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ORIGINAL RESEARCH

Safety and effectiveness of tocilizumab in systemic sclerosis: a multicentre French-Italian study

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ABSTRACT

Background Tocilizumab (TCZ) has shown beneficial effects on interstitial lung disease (ILD) in systemic sclerosis (SSc). We aimed to assess the real-life safety and effectiveness of TCZ on several SSc-related domains using data from a French-Italian multicentre cohort.

Methods We conducted a retrospective analysis of patients with SSc treated with TCZ across 15 referral centres. The following clinical data were collected at 12 months before TCZ initiation, at baseline and at 12 and 24 months of treatment: modified Rodnan skin score (mRSS), pulmonary function tests, Disease Activity Score in 28 joints using C reactive protein, digital ulcers and cardiac biomarkers. ILD progression was defined as a decline ≥5 in %predicted forced vital capacity (%pFVC) over 12±3 months.

Results 197 patients were included (88% female; median age 57 years; median disease duration 9 years); 67% were antitopoisomerase I positive. TCZ monotherapy was used in 29% of cases, methotrexate was the most frequent combined treatment (35%). In SSc-associated ILD, %pFVC declined significantly from −12 months to baseline (81% to 77%; p=0.003). On TCZ introduction, %pFVC stabilised and the proportion of progressors declined from 43% to 24% (p=0.015). Among diffuse cutaneous patients, mRSS decreased significantly at 12 and 24 months. Digital ulcers, arthritis activity and cardiac biomarkers also improved. Infections were the most frequent adverse events (22.8%). TCZ was discontinued in 32% of patients, mainly for inefficacy. Pulmonary arterial hypertension and older age predicted TCZ failure, whereas elevated CRP predicted better response.

Conclusions In this large real-life cohort, TCZ was safe and associated with consistent benefits across different domains, supporting its role as a potential disease-modifying treatment in selected patients with SSc.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Tocilizumab is approved for the treatment of systemic sclerosis-associated interstitial lung disease, but real-world data on its multidomain effectiveness remain limited.

WHAT THIS STUDY ADDS

⇒ In a large real-world cohort, tocilizumab was associated with lung stabilisation and improvement in skin and articular involvement, with good safety profile.

⇒ Baseline clinical features, especially raised C reactive protein levels, are associated with treatment persistence, suggesting a potential role for patient stratification.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These findings support broader use of tocilizumab, including in combination strategies, and highlight the role of clinical phenotyping to guide treatment.

INTRODUCTION

Systemic sclerosis (SSc) is a chronic connective tissue disease characterised by vasculopathy and immune dysfunction leading to widespread skin and internal organs fibrosis.[1] Survival rates indicate that 75% of patients survive up to 5 years, while 62.5% survive up to 10 years.[2] Interstitial lung disease (ILD) is a major cause of morbidity in SSc[3] and it represents now the leading cause of death.[4] Although recent years have seen significant advances in the understanding of SSc-ILD and in the development of new therapeutic strategies, SSc mortality rate remains higher than that of other rheumatic diseases, indicating that key clinical challenges persist.[5]

Interleukin-6 (IL-6) plays a crucial role in the pathogenesis of SSc,[6] particularly in early

diffuse cutaneous forms where inflammation is prominent.[7] Elevated IL-6 levels are associated with more severe disease phenotype and have also been linked to the development and progression of SSc-ILD, predicting FVC decline and poor outcomes.[8] These findings have supported IL-6 blockade as a promising therapeutic strategy in SSc.[9]

Tocilizumab (TCZ) is a monoclonal antibody targeting the IL-6 receptor and its use in SSc has been investigated in two pivotal randomised controlled trials. The phase II faSScinate trial[10] enrolled patients with early diffuse cutaneous SSc (dcSSc) and elevated acute-phase reactants. Although the primary end point (change in modified Rodnan skin score (mRSS)) was not reached, there was a trend favouring TCZ for both skin fibrosis and lung function preservation over placebo. The subsequent phase III focuSSced trial[11] replicated a similar design, including patients with dcSSc of ≤5 years duration, high mRSS (10–35) and elevated inflammatory markers. Again, the primary end point of skin improvement was not met, but secondary outcomes showed that TCZ significantly protected against the decline in FVC in patients with SSc-ILD. Post hoc analyses further emphasised TCZ's stabilising effect on lung function, regardless of radiographic fibrosis extent.[12] Long-term follow-up confirmed the durability of this lung-preserving effect up to 96 weeks.[13] Of note, TCZ was investigated as a monotherapy in both trials and these led to the approval of TCZ by the Food and Drug Administration for patients with SSc-ILD.

