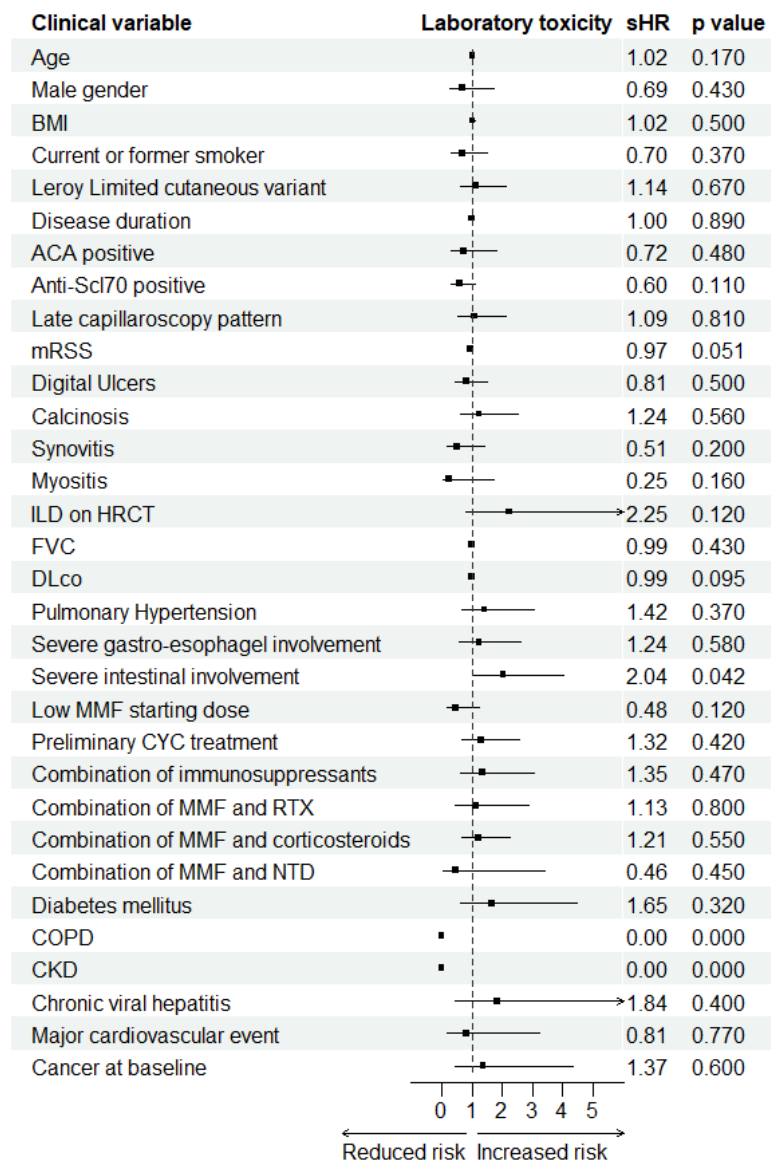
A sample size of at least 546 patients was estimated for the study for nominal type I error rate 0.05 and power 0.80, a minimum sHR of 1.5 for the association between outcome and prediction, and a 30% censoring rate.

1 Austin PC, Fine JP. Practical recommendations for reporting Fine-Gray model analyses for competing risk data. Stat Med. 2017;36(27):4391-4400. doi:10.1002/sim.7501

