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Real-World Safety and Effectiveness of JAK Inhibitors in Systemic Sclerosis: A Propensity-Matched Study From the EUSTAR Cohort

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Objective. JAK inhibitors (JAKi) have shown promising effects in early-phase studies of systemic sclerosis (SSc). We aimed to assess the safety and explore the effectiveness of JAKi compared to conventional immunosuppressants in SSc.

Methods. A longitudinal retrospective study of the European Scleroderma Trials and Research Group (EUSTAR) cohort was performed. JAKi-treated patients were compared to patients receiving mycophenolate mofetil (MMF), rituximab (RTX), and methotrexate (MTX) using nearest-neighbor propensity score matching. Primary outcomes were safety and drug survival. Secondary outcomes included change in forced vital capacity (FVC), change in modified Rodnan skin scores (mRSS) in patients with diffuse cutaneous SSc (dcSSc), improvement in swollen joint count, digital ulcer (DU) recurrence, and a composite disease progression endpoint. Comparative analyses were performed using generalized linear models and time-to-event methods, including Kaplan–Meier and restricted mean survival time analyses.

Results. Thirty-six JAKi-treated patients from 19,601 were included (median drug exposure 37 months). Median disease duration was seven years, and 33% had dcSSc. For 98.7 patient-years, 23 adverse events were recorded, including 12 infections, 7 laboratory abnormalities, and 3 malignancies. Treatment was discontinued permanently in 39% and transiently in 19%. At 12 months, lung function remained stable (mean FVC% +1.7%, $P = 0.530$) during follow-up and skin fibrosis showed a numerical improvement (mean mRSS –1.8) in patients with dcSSc. These results were comparable to those observed in MMF, RTX, and MTX groups. Swollen joint counts decreased in patients with baseline synovitis (median change –1, $P = 0.052$). DU recurrence rates and disease progression events were comparable to those in matched immunosuppressive groups. No new calcinotic burden was observed.

Conclusion. JAKi showed similar effectiveness compared to standard-of-care immunosuppressants. However, drug persistence and safety concerns may be a limiting factor in patients with SSc.

INTRODUCTION

Systemic sclerosis (SSc) is a rare disease marked by widespread vascular dysfunction, immune dysregulation, and

progressive tissue fibrosis, leading to high morbidity and mortality.^{1–4} Patients' survival is significantly influenced through major internal organ involvement (eg, heart, lungs, and kidney). Furthermore, there is a significant burden of lived nonlethal

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SIGNIFICANCE & INNOVATIONS

- JAK inhibitors (JAKi) led to numerical improvements in skin scores in patients with diffuse cutaneous systemic sclerosis, and lung function remained stable over follow-up.
- A favorable signal for synovitis improvement was reported for JAKi, and no increase in disease worsening was observed compared to standard of care.
- Although adverse events were manageable, nearly half of patients discontinued JAKi due to side effects at five years' follow-up.
- Exploratory, nondefinitive effectiveness signals were observed for JAKi, reinforcing the need for larger trials to assess long-term safety and efficacy.

morbidity from painful digital ulcers (DUs) and calcinosis cutis. Current therapeutic strategies are limited by heterogeneous disease presentation and the lack of universally effective therapies for the different organ-based complications.^{5,6}

In this context, the JAK/STAT pathway has emerged as a promising therapeutic target given its central role in driving both inflammatory and fibrotic processes in SSc.^{7,8} Major advances have been seen in immune-mediated dermatological diseases, and although preliminary and stimulating data support the potential of JAK inhibitors (JAKi) in SSc,⁹ further efficacy data and dedicated clinical trials are needed, especially for severe refractory patients who may benefit from their pleiotropic mechanisms of action.

Aberrant activation of the JAK/STAT axis, often driven by type I interferon signaling, has been demonstrated in fibroblasts, endothelial cells, and immune cells involved in SSc pathogenesis.^{10–12} Elevated levels of JAK/STAT pathway activity have been identified in skin biopsy samples and preclinical SSc models, suggesting involvement in key effector mechanisms such as fibroblast activation, extracellular matrix deposition, and vascular remodeling.^{13–15} Experimental inhibition of this pathway was found to mitigate fibrosis of both skin and lung in animal models, providing a strong rationale for therapeutic exploitation in SSc.^{16–19}

The JAKi baricitinib, filgotinib, tofacitinib, and upadacitinib are currently approved for the treatment of rheumatoid arthritis (RA) and other immune-mediated diseases.^{20–22} In SSc, data are currently lacking, although small studies and case series have reported preliminary evidence of effectiveness.^{23,24} Notably,

significant improvements in skin scores and stabilization of lung function were observed, with greater effect in patients with early diffuse cutaneous disease.^{23,25} However, although real-world data for JAKi in SSc are emerging, larger cohorts and controlled studies are still needed to draw definitive conclusions.

Although the potential anti-inflammatory and antifibrotic effects of JAK inhibition make this class particularly appealing to SSc, safety concerns have emerged concerning JAKi in other treated populations, particularly with respect to cardiovascular events and malignancies, necessitating cautious evaluation. To this effect, the US Food and Drug Administration has issued a “black box warning” concerning the JAKi class of therapies, highlighting increased risks of thrombosis, major adverse cardiovascular events (MACEs), and certain malignancies, particularly in older patients or those with cardiovascular risk factors.^{26,27} Against this background, the aim of our study was to harness the power of the large international prospective European Scleroderma Trials and Research Group (EUSTAR) cohort to assess the safety profile and potential effectiveness of JAKi in patients with SSc.