Inclusion criteria in both trials selected a highly enriched subgroup of patients with early, diffuse, skin-progressive and inflammatory SSc. Notably, patients with pulmonary arterial hypertension (PAH), low FVC, reduced ejection fraction or overlapping syndromes were excluded. As a result, the trials left unanswered questions about the real-world effectiveness and safety of TCZ in a broader and more diverse SSc population. Preliminary observational studies have attempted to address this. The EULAR Scleroderma Trials and Research (EUSTAR) analysis by Kuster *et al*[14] did not show statistically significant differences between TCZ and standard of care, but the consistency of direction in all end points suggested potential benefit in non-enriched populations. Similarly, the Royal Free cohort[15] found that TCZ, with background immunosuppressive drugs, helped stabilising lung function in refractory ILD cases, particularly among antitopoisomerase I-positive patients. A recent EUSTAR-based head-to-head comparison of immunosuppressants in patients with SSc-ILD[16] suggested TCZ may be as effective as other ILD therapies such as rituximab (RTX), mycophenolate mofetil (MMF) or cyclophosphamide (CYC), supporting the need for a large efficacy and safety profile analysis.

To address these limitations, we conducted a retrospective study that aims to provide the first large-scale, real-world multidomain assessment of TCZ effectiveness and safety in SSc, using a multicentre cohort from France and Italy. As this was a real-life retrospective study, no single predefined primary end point was established. Instead, we assessed several clinical domains considered relevant to routine care, including lung function, skin involvement, arthritis, cardiac biomarkers and treatment discontinuation. In contrast to previous randomised controlled trials, our cohort reflects the heterogeneity of clinical practice, including patients with long-standing disease and cardiac involvement, as well as those without a prominent inflammatory profile. Moreover, while prior studies evaluated TCZ as monotherapy,[10 11] our investigation aligns with current therapeutic strategies, where biological agents are frequently combined with background immunosuppression. Finally, this study seeks to assess the safety and effectiveness of TCZ across multiple disease domains, and to identify potential predictors of treatment response in a broad SSc population.

METHODS

Study design and patients

Patients with SSc diagnosed according to the American College of Rheumatology/European League Against Rheumatism (EULAR) 2013 criteria[17] and treated with TCZ were identified among 15 centres from Italy and France.

Procedures

At TCZ introduction, the following disease characteristics were collected: age, disease duration, disease subset (limited cutaneous, diffuse cutaneous or sine scleroderma), autoantibody profile, presence of SSc-related major organ involvement (ILD on high-resolution CT (HRCT), PAH diagnosed by right heart catheterisation and multidisciplinary evaluation at each centre, inflammatory arthritis and clinical synovitis (defined as the presence of clinically detectable synovitis, as assessed by the treating physician), previous or active digital ulcer, myositis, myocardial involvement, gastrointestinal involvement and rheumatoid arthritis (RA) overlap), concomitant and previous immunosuppressive therapies (corticosteroids, methotrexate (MTX), MMF, hydroxychloroquine, CYC, azathioprine (AZA), RTX, nintedanib) and reasons for TCZ initiation. Disease duration was defined as the duration of the disease since the onset of the first non-Raynaud's phenomenon manifestation.

Then, the following features were collected at baseline, 12 and 24 months after TCZ: mRSS, pulmonary function tests (PFTs) including %predicted forced vital capacity (%pFVC) and %predicted diffusing lung carbon monoxide (%pDLCO), swollen joint count (SJC), tender joint count (TJC) and joint Disease Activity Score in 28 joints using C reactive protein (DAS28-CRP), troponin and N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels, ejection fraction (EF) and need for anti-arrhythmic medications. Moreover, key outcomes measures were also recorded 12 months prior to the start of TCZ including mRSS, %pFVC and %pDLCO, TJC, SJC and DAS28-CRP.