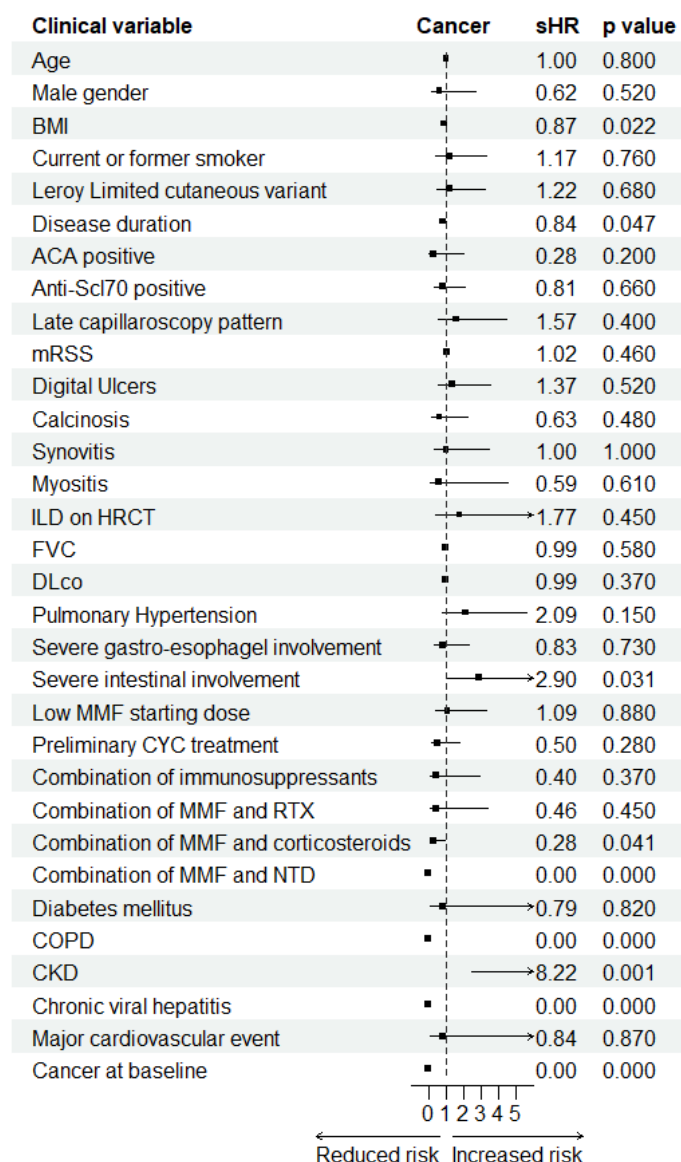
Supplementary Figure 1: Association of baseline clinical characteristics and risk of MMF discontinuation due to gastrointestinal intolerance ACA (Anti-centromere Antibody), BMI (Body Mass Index), CKD (chronic kidney disease), COPD (chronic obstructive pulmonary disease), CYC (Cyclophosphamide), DLco (Diffusion Capacity of the Lung for Carbon Monoxide), FVC (Forced Vital Capacity) HRCT (High-Resolution Computed Tomography), ILD (Interstitial Lung Disease), MMF (Mycophenolate Mofetil), NTD (Nintedanib), mRSS (Modified Rodnan Skin Score), PH (Pulmonary Hypertension), RTX (Rituximab), sHR (sub Hazard Ratio). The formal threshold for statistical significance was set at a p-value of 0.003, following adjustment for multiple comparisons.