PATIENTS AND METHODS

Study design and patients. Ours was an analysis of patients from the multicenter EUSTAR database fulfilling the 2013 ACR/EULAR classification criteria for SSc²⁸ (EUSTAR clinical project number 150). The structure of the database, content of the standardized collected data, and definitions of the clinical variables have been previously reported.^{29,30} The Strengthening the Reporting of OBservational Studies in Epidemiology checklist for our study is presented in Supplementary Table 1.

EUSTAR is part of the World Scleroderma Foundation, which has patient representatives from the Federation of European Scleroderma Associations in its governing board. All the included patients in our analysis agreed to participate in the EUSTAR cohort by signing informed consent forms, which were approved by the local ethics committees. Individual centers had appropriate ethics/regulatory approvals (which is mandatory to EUSTAR center participation). The study complied with the Declaration of Helsinki.

A baseline was defined for each patient as the date of the first recorded visit while receiving JAKi therapy. Follow-up was calculated in months as the interval from baseline to the earliest occurrence of an outcome event or, in the absence of events, to the

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date of the last available visit. For patients who permanently discontinued JAKi treatment without experiencing any predefined outcome, follow-up was censored at the time of drug discontinuation. This approach ensures that follow-up reflects the actual period of therapeutic exposure, thereby reducing bias of time-to-event analyses.

For all patients in the analysis, the following variables were collected at baseline: disease duration; LeRoy cutaneous subset (limited and diffuse)³¹; autoantibody status (namely antinuclear antibody [ANA], rheumatoid factor, anti-cyclic citrullinated peptide, anti-Ro52, anticentromere, anti-topoisomerase I [anti-topo I], and anti-RNA polymerase III [anti-RNAP III]); presence of active DUs; and history of DUs, telangiectasias, puffy fingers, calcinosis, pulmonary arterial hypertension (PAH), interstitial lung disease (ILD), and scleroderma renal crisis (SRC). Immunosuppressive or targeted treatments, including glucocorticoids, were recorded. For patients receiving JAKi, treatment discontinuation was also documented, including stop date, whether the stop was permanent or transient, and the reason for discontinuation. Disease severity measures included the modified Rodnan skin score (mRSS), forced vital capacity (FVC) percentage predicted, diffusing capacity of the lung for carbon monoxide (DL_{CO}) percentage predicted, and swollen joint count (SJC). Inflammatory activity was assessed through the C-reactive protein level.

In addition to the standardized EUSTAR data set, centers contributing JAKi-treated patients also completed a dedicated study case report form. This captured additional clinical data, including adverse events (AEs), treatment discontinuation and reintroduction, reasons for discontinuation, death and its cause, malignancies, MACEs, and thromboembolic events, reflecting previously reported safety concerns associated with JAKi.

Safety and effectiveness. The primary objective of the study was to evaluate the safety and tolerability of JAKi in patients with SSc by assessing the following:

1. The incidence of AEs, namely new onset of serious infection (defined as infection necessitating hospital admission, intravenous antimicrobial treatment, or associated with fatal outcome), new onset of nonsevere infection (included self-limiting or outpatient-treated infections), new malignancy, onset of venous thromboembolism, and MACE (cardiovascular death, nonfatal stroke, nonfatal myocardial infarction)
2. Drug survival, defined as the time to permanent treatment discontinuation

Effectiveness outcomes were evaluated as secondary end points and included the following:

1. Change in FVC% predicted from baseline at 12 and 24 months (± 2 months), adopted as a marker of longitudinal pulmonary response

2. Change in mRSS from baseline at 12 and 24 months (± 2 months), adopted as a marker of longitudinal skin effectiveness in patients with diffuse cutaneous SSc (dcSSc)
3. Improvement in SJC from baseline at 12 and 24 months' follow-up (± 2 months) in patients with SSc with baseline synovitis
4. A time-to-event end point for recurrent events, capturing the occurrence of one or more new DUs at the patient level
5. The effect of JAKi on existing calcinosis and new calcinosis onset
6. A time-to-event composite endpoint, capturing the occurrence of clinically relevant complications such as incident PAH, SRC, and sustained ILD progression, which was defined as a relative decline in FVC $\geq 10\%$ or a relative decline in FVC between 5% and 9% accompanied by a relative decline in DL_{CO} $\geq 15\%$, according to the Outcome Measures in Rheumatology (OMERACT) definition,³² without subsequent recovery, as assessed over the entire follow-up

Selection of comparator arms. To ensure a balanced and clinically meaningful comparison across treatments, comparator arms were composed of, and limited to, patients initiating mycophenolate mofetil (MMF), rituximab (RTX), or methotrexate (MTX) for the first time. These patients were identified as having no prior exposure to the treatment and having at least two subsequent visits confirming continuation after drug initiation. This strategy was designed to emulate a real-world treatment initiation scenario, minimizing biases from prior therapy or selective continuation. Comparator groups were thus aligned with the JAKi cohort, reflecting patients at the actual start of therapy and approximating a pragmatic head-to-head study context. After propensity score matching (PSM) with a ratio of 1 to 5, all comparator arms were each composed of 180 patients. From these groups, following additional exclusions for missing active DUs data, 162 patients receiving MMF, 160 patients receiving MTX, and 164 patients receiving RTX were evaluable for recurrent DU event analysis.