Lung disease progression was defined as an absolute decline in %pFVC ≥5 over 12±3 months.

Drug-related adverse events and deaths were recorded throughout the study period, together with definitive suspension and temporary discontinuation of TCZ. Definite suspension of TCZ due to inefficacy was defined by the treating physician at each centre.

Statistical analysis

Descriptive statistics were used to summarise baseline characteristics using means±SD or medians (IQRs) and proportions, as appropriate. Paired t-tests or Wilcoxon signed-rank test were used to compare variables over time, as appropriate.

Univariable and multivariable logistic regression analyses with OR and 95% CI were applied to analyse the impact of clinical characteristics on TCZ discontinuation due to inefficacy. Candidate baseline variables associated with TCZ discontinuation were retrieved from previous post hoc analysis on the phase III study[18] and together with major disease features and combination therapy as follows: sex, age, SSc subtype, antitopoisomerase I antibody (ATA) positivity, disease duration, CRP elevation, inflammatory arthritis, PAH and combination therapy. Missing data on the candidate predictors were not imputed. Variables were included if missing values were <30%. In multivariable models, variables were selected with a threshold of p=0.1. Before entering variables into the multivariable logistic regression models, we assessed collinearity among all candidate predictors using variance inflation factors (VIFs) and pairwise correlation matrices. Variables showing VIF >2.5 or correlation coefficients >0.6 were not included simultaneously in the model. All analyses were performed using SPSS Statistics V.26 (IBM, Armonk, New York, USA). A p value of <0.05 was considered statistically significant.

RESULTS

Patient demographics and baseline characteristics

One hundred and ninety-seven patients with SSc were included: 168 (88%) women, median age 57 (46–69) years, median disease duration 9 (4–15) years. The majority of patients had a diffuse cutaneous subset (126 patients, 64%), while 58 (29%) had the limited cutaneous form, and only 12 (6%) had SSc sine scleroderma. The most frequently detected autoantibody was antitopoisomerase I (132 patients, 67%), 27 (14%) had a positivity for anticentromere antibody and 13 (7%) for anti-RNA-polymerase III. Disease features at baseline are summarised in table 1. Most of the patients had ongoing inflammatory arthritis (156 patients, 80%), with 19 patients (9.6%) having an overlap RA/SSc diagnosis. One hundred and thirty-nine (71%) patients had SSc-ILD on HRCT. Reasons for TCZ introduction are described in the online supplemental table 1s. In the majority of patients (76%), TCZ was introduced subcutaneously, at a fixed dose of 162 mg weekly. At the time of TCZ introduction, 137 (71%) patients were being treated with steroids and 140 (71%) patients were also on concomitant immunosuppressants, the most common being MTX in 69 (36%) patients, at a median dose of 15 (10–17.5) mg weekly. In addition, 49 (25%) patients were on MMF at a median dose of 2 (1.5–2) g, three (2%) on AZA and three (2%) on CYC. Eleven (6%) patients were treated

Table 1 Clinical and demographic characteristics of our multicentre cohort of patients with SSc

Clinical and demographic characteristics	Patients (n=197)
Females, n (%)	168 (88)
Age (years), median (IQR)	57 (46–69)
Disease duration (years), median (IQR)	9 (4–15)
Cutaneous subset, n (%)	
Diffuse	126 (64)
Limited	58 (29)
Sine scleroderma	12 (6)
Autoantibodies, n (%)	
Antitopoisomerase I Ab	132 (67)
Anti-RNA-polymerase III Ab	13 (7)
Anticentromere Ab	27 (14)
Organ involvement, n (%)	
Interstitial lung disease	139 (71)
Pulmonary arterial hypertension	16 (8)
Inflammatory arthritis	156 (80)
Previous or active digital ulcer	110 (56)
Myositis	12 (6)
Myocardial involvement	31 (16)
GERD	150 (76)
Lower GI involvement	26 (13)
RA overlap	50 (25)
Previous therapies	
Methotrexate, n (%)	115 (58)
Mycophenolate mofetil, n (%)	84 (43)
Hydroxychloroquine, n (%)	53 (27)
Rituximab, n (%)	56 (28)
Cyclophosphamide, n (%)	28 (14)
Azathioprine, n (%)	23 (12)
Concomitant therapies	
Corticosteroids, n (%)	137 (71)
Methotrexate, n (%)	69 (36)
Mycophenolate mofetil, n (%)	49 (25)
Cyclophosphamide, n (%)	3 (2)
Azathioprine, n (%)	3 (2)
Nintedanib, n (%)	13 (7)