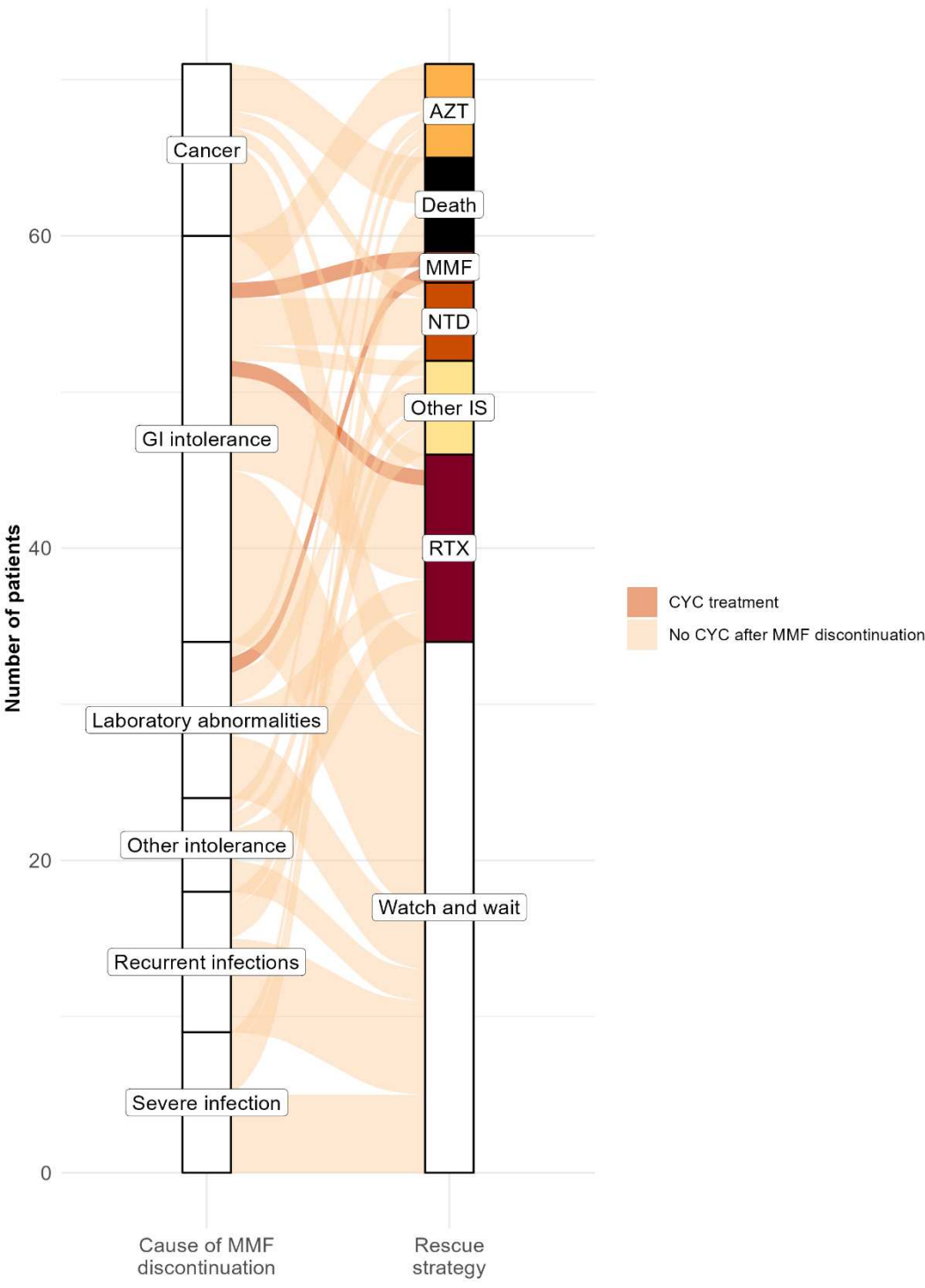
Supplementary Figure 2: Association of baseline clinical characteristics and risk of laboratory toxicity. ACA (Anti-centromere Antibody), BMI (Body Mass Index), CKD (chronic kidney disease), COPD (chronic obstructive pulmonary disease), CYC (Cyclophosphamide), DLco (Diffusion Capacity of the Lung for Carbon Monoxide), FVC (Forced Vital Capacity) HRCT (High-Resolution Computed Tomography), ILD (Interstitial Lung Disease), MMF (Mycophenolate Mofetil), NTD (Nintedanib), mRSS (Modified Rodnan Skin Score), PH (Pulmonary Hypertension), RTX (Rituximab), sHR (sub-Hazard Ratio). The formal threshold for statistical significance was set at a p-value of 0.003, following adjustment for multiple comparisons.



Supplementary Figure 3: Association of baseline clinical characteristics and risk of cancer. ACA (Anti-centromere Antibody), BMI (Body Mass Index), CKD (chronic kidney disease), COPD (chronic obstructive pulmonary disease), CYC (Cyclophosphamide), DLco (Diffusion Capacity of the Lung for Carbon Monoxide), FVC (Forced Vital Capacity) HRCT (High-Resolution Computed Tomography), ILD (Interstitial Lung Disease), MMF (Mycophenolate Mofetil), NTD (Nintedanib), mRSS (Modified Rodnan Skin Score), PH (Pulmonary Hypertension), RTX (Rituximab), sHR (sub-Hazard Ratio). The formal threshold for statistical significance was set at a p-value of 0.003, following adjustment for multiple comparisons.



Supplementary Figure 4: Rescue treatments after MMF discontinuation due to AEs. AE (Adverse Event), AZT (Azathioprine), CYC (Cyclophosphamide), GI (Gastrointestinal), IS (Immunosuppressant), MMF (Mycophenolate Mofetil), NTD (Nintedanib), RTX (Rituximab).