For longitudinal pulmonary and skin response, patients were selected from those previously matched to the JAKi cohort if they had available mRSS and FVC% predicted values at baseline and at follow-up visits occurring within a window of ± 2 months from the 12- and 24-month time points. This allowed for comparison of mean mRSS and FVC% predicted changes between treatment groups, adjusting for baseline mRSS and lung function. For lung effectiveness analysis, 18 patients receiving JAKi, 97 receiving MMF, 73 receiving MTX, and 92 receiving RTX were available at 12 months. Of these, 13 receiving JAKi, 80 receiving MMF, 67 receiving MTX, and 65 receiving RTX had available FVC data for effectiveness analysis at 24 months. For the skin effectiveness

analysis 12 patients receiving JAKi, 47 receiving MMF, 39 receiving MTX, and 42 receiving RTX were available at 12 months. Of these, 3 patients receiving JAKi, 26 receiving MMF, 23 receiving MTX, and receiving 24 RTX had available mRSS data for the following analysis at 24 months. JAKi-treated patient selection, matched groups, and outcome-specific sample sizes are summarized in a flowchart provided in Supplementary Figure 1.

Statistical analysis. Continuous variables were reported as means with SDs or medians with interquartile ranges (IQRs), as appropriate based on distribution. Categorical variables were presented as frequencies and percentages. Comparisons of baseline characteristics between treatment groups were adjusted for multiple testing using a false discovery rate correction.

PSM was performed using a nearest-neighbor algorithm without replacement, with a 1:5 matching ratio to compare patients receiving JAKi with those receiving MMF, RTX, or MTX. Matching was conducted separately for each comparator arm (MMF, MTX, and RTX) using the same covariates and matching procedure.

Matching variables included age at drug initiation, sex, disease duration, anti-topo I positivity, Leroy cutaneous subset, presence of DUs, and baseline FVC%. Balance between matched groups was assessed using standardized mean differences, with values <0.2 considered indicative of acceptable balance. A wider matching ratio was chosen to maximize statistical efficiency given the limited number of JAKi-treated patients. Covariate balance before and after PSM is reported in Supplementary Figure 2. In addition, propensity score distributions before and after matching are reported in Supplementary Figure 3.

Changes in mRSS and FVC% predicted were assessed using generalized linear models adjusted for baseline FVC values, comparing patients receiving JAKi to those receiving MMF, RTX, and MTX at 12 and 24 months. Longitudinal pulmonary response was defined as the difference between baseline and follow-up values within ± 2 -month time windows of the 12- and 24-month time points. Longitudinal analyses were performed using predefined follow-up windows at 12 and 24 months relative to baseline. Between-group comparisons were performed using linear models adjusted for baseline values (analysis of covariance), and *P* values for the treatment group effect were derived from the model *F* test. In JAKi-treated patients presenting with synovitis at baseline, paired comparisons of SJC at baseline with SJC at 12 and at 24 months' follow-up were performed using the Wilcoxon signed rank test with one-sided alternative hypothesis testing under the *a priori* hypothesis of treatment-related improvement. Due to the presence of ties and zero differences, exact *P* values were computed, and results were reported using the continuity correction approximation. A *P* value of <0.05 was considered statistically significant.

Time-to-event analyses were conducted for drug survival, the composite disease progression end point, and recurrence of

DUs. Drug survival was analyzed for JAKi-treated patients using the Kaplan–Meier (KM) method. Comparable time-to-discontinuation analyses across treatment groups were not performed, as information on permanent treatment discontinuation and reasons for stopping were systematically available on a dedicated case report form only for patients receiving JAKi. KM curves were generated for the time to composite disease progression. Pairwise comparisons between treatment groups were performed using restricted mean survival time (RMST) analyses with unadjusted contrasts; results were reported as absolute RMST differences and relative RMST ratios. Time to first DU occurrence was analyzed using KM methods, with global comparisons performed using log-rank tests. To account for recurrent DU events, a Cox proportional hazards model with the Andersen–Gill counting process was applied, with robust variance estimation clustered by patient (sandwich estimator). This approach models the hazard of DU occurrence over time while accounting for within-patient correlation due to repeated events. An overview of outcome definitions, statistical models, and corresponding summary measures is provided in Supplementary Table 2. No formal imputation was performed. Analyses were conducted using complete-case data for each outcome. All statistical analyses were performed using R (version 4.3.3).

Data availability. Data are available upon reasonable request to the corresponding author.

RESULTS

A total of 36 patients treated with JAKi were included and followed up between November 2017 and December 2024. Their demographic and clinical features and those of their matched comparator groups are reported in Table 1. Among JAKi-treated patients, 16 (44.4%) received baricitinib, 15 (41.7%) received tofacitinib, and 5 (13.9%) received upadacitinib. Fourteen patients (39%) received concomitant MTX, and 17 (47%) received glucocorticoids, including 12 of the 14 MTX users (86%).

Drug safety and survival. The median duration of drug exposure was 37 (IQR 33) months, amounting to an estimated 98.7 patient-years. A total of 23 AEs occurred during follow-up, corresponding to a rate of 23.3 events per 100 patient-years. Among reported safety events, 12 were new infections (8 severe, including one fatal sepsis, and 4 nonsevere), 7 were laboratory abnormalities (5 hematologic and 2 hepatic), and 3 were new malignancies. Overall, one fatal event (sepsis with multiorgan failure) was observed. Among the 12 infections, distributed across 8 patients and representing the most frequent safety events, 9 involved the upper or lower respiratory tract, 2 were varicella-zoster virus reactivations, and 1 was a case of osteomyelitis.