Ab, antibodies; GERD, gastro-oesophageal reflux disease; GI, gastrointestinal; RA, rheumatoid arthritis; SSc, systemic sclerosis.

by nintedanib. All patients had previously been treated with other immunosuppressants (table 1) and at baseline CRP levels were raised (≥5 mg/L) in 66 (33.5%) of patients. No significant difference was found in patients with raised CRP who were already on disease-modifying antirheumatic drugs (DMARDs) compared with those who were not in DMARDs (68% vs 72%, p=0.864).

Interstitial lung disease

Among patients with SSc-ILD (n=139), in the 12 months prior to TCZ introduction, %pFVC showed a significant decline from 81±21 to 77±22 (p=0.003) in 81 patients with available PFTs, with 36 patients (44%) showing a %pFVC decline ≥5% and therefore classified as progressors. After TCZ initiation, a stabilisation in %pFVC was observed at 12 months, from 78±21 to 80±21 (p=0.07) in 92 patients with available repeated PFTs, with a decrease to 22% (p=0.001) in the rate of progressors (see table 2). This was not statistically different in patients treated with TCZ monotherapy (n=66 patients) compared with those on TCZ combination therapy with MMF or MTX (n=26

Table 2 Modification of parameters over time in patients with SSc treated with tocilizumab

Domain	Time points	Value (mean±SD or median (range))	P value	No. of patients
Lung				
% Predicted FVC in SSc-ILD	12 m prior→baseline	81±21→77±22	0.003	81
	Baseline→12 m	78±21→80±21	0.07	92
	Baseline→24 m	77±23→82±23	0.005	59
Skin mRSS in dcSSc	12 m prior→baseline	12±8→14±8	0.014	76
	Baseline→12 m	14±8→11±8	<0.001	84
	Baseline→24 m	14±8→9±8	<0.001	67
Joints				
Median TJC	12 m prior→baseline	2.5 (0–7.7)→5.5 (2–10.7)	<0.001	140
	Baseline→12 m	6 (2–12)→0 (0–2.7)	<0.001	111
	Baseline→24 m	5 (2–12)→0 (0–2)	0.008	69
Median SJC	12 m prior→baseline	0 (0–2)→0 (0–4)	<0.001	77
	Baseline→12 m	1 (0–4)→0 (0–4)	<0.001	70
	Baseline→24 m	2 (0–6)→0 (0–0)	<0.001	46
DAS28-CRP	12 m prior→baseline	3.1±1.9→3.7±1.9	<0.001	98
	Baseline→12 m	3.9±1.8→2.2±1.0	<0.001	66
	Baseline→24 m	4.1±1.7→2.0±0.9	0.040	44
Quality of life				
HAQ score	12 m prior→baseline	1.0 (0.37–1.28)→1.18 (0.63–1.56)	0.019	24
	Baseline→12 m	1.25 (0.66–1.56)→1.0 (0.5–1.5)	0.311	40
	Baseline→24 m	1.31 (0.90–1.75)→1.12 (0.72–1.53)	0.0471	24
Heart				
Troponin T	Baseline→12 m	39.2 (2.65–155)→6.8 (1.25–34.4)	0.003	15
	Baseline→24 m	65.0 (22–155)→4.6 (1.5–7.25)	0.018	7
NT-proBNP	Baseline→12 m	173 (58.2–648)→143.5 (68.7–618)	0.687	18
	Baseline→24 m	65 (41–243)→108 (51–123)	0.328	10
Ejection fraction (%)	Baseline→12 m	64 (59.5–68.3)→60 (60–65)	0.129	16
	Baseline→24 m	62 (60–66.7)→59 (53.7–61.5)	0.473	10
Arrhythmias requiring therapy (%)	Baseline→12 m	21→26	0.729	23
	Baseline→24 m	21→16	0.675	19
Steroids	Baseline→12 m	6.4±5.2→3.9±3.4	<0.001	114
	Baseline→24 m	6.6±5.3→3.1±2.9	<0.001	75