Supplementary Table 1: Local Ethical Committee approval information

Site of patient enrolment	City	Ethical Authority
Unit of Rheumatology, Catholic University of the Sacred Heart, Fondazione Policlinico Universitario A. Gemelli IRCCS	Rome (Italy)	Comitato Etico Policlinico A. Gemelli protocol code 0002461/23
Scleroderma Program, Leeds Institute of Rheumatic and Musculoskeletal Diseases, University of Leeds	Leeds (United Kingdom)	English Health Research Ref. Authority protocol code 15/NE/0211
Rheumatology Unit, Department of Clinical Internal, Anaesthesiologic and Cardiovascular Sciences, Policlinico Umberto I, Sapienza University of Rome	Rome (Italy)	Comitato Etico Sapienza University of Rome protocol code 2125 416/11
Unit of Immunology, Rheumatology, Allergy and Rare Diseases, IRCCS San Raffaele Hospital	Milan (Italy)	Comitato Etico IRCCS San Raffaele Hospital protocol code IMMUNORADAR DSAN 1178/9
Rheumatology Unit, Department of Clinical and Experimental Medicine, University of Florence	Florence (Italy)	Comitato etico Univerisità di Firenze 37/2008
Rheumatology Unit, Department of Emergency and Organs Transplantation, University of Bari	Bari (Italy)	Comitato Etico Poclino di Bari, protocol code 5277
Scleroderma Clinic, Dip. Reumatologia, ASST Gaetano Pini-CTO, Università degli Studi di Milano	Milan (Italy)	Comitato Etico ASST Gaetano Pini CTO protocol code 339/6549
Department of Rheumatology, University of Modena and Reggio Emilia	Modena (Italy)	Comitato Etico Università di Modena e Reggio Emilia Studio SCLERORER 3826
Rheumatology and Clinical Immunology, IRCCS Humanitas Research Hospital	Rozzano (Italy)	Comitato Etico Humanitas Research Hospital protocol code 0831

Supplementary table 2: Definition of SSc-related organ involvement, comorbidities, and medication exposure adopted in the medical chart review process.

SSc-related organ involvement
• Digital ulcers: SSc-related ulcers as reported in the patient's health record by the physicians during the clinical examination; any other documentation substantiating a loss of skin continuity involving at least the epidermis and basal membrane of any area of skin covering the digits, including those overlying calcinotic lesions and bony prominences. • Skin calcinosis: SSc-related calcinosis as reported in the patient's health record by the physicians during the clinical examination; any other documentation substantiating subcutaneous calcium salt deposits including medical report following surgical curettage or X-ray. • Myositis: confirmed evidence of raised CK values without alternative explanation to muscular inflammatory involvement with or without symptoms or imaging evidence of inflammatory involvement according to the corresponding medical record. • Synovitis: swollen and tender joint or tendon reported in the patient's health record by the physicians during the clinical examination; ultrasound or magnetic resonance imaging evidence of synovitis according to the corresponding medical record. • Interstitial lung disease: evidence of fibrotic parenchymal changes involving at least 10% of the lung volume on the HRCT. • Pulmonary Hypertension: PASP ≥ 40 mmHg on ecocardiocolordoppler or mPAP ≥ 25 mmHg on right heart characterization. Precapillary and postcapillary pulmonary hypertension were grouped together. • Severe SSc gastro-esophageal disease: symptoms of gastroesophageal diseases, including both dysphagia, reflux, dyspepsia without alternative cause; need for PPI and/or prokinetic to control symptoms of gastroesophageal disease; instrumental evidence (morphological or functional) of esophageal dilation, reduced peristalsis or lower esophageal sphincter dysfunction or gastric antral vascular ectasia. • Severe SSc intestinal disease: clinical or laboratory evidence of malabsorption, chronic intestinal motility disorders including both diarrhea or constipation, or fecal incontinence.
MMF combination treatment
• Corticosteroids: Combination with MMF for at least 3 months with a median dose equivalent of at least 5 mg of prednisone. • Rituximab: At least one cycle of treatment (according to the scheme adopted at the reference center) in combination with MMF. • Tocilizumab: Combination with MMF for at least 3 months. • Nintedanib: Combination with MMF for at least 3 months.
Comorbidities
• Diabetes mellitus: fasting plasma glucose ≥ 126 mg/dL, plasma glucose ≥ 200 mg/dL during a 2-hour oral glucose tolerance test, random plasma glucose ≥ 200 mg/dL, hemoglobin A1c $\geq 6.5\%$, or currently on anti-diabetic medications. • COPD: undergoing treatment for COPD or post-bronchodilator forced expiratory volume in the first second/forced vital capacity ratio < 0.7. • CKD: GFR less than 60 mL/min. • Cancer: histologically confirmed malignant neoplasm, including either primary or metastatic sites • Viral chronic hepatitis: serologically confirmed chronic hepatitis B or C infection. Hepatitis testing was performed in all patients treated with rituximab, in those with abnormal liver enzymes, or in those with at-risk behaviours, as per common clinical practice. • Major cardiovascular event: previous myocardial infarction, stroke, or coronary artery bypass surgery or angioplasty