During follow-up, 14 (33.3%) patients permanently discontinued JAKi therapy, 4 following a transient interruption and 8 without

Table 1. Clinical and demographic characteristics of the matched cohorts treated with JAKi and matched immuno-suppressive arms*

Characteristic	JAKi (n = 36)	MMF (n = 180)	MTX (n = 180)	RTX (n = 180)	P value ^a	q value ^b
Follow-up, mo	44 (26, 71)	50 (25, 87)	48 (25, 89)	50 (22, 86)	0.8	0.9
Disease duration, mo	76 (38, 161)	82 (40, 138)	94 (45, 160)	78 (46, 133)	0.5	0.7
Age at baseline, y	57 (51, 63)	57 (48, 67)	57 (47, 68)	55 (45, 63)	0.2	0.3
Sex					0.3	0.4
Female	29 (81%)	144 (80%)	156 (87%)	143 (79%)		
Male	7 (19%)	36 (20%)	24 (13%)	37 (21%)		
LeRoy subset					0.058	0.13
Diffuse cutaneous	12 (33%)	59 (33%)	53 (29%)	72 (40%)		
Limited cutaneous	24 (67%)	121 (67%)	127 (71%)	108 (60%)		
anti-topoisomerase I	14 (39%)	76 (42%)	80 (44%)	74 (41%)	0.9	>0.9
Anticentromere	10 (28%)	30 (17%)	44 (24%)	24 (13%)	0.021	0.054
Anti-RNA polymerase III	3 (8.3%)	6 (6.4%)	7 (8.4%)	9 (10%)	0.8	>0.9
Interstitial lung disease on HRCT	12 (33%)	74 (41%)	55 (31%)	73 (40%)	0.3	0.4
MMF	0 (0%)	180 (100%)	8 (4.4%)	20 (11%)	<0.001	<0.001
RTX	0 (0%)	6 (3.3%)	10 (5.6%)	180 (100%)	<0.001	<0.001
MTX	14 (39%)	10 (5.6%)	180 (100%)	19 (11%)	<0.001	<0.001
Glucocorticoids	17 (47%)	34 (19%)	25 (14%)	27 (15%)	<0.001	<0.001
Endothelin receptor antagonists	6 (17%)	13 (7.2%)	20 (11%)	11 (6.1%)	0.10	0.2
Calcium channel blockers	11 (31%)	28 (16%)	31 (17%)	19 (11%)	0.018	0.053
Phosphodiesterase inhibitors	8 (22%)	11 (6.1%)	9 (5.0%)	7 (3.9%)	0.003	0.016
Forced vital capacity, %	96 (85, 109)	87 (81, 110)	94 (88, 101)	89 (82, 105)	0.3	0.4
DLco, %	69 (58, 80)	57 (56, 75)	69 (57, 73)	58 (57, 70)	<0.001	<0.001
Raised C-reactive protein level	13 (45%)	24 (27%)	31 (31%)	32 (30%)	0.3	0.5
Pitting scars	7 (19%)	82 (46%)	56 (31%)	68 (38%)	0.004	0.017
History of DUs	15 (42%)	81 (55%)	77 (52%)	79 (55%)	0.5	0.7
Active DUs at baseline	10 (28%)	51 (28%)	54 (30%)	49 (27%)	>0.9	>0.9
Telangiectasia	19 (53%)	139 (77%)	130 (72%)	122 (68%)	0.017	0.053
Calcinosis	8 (22%)	16 (16%)	16 (17%)	14 (15%)	0.8	0.9
Pulmonary arterial hypertension	4 (11%)	9 (13%)	16 (19%)	14 (16%)	0.7	0.8

* Data are presented as median (Q1, Q3) or n (%). Disease duration was defined as months from first non-Raynaud phenomenon symptom. DLco, diffusing capacity of the lung for carbon monoxide; DU, digital ulcers; HRCT, high-resolution computed tomography; JAKi, JAK inhibitors; MMF, mycophenolate mofetil; MTX, methotrexate; RTX, rituximab.

^a Kruskal-Wallis rank sum test, Pearson's chi-square test, or Fisher's exact test.

^b False discovery rate correction for multiple testing.

any prior interruption (Figure 1). An additional 7 (19.4%) patients experienced a transient interruption only. Of the 14 patients who discontinued JAKi therapy, 5 did so due to secondary failure, 4 due to primary failure, 2 due to nonsevere infections, 2 due to new malignancy, and 1 due to a severe infection. The baseline clinical characteristics of patients developing a new malignancy are reported in Supplementary Table 3. The estimated drug retention rates for JAKi were 81% (95% confidence interval [CI] 66%–92%) at 12 months, 64% (95% CI 48%–78%) at 24 months, and 43% (95% CI 26%–62%) at 36 months (Figure 1).

Effectiveness exploratory analyses. Lung volumes.

The change in FVC% predicted at 12 and 24 months' follow-up was evaluated relative to baseline in patients treated with JAKi. In the whole study population, at 12 months, patients receiving JAKi showed a mean increase in FVC of +1.7% (95% CI –3.88 to 7.27, $P = 0.530$), which was not statistically significant. At 24 months, the mean difference in FVC was +0.15% (95% CI –9.90 to 10.21, $P = 0.974$) (Figure 2A). When comparing the change in FVC across treatment groups (JAKi, MMF, RTX, MTX),

no statistically significant differences were observed at 12 months ($F = 0.08$, $P = 0.973$) and 24 months ($F = 0.47$, $P = 0.705$).

Focusing on patients with ILD, JAKi treatment was associated with a nonsignificant mean FVC change of +5.8% at 12 months (95% CI –13.1 to 24.7, $P = 0.463$) and +5.0% at 24 months (95% CI –14.5 to 24.5, $P = 0.538$). No significant differences in FVC change across treatment groups were observed at either 12 months ($F = 0.44$, $P = 0.731$) or 24 months ($F = 0.17$, $P = 0.804$).