DAS28-CRP, Disease Activity Score in 28 joints using C reactive protein; dcSSc, diffuse cutaneous SSc; HAQ, Health Assessment Questionnaire; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SJC, swollen joint count; SSc-ILD, systemic sclerosis-associated interstitial lung disease; TJC, tender joint count.

patients): 74±21 to 76±23 (p=0.360) and 79±21 to 81±20 (p=0.145).

Among those with available PFTs at the three time points (12 months prior, baseline and 12 months after), the rate of progressors went from 43% (32 over 74) to 24% (18 over 74) (p=0.015). This was not significant when analysing only those on TCZ monotherapy (n=21 patients), as the rate of progressors went from 38% (8 over 21) to 23% (5 over 21) (p=0.317), whereas it was statistically significant in those on combination therapy: 43% (23 over 53) to 23% (12 over 53) (p=0.023).

An improvement in %pFVC was observed at 24 months, moving from 77±23 to 82±23 (p=0.005) in 59 patients. The number of progressors went from 22% at month 12 to 19% (10 over 53) at month 24 (p=0.680).

Of note, 13 patients (9%) were also receiving nintedanib at baseline; however, only four patients (3%) had both baseline and 12-month PFTs available for evaluation.

Cutaneous involvement

Among patients with dcSSc (n=126), mRSS moved from 12±8 at 12 months prior to TCZ introduction to 14±8 (p=0.014) at baseline, in 76 patients with available data. At 12 months after TCZ introduction, a significant decrease in mRSS was observed: from 14±8 to 11±8 (p<0.001) in 84 patients. Similarly, at 24 months, mRSS went from 14±8 to 9±8 (p<0.001) in 67 patients (see table 2). In patients with available data at the three time points (12 months prior, baseline and at 12 months after), mRSS went from 12±8 to 13±8 at baseline (p=0.021) and from 13±8 to 10±8 at 12 months (p<0.001) in 72 patients. When focusing on patients (n=28) with early (≤5 years) disease duration, we also confirmed a reduction in mRSS from 14±8 to 9±7 (p<0.001) and stabilisation from 12 to 24 months in 11 patients (8±4 vs 6±4, p=0.185). This was also confirmed when analysing patients on TCZ monotherapy (n=33) or on TCZ combination therapy (n=51) with MMF or MTX: 13±9 to 10±8 (p≤0.008) and 13±9 to 9±7 (p<0.001), respectively.

In addition, patients with ongoing digital ulcers remained stable at 24% in the 12 months prior to TCZ (p=0.99), while decreasing to 13% at month 12 (p=0.026) and to 9% from baseline to month 24 (p=0.001).

Arthritis

In patients with arthritis (n=156), median TJC and median SJC showed a significant reduction over time. In particular, at 12 months, TJC went from 6 (2–12) to 0 (0–2.7) (p<0.001) and SJC went from 1 (0–4) to 0 (0–0) (p<0.001). At 24 months, TJC went from 5 (2–12) to 0 (0–2) (p=0.040) and SJC went from 2 (0–6) to 0 (0–0) (p=0.008). DAS28-CRP had a significant worsening in the 12 months prior to TCZ, going from 3.1±1.9 to 3.7±1.9 at baseline (p<0.001) in the 77 patients with available scores. After 12 months on TCZ introduction, DAS28-CRP improved significantly from 3.9±1.8 to 2.2±1.0 (p<0.001) in 70 patients. The same result was observed at 24 months, from 4.1±1.7 to 2.0±0.9 (p<0.001, 46 patients) (see table 2).