Abbreviations: COPD (Chronic Obstructive Pulmonary Disease), CKD (chronic kidney disease), GFR (glomerular filtration rate), MMF (Mycophenolate Mofetil), PPI (Proton Pump Inhibitor), MRI (Magnetic Resonance Imaging), mPAP (Mean Pulmonary Arterial Pressure), PASP (Pulmonary Artery Systolic Pressure), SSc (Systemic Sclerosis).

Supplementary Table 3 - Severity classification of infections adopted in the medical chart review process.

Etiology	Severe	Life-threatening
Bacterial	• Bacteriemia without sepsis or deep organ involvement • Bacterial focus requiring inpatient management	• Bacteriemia with sepsis or deep organ involvement
Viral	• Symptomatic Citomegalovirus infection without lower respiratory tract or intestinal involvement • Varicella Zooster Virus infection without coagulopathy or organ involvement	• Citomegalovirus lower respiratory tract or intestinal Citomegalovirus • Varicella Zooster Virus infection with coagulopathy or organ involvement • Any viral encephalitis
Fungal	• Candidemia without sepsis or deep organ involvement • Deep organ candida infection without sepsis or candidemia • Aspergillus sinusitis without bone involvement	• Candidemia with sepsis or deep organ involvement • Aspergillus sinusitis with bone involvement or aspergillus pneumonia • Any <i>Pneumocystis jirovecii</i> pneumonia
Parasitic	• Toxoplasma infection without organ involvement.	• Toxoplasma infection with organ involvement
Microbiological undetermined	• Any lower respiratory tract infection not needing oxygen supplementation. • Any infectious symptoms requiring inpatient management.	• Any lower respiratory tract infection needing oxygen supplementation. • Any sepsis syndrome requiring intensive care unit admission.

Supplementary Table 4: Clinical characteristics of the enrolled patients across the different involved centres and of missing data.