In patients with dcSSc, JAKi treatment led to a nonsignificant mean FVC change of +1.3% at 12 months ($P = 0.622$). At 24 months, data were available for only two patients, with a mean change of –21.0% ($P = 0.374$). No significant differences were observed across treatment groups at 12 ($F = 0.75$, $P = 0.445$) and 24 months ($F = 0.53$, $P = 0.683$).

Skin disease. The change in mRSS at 12 and 24 months was assessed relative to baseline within the same individuals among patients with dcSSc treated with JAKi. At 12 months, JAKi treatment led to a mean mRSS reduction of –1.8 points (95% CI –5.1 to 1.4, $P = 0.411$). At 24 months, only three patients had available data, with a mean change of –0.3 points (95% CI

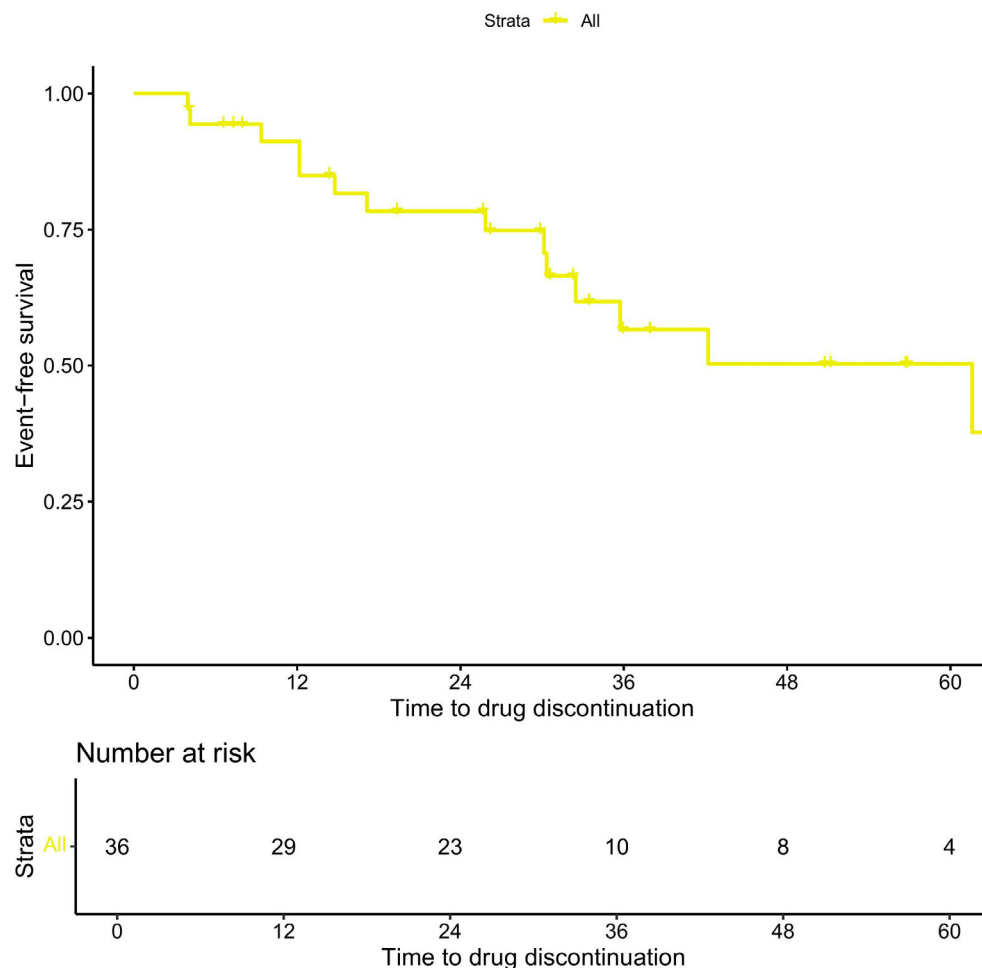


Figure 1. Kaplan–Meier curve for drug survival in patients with JAK inhibitor (JAKi) treatment (time to suspension of JAKi drug). The number of patients at risk at 12-month intervals is reported.

–11.5 to 10.9, $P = 0.910$). No significant differences in mRSS changes were observed across treatment groups (JAKi, MMF, RTX, MTX) at 12 ($F = 0.97$, $P = 0.349$) and 24 months ($F = 0.45$, $P = 0.744$).

Joint disease. In patients treated with JAKi and presenting with synovitis at baseline ($n = 25$), the median SJC decreased from baseline to 12 months (mean difference -2.62 , median difference -1 , IQR -3 to 0 , $P = 0.052$) and remained unchanged at 24 months (mean difference -0.87 , median difference 0 , IQR -1.5 to 1 , $P = 0.428$).

DU disease. The proportion of patients receiving calcium channel blockers, phosphodiesterase inhibitors, and endothelin receptor antagonists was comparable across treatment groups (all q values > 0.05) (Table 1). In the JAKi cohort, 11 (30.5%) patients experienced at least one active DU during follow-up.

In the analysis of time to first DU occurrence over 60 months, no statistically significant differences were observed between JAKi-treated patients and comparator immunosuppressive treatment groups. KM curves showed comparable event-free probability over time across JAKi, MMF, MTX, and RTX groups (log-rank

test, $P = 0.24$) (Figure 3A). Consistent results were observed when recurrent DU events were analyzed using a Cox proportional hazards model under the Andersen–Gill framework, with no significant differences in hazard of DU occurrence between treatment groups.