Myocardial involvement

Patients with myocardial involvement at TCZ introduction were defined as those exhibiting primary cardiac abnormalities attributable to SSc, including myocardial fibrosis, inflammation or systolic/diastolic dysfunction on imaging (echocardiography and cardiac MRI if available), elevated cardiac biomarkers or clinically significant arrhythmias judged to be related to SSc involvement. Among these patients (n=31), excluding those with concomitant PAH, troponin T and NT-proBNP levels were analysed. Troponin T levels reduced significantly over time, going from 39.2 (2.65–155) ng/L at baseline to 6.8 (1.25–34.4) ng/L at 12 months (p=0.003), and from 65.0 (22.0–155.0) ng/L to 4.6 (1.5–7.25) ng/L at month 24 (p=0.018). NT-proBNP levels stabilised from 173 (58.2–648) ng/L at baseline to 143.5 (68.7–618) ng/L at month 12 (p=0.687), and from 65 (41–243) ng/L to 108 (51–123) ng/L at month 24 (p=0.328). A stabilisation was also seen in %EF calculated at echocardiography: from 64 (59.5–68.2) at baseline to 60 (60–65) at 12 months (p=0.129), and from 62 (60–66.7) to 59 (53.7–61.5) at 24 months (p=0.473). The percentage of patients with an EF <55% went from 15% in the 12 months prior to TCZ, to 23% at baseline (p=0.618), to then 18% at 12 months (p=0.626) in patients with available data at the three time points. The percentage of patients with arrhythmia requiring therapy was also investigated. Twelve months after TCZ introduction, it went from 21% at baseline to 26% (p=0.729), and at 24 months, it went from 21% at baseline to 15.7% (p=0.675), showing a stabilisation (see table 2).

Predictors of response

When analysing the predictors of response to TCZ in patients treated with TCZ for at least 6 months (n=171), a total of 53 patients (31%) suspended TCZ treatment and 29 patients (55%) due to inefficacy. At multivariate analysis, the presence of PAH (OR 6.239 (95% CI 1.322 to 29.450)) and age at TCZ introduction (1.043 (1.011 to 1.076)) were significantly associated with TCZ discontinuation due to inefficacy, while elevated baseline elevated CRP levels (0.175 (0.042 to 0.739)) were protective against treatment interruption (see online supplemental table 2s).

Of note, no differences were found in the rate of inefficacy when comparing TCZ monotherapy versus TCZ in combination with other immunosuppressants (10% vs 14.7%, p=0.494).

Safety and adverse events

The most common adverse events during the follow-up were infections (45 patients, 23%), the majority of them concerning the respiratory tract (38 patients; 84%) and urinary tract (nine patients; 19%). No cases of osteomyelitis or infected digital ulcers were recorded during

the follow-up period. Four patients (2%) experienced cardiac rhythm disorders, two of them having myocardial involvement also at baseline. No case of diverticulitis or herpes zoster virus reactivation was recorded. Three deaths were observed during the follow-up period. Treatment was suspended in 63 patients (32%) after a median time of 8 (4–22) months since the introduction. The main reason was inefficacy in 29 patients (46%), attributed to worsening of respiratory function, arthritis or skin fibrosis, either alone or concurrently. Infections accounted for treatment discontinuation in 12 patients (19%). No differences were found in the rate of adverse events when comparing TCZ monotherapy versus TCZ in combination with other immunosuppressants (21% vs 24%, p=0.709).

Changes in steroids and immunosuppressive therapies

Among patients on steroid therapy since baseline, a significant reduction in the mean steroids therapy was observed both at 12 (6.4±5.2 vs 3.9±3.4, p<0.001) and at 24 months (6.6±5.3→3.1±2.9, p<0.001). Moreover, only in seven patients an immunosuppressive therapy was introduced at 12 months (two MMF and four MTX), whereas at 24 months, only in one patient MTX was further introduced.