	ASST Gaetano Pini-CTO Institute, Milan	Azienda Ospedaliera Universitaria Careggi, Florence	Azienda Ospedaliera Universitaria di Modena	Fondazione Policlinico Gemelli IRCCS, Rome	IRCCS Humanitas Research Hospital, Rozzano	Leeds Institute of rheumatic and musculoskelet al diseases	Policlinico di Bari Giovanni XXIII	Policlinico Umberto I, Rome	San Raffaele Hospital IRCCS, Milan	Missing data
N	44	69	37	93	30	77	51	74	70	-
Age, years , mean±SD	54.2±13.5	50.4±15.0	51.6±14.8	50.0±15.2	54.8±13.2	50.2±13.2	58.7±12.7	55.4±12.8	56.0±14.6	0
Male , n (%)	4 (9.1%)	10 (14.5%)	5 (13.5%)	12 (12.9%)	4 (13.3%)	20 (26.0%)	9 (17.6%)	16 (21.6%)	17 (24.3%)	0
BMI, kg/m² , mean±SD	22.2±3.4	24.6±4.5	22.5±2.7	24.2±3.9	24.2±4.7	25.2±5.0	26.2±3.8	23.5±4.5	23.2±5.3	36
Current or former smoker , n (%)	7 (15.9%)	7 (10.1%)	13 (35.1%)	39 (41.9%)	6 (20.0%)	26 (34.2%)	6 (11.8%)	30 (40.5%)	21 (30.0%)	1
Disease duration, years , median (IQR)	4.0 (2.0, 9.0)	2.0 (1.0, 5.0)	3.0 (1.0, 8.0)	3.0 (0.0, 8.0)	1.0 (0.0, 5.0)	1.0 (0.0, 4.0)	10.0 (2.5, 16.0)	1.0 (0.0, 6.8)	2.0 (0.0, 6.0)	0
Le Roy Diffuse cutaneous variant , n (%)	41 (93.2%)	32 (46.4%)	19 (51.4%)	58 (62.4%)	20 (66.7%)	47 (61.0%)	7 (13.7%)	43 (58.1%)	31 (44.3%)	0
ACA positive , n (%)	0 (0.0%)	10 (14.5%)	11 (29.7%)	8 (8.6%)	4 (13.3%)	37 (48.1%)	2 (3.9%)	7 (9.5%)	9 (12.9%)	0
Anti-Scl70 positive , n (%)	35 (79.5%)	39 (56.5%)	19 (51.4%)	47 (50.5%)	15 (50.0%)	15 (19.5%)	37 (72.5%)	41 (55.4%)	39 (55.7%)	0
Capillaroscopy pattern										35
Nonspecific, n (%)	8 (18.2%)	11 (23.4%)	0 (0.0%)	15 (16.1%)	0 (0.0%)	13 (16.9%)	7 (13.7%)	20 (27.0%)	9 (15.8%)	
Early scleroderma, n (%)	15 (34.1%)	11 (23.4%)	11 (29.7%)	5 (5.4%)	7 (23.3%)	13 (16.9%)	2 (3.9%)	17 (23.0%)	11 (19.3%)	
Active scleroderma, n (%)	17 (36.2%)	14 (37.8%)	24 (25.8%)	22 (73.3%)	27 (35.1%)	22 (43.1%)	19 (25.7%)	25 (43.9%)		
Late scleroderma, n (%)	2 (4.5%)	8 (17.0%)	12 (32.4%)	49 (52.7%)	1 (3.3%)	24 (31.2%)	20 (39.2%)	18 (24.3%)	12 (21.1%)	
mRSS , median (IQR)	7.0 (5.0, 12.0)	4.0 (0.0, 9.5)	9.0 (6.0, 18.0)	9.5 (4.0, 14.0)	10.5 (6.0, 15.5)	4.0 (2.0, 9.0)	2.0 (1.0, 4.5)	6.5 (4.0, 16.0)	7.5 (2.0, 13.0)	55
Digital ulcers , n (%)	18 (40.9%)	34 (49.3%)	19 (51.4%)	45 (48.4%)	7 (23.3%)	45 (58.4%)	29 (56.9%)	34 (45.9%)	22 (31.4%)	0
Skin calcinosis , n (%)	4 (9.1%)	7 (10.1%)	19 (51.4%)	20 (21.5%)	3 (10.0%)	29 (37.7%)	7 (13.7%)	11 (14.9%)	7 (10.0%)	0
Synovitis , n (%)	11 (25.0%)	7 (10.1%)	13 (35.1%)	22 (23.7%)	5 (16.7%)	10 (13.0%)	3 (5.9%)	8 (10.8%)	19 (27.1%)	0
Myositis , n (%)	2 (4.5%)	8 (11.6%)	5 (13.5%)	13 (14.0%)	4 (13.3%)	8 (10.4%)	0 (0.0%)	2 (2.7%)	9 (12.9%)	0
ILD on HRCT , n (%)	44 (100.0%)	50 (72.5%)	33 (89.2%)	78 (83.9%)	24 (80.0%)	51 (66.2%)	47 (92.2%)	57 (77.0%)	50 (71.4%)	0
FVC, % of predicted , mean±SD	90.8±17.9	94.8±19.9	94.5±23.1	84.4±22.3	91.9±19.4	87.9±20.3	93.7±21.3	91.8±24.7	92.2±20.3	11
DLco, % of predicted , mean±SD	58.4±15.5	72.0±22.1	65.6±15.2	56.7±24.8	65.5±20.4	54.2±12.1	60.9±22.2	63.4±18.2	64.2±21.6	18
PH , n (%)	6 (13.6%)	3 (4.3%)	9 (24.3%)	22 (23.7%)	3 (10.0%)	13 (16.9%)	15 (29.4%)	3 (4.1%)	7 (10.0%)	0
Severe gastro-esophageal involvement , n (%)	30 (68.2%)	50 (72.5%)	32 (86.5%)	76 (81.7%)	14 (46.7%)	53 (68.8%)	45 (88.2%)	39 (52.7%)	49 (70.0%)	0
Severe intestinal involvement , n (%)	1 (2.3%)	7 (10.1%)	14 (37.8%)	27 (29.0%)	1 (3.3%)	14 (18.2%)	8 (15.7%)	13 (17.6%)	11 (15.7%)	0
MMF starting dose										0
Full dose (3.0 g/die), n (%)	2 (4.5%)	2 (2.9%)	0 (0.0%)	0 (0.0%)	10 (33.3%)	3 (3.9%)	0 (0.0%)	0 (0.0%)	18 (25.7%)	
Low dose (0.5-1.5 g/die), n (%)	14 (31.8%)	10 (14.5%)	24 (64.9%)	2 (2.2%)	12 (40.0%)	10 (13.0%)	10 (19.6%)	36 (48.6%)	11 (15.7%)	