Calcinosis. Calcinosis, defined as the presence of subcutaneous hard nodules compatible with calcium deposits and detected on physical examination, was observed in 10 patients (27.7%) at baseline. Notably, all cases of calcinosis persisted throughout follow-up, with two patients showing evidence of improvement and no patient showing evidence of worsening according to clinician judgment. Among the remaining 28 patients (75.7%) without calcinosis at baseline, no new cases developed after JAKi initiation. No formal statistics were performed due to the small sample size and low event rate.

Exploratory composite disease progression outcome analysis. In the time-to-event composite disease progression analysis at 60 months, the RMST was estimated at 51.8 months (95% CI 46.1–57.6) in the JAKi group. Compared with JAKi, RMSTs were 54.1 months (95% CI 51.9–56.4) for MMF, 53.8 months (95% CI 51.4–56.1) for RTX, and

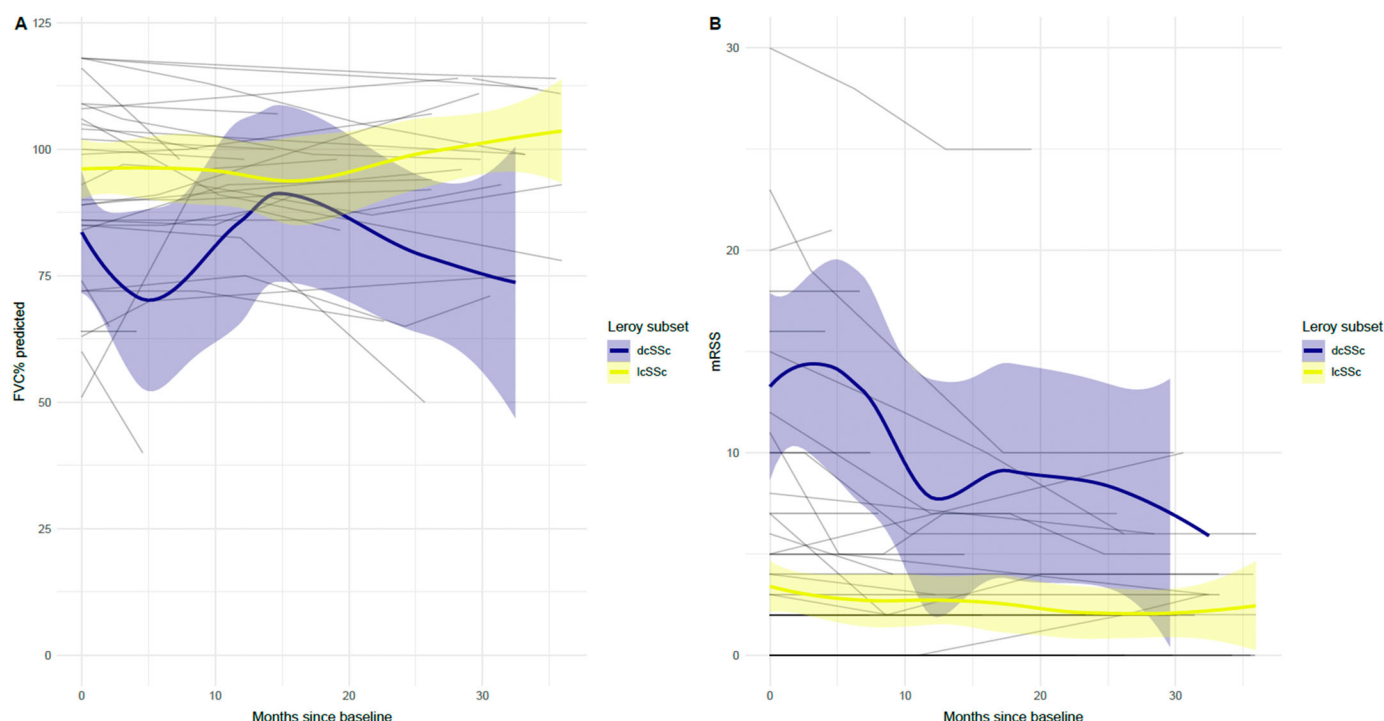


Figure 2. Longitudinal trends of (A) pulmonary function and (B) skin fibrosis in patients treated with JAK inhibitors (JAKi), stratified by Leroy cutaneous subset.³¹ Individual patient trajectories are shown in gray, whereas smoothed average trends (loess curves) are displayed in blue for diffuse cutaneous systemic sclerosis (dcSSc) and yellow for limited cutaneous systemic sclerosis (lcSSc), with shaded areas representing 95% confidence intervals. FVC, forced vital capacity; mRSS, modified Rodnan skin score.

52.8 months (95% CI 50.4–55.3) for MTX. For JAKi, the RMST difference was -2.3 months (95% CI -8.5 to 3.9 , $P = 0.46$) versus MMF, -1.9 months (95% CI -8.2 to 4.3 , $P = 0.54$) versus RTX, and -1.0 months (95% CI -7.3 to 5.2 , $P = 0.75$) versus MTX, with none reaching statistical significance (Figure 3B).

DISCUSSION

Our study provides important real-world safety and comparative effectiveness data of multiple JAKi drug therapies in patients with SSc. A key finding is that drug persistence is limited, with only around half of patients estimated to continue receiving therapy at five years and with transient treatment discontinuation not uncommon. Our data are consistent with those reported for JAKi in other indications. In RA, multicentric data showed five-year retention rates ranging from 37.5% for tofacitinib to 53.5% for filgotinib, 46.6% for baricitinib, and up to 69.4% for upadacitinib.³³ In psoriatic arthritis, five-year retention of JAKi was found to be 53.3%.³⁴ When comparing JAKi to other immunosuppressants in SSc, no dedicated data were available for the MMF, MTX, and RTX arms in our cohort. However, in dedicated studies, five-year drug survival was reported at 70% for MMF (with 20% of patients discontinuing due to AEs and 25% requiring dose reduction or temporary discontinuation) and at 60% for RTX (with AEs being

the less common discontinuation cause, preceded by treatment failure and sustained response).^{35,36}

In terms of safety, given the prominent vascular involvement in SSc and the reported increased risk of MACEs and venous thromboembolism with JAKi in other conditions, the absence of cardiovascular safety signals in this cohort is encouraging. In our cohort, although the most common safety events were infections, three malignancies were observed in JAKi-treated patients (8.3%) over a relatively short follow-up. Although definitive conclusions cannot be drawn, this warrants attention. Of the three patients with malignancies in our cohort, one was anti-RNAP III positive, one was anti-topo I positive, and one was ANA positive only. An increased cancer risk is recognized in SSc, particularly in anti-RNAP III-positive patients,^{37,38} and is a known warning in the JAKi safety profile, especially in older patients and after two years of treatment.³⁹ These findings underscore the need for careful cancer monitoring in future studies. In a recent analysis, cancer risk appeared similar between RTX and MMF in SSc.⁴⁰

In the exploratory effectiveness analyses, JAKi-treated patients showed no changes in FVC% at 12 and 24 months' follow-up, and there were no significant differences with comparator groups. Although these findings do not allow conclusions on treatment-related stabilization or comparative effectiveness, they suggest that lung function did not worsen over the observation period in JAKi-treated patients. Indeed, inhibition of interleukin-6-mediated inflammatory and profibrotic mechanism through

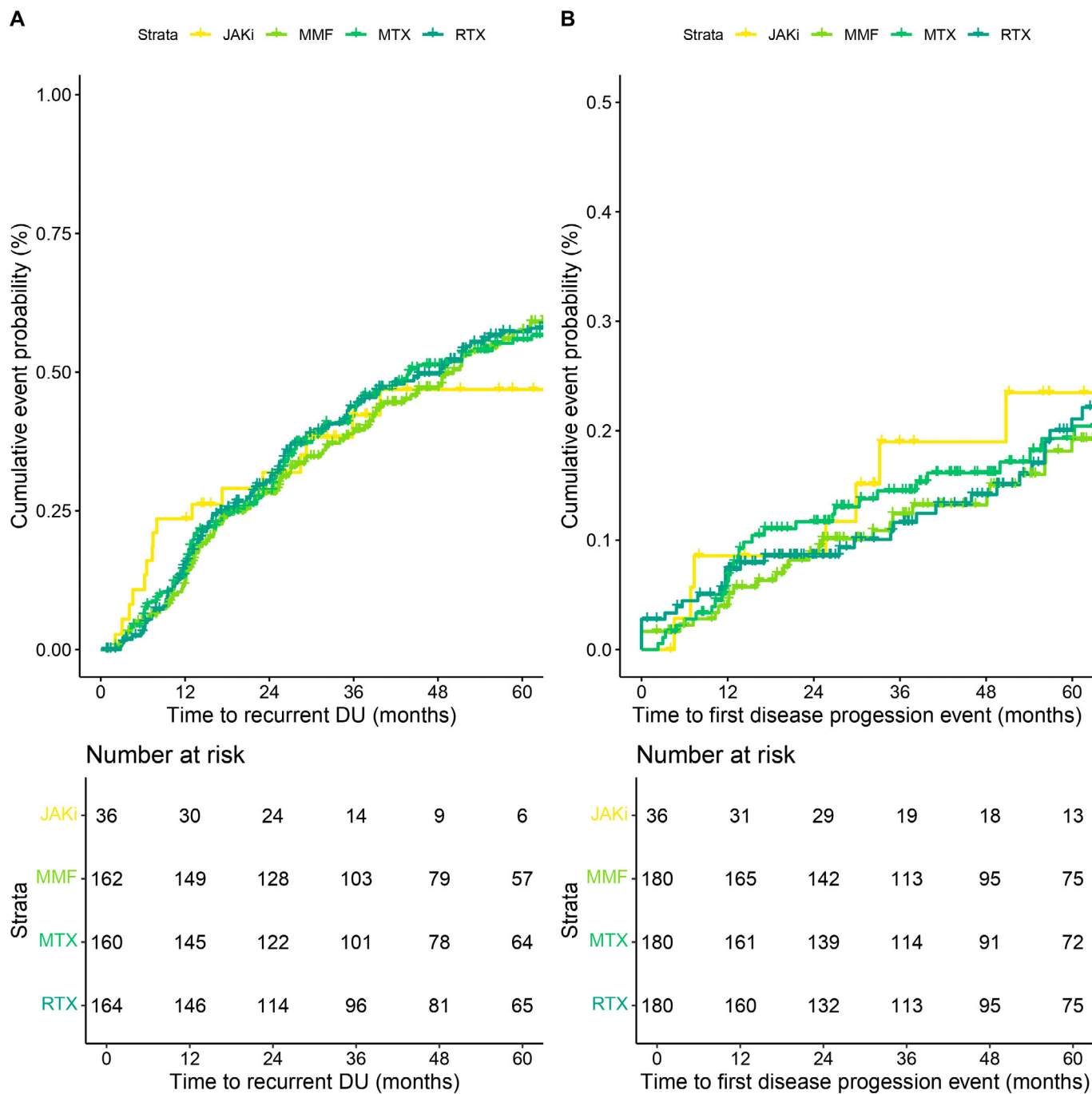


Figure 3. Kaplan–Meier curves showing cumulative event probability for (A) time to first digital ulcer (DU) and (B) time to first disease progression event, stratified by treatment group. The number of patients at risk at each 12-month interval is reported. JAKi, JAK inhibitors; MMF, mycophenolate mofetil; MTX, methotrexate; RTX, rituximab.