	ASST Gaetano Pini-CTO Institute, Milan	Azienda Ospedaliera Universitaria Careggi, Florence	Azienda Ospedaliera Universitaria di Modena	Fondazione Policlinico Gemelli IRCCS, Rome	IRCCS Humanitas Research Hospital, Rozzano	Leeds Institute of rheumatic and musculoskeletal diseases	Policlinico di Bari Giovanni XXIII	Policlinico Umberto I, Rome	San Raffaele Hospital IRCCS, Milan	Missing data
Standard dose (2.0-2.5 g/die) , n (%)	28 (63.6%)	57 (82.6%)	13 (35.1%)	91 (97.8%)	8 (26.7%)	64 (83.1%)	41 (80.4%)	38 (51.4%)	41 (58.6%)	
Preliminary CYC treatment, n (%)	14 (31.8%)	19 (27.5%)	3 (8.1%)	34 (36.6%)	1 (3.3%)	34 (44.2%)	2 (3.9%)	10 (13.5%)	5 (7.1%)	0
Combination of immunosuppressants, n (%)	10 (22.7%)	2 (2.9%)	10 (27.0%)	13 (14.0%)	6 (20.0%)	9 (11.7%)	10 (19.6%)	2 (2.7%)	18 (25.7%)	0
Combination of MMF and RTX, n (%)	9 (20.5%)	2 (2.9%)	8 (21.6%)	9 (9.7%)	6 (20.0%)	8 (10.4%)	6 (11.8%)	2 (2.7%)	12 (17.1%)	0
Combination of MMF and corticosteroids, n (%)	22 (50.0%)	20 (29.0%)	16 (43.2%)	23 (24.7%)	5 (16.7%)	28 (36.4%)	32 (62.7%)	43 (58.1%)	25 (35.7%)	0
Combination of MMF and NTD, n (%)	7 (15.9%)	1 (1.4%)	0 (0.0%)	2 (2.2%)	2 (6.7%)	2 (2.6%)	0 (0.0%)	3 (4.1%)	12 (17.1%)	0
Diabetes mellitus, n (%)	1 (2.3%)	2 (2.9%)	2 (5.4%)	6 (6.5%)	0 (0.0%)	2 (2.6%)	5 (9.8%)	9 (12.2%)	5 (7.1%)	0
COPD, n (%)	0 (0.0%)	0 (0.0%)	1 (2.7%)	2 (2.2%)	0 (0.0%)	3 (3.9%)	4 (7.8%)	3 (4.1%)	1 (1.4%)	0
CKD, n (%)	0 (0.0%)	0 (0.0%)	6 (16.2%)	2 (2.2%)	0 (0.0%)	1 (1.3%)	2 (3.9%)	6 (8.1%)	1 (1.4%)	0
Chronic viral hepatitis, n (%)	1 (2.3%)	4 (5.8%)	0 (0.0%)	5 (5.4%)	2 (6.7%)	1 (1.3%)	4 (7.8%)	0 (0.0%)	1 (1.4%)	0
Major cardiovascular events, n (%)	1 (2.3%)	0 (0.0%)	3 (8.1%)	4 (4.3%)	5 (16.7%)	7 (9.1%)	5 (9.8%)	0 (0.0%)	8 (11.4%)	0
Cancer, n (%)	3 (6.8%)	2 (2.9%)	4 (10.8%)	7 (7.5%)	3 (10.0%)	1 (1.3%)	8 (15.7%)	3 (4.1%)	4 (5.7%)	0

ACA (Anti-centromere Antibody), BMI (Body Mass Index), CKD (chronic kidney disease), COPD (Chronic obstructive pulmonary disease), CYC (Cyclophosphamide), 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), MMF (Mycophenolate Mofetil), NTD (Nintedanib), mRSS (Modified Rodnan Skin Score), PH (Pulmonary Hypertension), RTX (Rituximab), SD (Standard Deviation).

Supplementary Table 5: Comparison of clinical characteristics according to the clinical strategy after AEs-related MMF discontinuation.