JAK/STAT signaling has been successfully exploited in SSc-ILD with the approval of tocilizumab.^{41–43}

At 12 months (but not 24 months due to low numbers), a numerical improvement in mRSS was observed in JAKi-treated patients with dcSSc. Locally estimated scatterplot smoothing trajectories suggested a downward trend in this subset; however, these observations did not reach statistical significance. In this

regard, the majority of patients in the cohort had limited cutaneous SSc, thus restricting the analysis power. These findings should be interpreted cautiously and are hypothesis generating, highlighting the need for adequately powered studies specifically focused on dcSSc populations.⁴⁴

Moreover, SJC/s decreased over time in patients with baseline synovitis, suggesting a musculoskeletal benefit of

JAKi in SSc, as seen in individual case reports,⁴⁵ although the results had borderline significance, likely due to the small numbers of synovitis cases in our cohort. These data provide further value and insight for clinicians treating inflammatory joint disease in patients with SSc, which is lacking dedicated studies and is generally treated similarly to more common conditions such as RA.

Similarly, in the analysis of time-to-recurrent DUs, despite the relatively high burden of active DUs at baseline in the JAKi-treated cohort and more frequent concomitant use of vasodilatory therapies, JAKi treatment demonstrated a comparable profile to that of standard immunosuppressants, with no statistically significant differences observed between treatment groups over five years. Our data were consistent with data in other published studies and cohorts, with around half of patients having a history of DU or presence of digital pitting scars.^{46,47}

Calcinosis is common in patients with SSc and is significantly impactful through cutaneous ulcerations, cosmetic appearance concerns, and recurrent infections. To date, there is no disease-modifying treatment for calcinosis, and management is largely conservative, with monitoring and prompt treatment of infection and surgical debulking as a last resort. Despite small numbers, we observed no new and/or progressive calcinosis in our cohort, with improvements in two patients. This is of interest, as encouraging reports have emerged on the use of JAKi in treating calcinosis associated with dermatomyositis and SSc.^{48–50}

We observed no statistically significant differences in clinically relevant disease progression in the time-to-event analyses. This suggests that disease progression rates with JAKi therapy are comparable to those with conventional immunosuppressants used in SSc. These observations support the potential utility of JAKi as a general treatment approach for SSc, including to positively modify disease progression (especially in those with diffuse disease). These findings strengthen insights from preclinical models of JAK inhibition in SSc and limited clinical evidence to date.^{23,24}

A key strength of our study is the evaluation of JAKi clinical effectiveness and drug survival within the large international EUSTAR cohort, leveraging standardized follow-up data. After PSM, baseline characteristics between groups were adequately balanced, as confirmed by the low standardized mean differences in key covariates. However, our study presents some limitations. First, the sample size was limited, with only 36 patients receiving JAKi (reflecting current clinician access and practice). As such, our analysis is underpowered for definitive inference, and our findings should be interpreted as exploratory. Second, the small number of events restricted our ability to conduct multivariable analyses or adjust for confounders beyond PSM. Therefore, despite PSM for key variables, residual confounding and limited generalizability remain possible. Third, information on permanent treatment discontinuation was systematically collected only in the JAKi group. Consequently, time-to-event analyses in

comparator arms lacked censoring for treatment withdrawal, precluding formal comparison of drug survival. Similarly, safety data were available only for patients receiving JAKi, preventing comparison with MMF, RTX, or MTX. This might introduce confounding-by-indication bias, considering that patients treated with JAKi are likely to represent a more severe, treatment-refractory population. As such, the safety findings may not be generalizable and could reflect underlying disease severity rather than drug-specific effects. The patients included in this study reflect a real-world, unselected SSc cohort, with heterogeneity in phenotype, severity, and timing of assessments. In particular, patients contributing to the FVC% and mRSS analyses were not selected according to standardized trial inclusion criteria (eg, early diffuse disease, active ILD indicators, baseline FVC thresholds, and/or imaging confirmation of ILD). As a result, effectiveness outcomes, such as FVC% and mRSS change, should be interpreted cautiously, despite adjustment for baseline value, and may not be directly comparable to randomized controlled trials data. Finally, the retrospective design and use of registry data present inherent limitations, including potential misclassification, missing data, and variability in clinical assessment standardization.

Our study provides real-world safety and effectiveness data for JAKi in patients with SSc, including comparison with commonly used immunosuppressants. Taken together, our findings are encouraging, although safety concerns are important practical considerations, in particular cancer and infection risk. There were tentative signals of effectiveness for fibrotic lung and skin manifestations as well as musculoskeletal and vascular complications. Our findings may point to a potential signal of benefit in patients within the diffuse subset and with features of an inflammatory phenotype; however, these observations are exploratory and hypothesis generating. Further larger prospective studies are needed to confirm the long-term effectiveness and safety profile of JAKi in SSc, including to define the optimal indications and timing.

AUTHOR CONTRIBUTIONS

All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding author, Dr Hughes confirms that all authors have provided the final approval of the version to be published and takes responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements.

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