	Wait and see N = 33	Active rescue N = 32	p-value
Age, years, mean±SD	53.6±13.6	56.4±12.9	0.4
Male gender	5 (15.2%)	4 (12.5%)	>0.9
BMI, kg/m ² , mean±SD	24.8±5.3	22.6±4.8	0.081
Current or former smoker	12 (36.4%)	11 (34.4%)	0.9
Disease duration, years, median (IQR)	2.0 (0.0, 5.0)	6.0 (2.0, 13.3)	0.004
Le Roy Diffuse cutaneous variant	14 (42.4%)	17 (53.1%)	0.4
ACA positive	5 (15.2%)	6 (18.8%)	0.7
Anti-Scl70 positive	10 (30.3%)	16 (50.0%)	0.11
Capillaroscopy pattern			>0.9
Nonspecific	3 (9.7%)	4 (13.8%)	
Early scleroderma	12 (38.7%)	10 (33.4%)	
Active scleroderma	5 (16.1%)	4 (13.8%)	
Late scleroderma	11 (35.5%)	11 (37.9%)	
mRSS, median (IQR)	10.0 (4.0, 13.5)	5.0 (3.0, 12.0)	0.5
Digital ulcers	15 (45.5%)	17 (53.1%)	0.5
Skin calcinosis	10 (30.3%)	10 (31.3%)	>0.9
Synovitis	5 (15.2%)	10 (31.3%)	0.12
Myositis	5 (15.2%)	2 (6.3%)	0.4
ILD on HRCT	26 (78.8%)	28 (87.5%)	0.3
FVC, % of predicted, mean±SD	93.5±17.5	82.5±21.0	0.025
DLco, % of predicted, mean±SD	57.9±20.2	50.5±19.9	0.15
Pulmonary Hypertension	6 (18.2%)	9 (28.1%)	0.3
Severe gastro-esophageal involvement	22 (66.7%)	25 (78.1%)	0.3
Severe intestinal involvement	9 (27.3%)	12 (37.5%)	0.4
MMF starting dose			0.7
Low dose (0.5-1.5 g/die)	6 (18.2%)	9 (28.1%)	
Standard dose (2.0-2.5 g/die)	26 (78.8%)	22 (68.8%)	
Full dose (3.0 g/die)	1 (3.0%)	1 (3.1%)	
Preliminary CYC treatment	11 (33.3%)	7 (21.9%)	0.3
Combination of immunosuppressants	1 (3.0%)	6 (18.8%)	0.054
Combination of MMF and RTX	0 (0.0%)	6 (18.8%)	0.011
Combination of MMF and corticosteroids	8 (24.2%)	14 (43.8%)	0.10
Combination of MMF and NTD	0 (0.0%)	2 (6.3%)	0.2
Diabetes mellitus	3 (9.1%)	2 (6.3%)	>0.9
COPD	1 (3.0%)	2 (6.3%)	0.6
CKD	0 (0.0%)	3 (9.4%)	0.11
Chronic viral hepatitis	1 (3.0%)	1 (3.1%)	>0.9
Chronic viral hepatitis	1 (3.0%)	4 (12.5%)	0.2
Major cardiovascular events	2 (6.1%)	1 (3.1%)	>0.9
Discontinuation due to GI intolerance	11 (33.3%)	15 (46.9%)	0.3
Discontinuation due to laboratory toxicity	4 (12.1%)	6 (18.8%)	0.5
Discontinuation due to severe infection	5 (15.2%)	1 (3.1%)	0.2
Discontinuation due to recurrent infection	6 (18.2%)	3 (9.4%)	0.5
Discontinuation due to cancer	5 (15.2%)	3 (9.4%)	0.7

ACA (Anti-centromere Antibody), AE (Adverse event), BMI (Body Mass Index), CKD (chronic kidney disease), COPD (chronic obstructive pulmonary disease), CYC (Cyclophosphamide), DLco (Diffusion Capacity of the Lung for Carbon Monoxide), FVC (Forced Vital Capacity), GI (Gastro-intestinal), HRCT (High-Resolution Computed Tomography), ILD (Interstitial Lung Disease), IQR (Interquartile Range), MMF (Mycophenolate Mofetil), NTD (Nintedanib), mRSS (Modified Rodnan Skin Score), PH (Pulmonary Hypertension), RTX (Rituximab), SD (Standard Deviation).