DISCUSSION

This large, multicentre French-Italian cohort study provides the most extensive real-world evaluation of TCZ in SSc to date, offering a multidomain assessment of its long-term effectiveness and safety across a heterogeneous population. Our results confirm that TCZ may stabilise or improve key disease manifestations such as ILD, inflammatory arthritis and skin involvement, and that it is well tolerated in routine clinical practice even when combined with other immunosuppressive therapies. Unlike prior RCTs[10 11] that focused on narrowly selected populations and on disease-specific outcomes, our cohort included patients with longer disease duration, multidomain involvement and background immunosuppression, better reflecting the complexity of daily care. Nonetheless, it must be pointed out that our population reflects the choice of the practitioners, includes a majority of patients with dcSSc, commonly having recent active skin, ILD or joint disease, as highlighted by the trajectory of the disease in these different domains in the year preceding TCZ introduction. Indeed, TCZ was introduced in patients with early inflammatory disease, as suggested by recent EULAR recommendations,[5] and in those presenting with a broader multidomain inflammatory profile. In line with several reports, physicians also treated a majority of topoisomerase I-positive patients. One key difference is the common use of synthetic immunosuppressants in association with TCZ. Our findings are in line with a previous real-world study reporting a potential multidomain efficacy of TCZ in SSc, including beneficial effects on skin and articular involvement.[19]

In addition, emerging data support the use of TCZ in combination with other immunosuppressive therapies and antifibrotic therapy, suggesting that combination strategies may be both effective and well tolerated in selected patients.[20–23] These observations further reinforce the relevance of our results in a real-world setting.

In SSc-ILD, where FVC decline is a known predictor of poor survival, we observed a stabilisation of %pFVC following TCZ introduction, after a period of prior decline. This was paralleled by a marked reduction in the proportion of patients meeting ILD progression criteria, with durable benefit up to 24 months. These findings echo the faSScinate and focuSSced trials,[10 11] where TCZ was shown to stabilise lung function, although in highly enriched populations with early, inflammatory disease. Our study extends these findings to a broader, less-selected cohort, supporting a role for TCZ even in patients with progressive ILD phenotypes and comorbidities. The lack of systematic follow-up HRCT scans limits conclusions on radiological progression but does not detract from the functional data observed. Moreover, as already pointed out, even in the majority of patients with SSc-ILD in our cohort, a combined treatment strategy (including TCZ plus MTX or MMF) was preferred, thus highlighting the need to carefully evaluate the role of TCZ combined treatment in future prospective studies. Additionally, the definition of ILD progression in this study was based solely on functional decline, as systematic data on symptoms and radiological progression were not available. This approach does not fully align with recent definitions of progressive pulmonary fibrosis and may have led to misclassification; therefore, analyses based on progressors should be considered exploratory. Moreover, the high prevalence of ATA positivity in our cohort reflects an ILD-enriched population and may limit the generalisability of these findings to other SSc subgroups, particularly those with different serological profiles.

With regard to skin involvement, we documented a statistically significant decline in mRSS over 24 months, mirroring the direction of change seen in the pivotal RCTs.[10 11] However, the magnitude of mRSS change did not reach the predefined threshold for clinical relevance of 5 points,[24 25] likely due to lower baseline mRSS and longer disease duration in our population. This is also consistent with current clinical practice: given the negative results of the phase III trials on skin involvement, TCZ is likely not routinely used with a focused skin-driven rationale in dcSSc. For this reason, it is expected that our cohort was not enriched for patients with only prominent cutaneous progression. Nonetheless, the interpretation of mRSS improvement should be cautious, as skin fibrosis in patients with SSc may improve over time independently of treatment. In this context, the favourable safety profile of TCZ, including in combination with immunosuppressive therapies, and the observation that some patients maintained disease control under TCZ monotherapy, represent clinically relevant findings.

A significant reduction in the prevalence of digital ulcers was also observed, suggesting a potential effect of TCZ on vascular manifestations, although this requires further exploration, but interestingly highlighting a role of IL-6 blockade in SSc-vasculopathy as already suggested by a previous study.[26]

In patients with SSc-associated inflammatory arthritis, the benefit of TCZ was also observed. Both TJC and SJC showed a significant improvement since TCZ introduction and this was also mirrored by a significant and durable decline in the DAS28-CRP, reinforcing TCZ's established role in inflammatory arthritis. Notably, MTX, still the only immunosuppressant specifically recommended for musculoskeletal involvement in the 2023 EULAR guidelines,[5] was the most frequent concomitant therapy in our study, highlighting that TCZ is commonly used in patients with both ILD and arthritis. This combination may reflect the need for multidomain disease control in clinical practice and supports the rationale for combining targeted biologics with conventional agents for articular involvement in SSc. Of note, the relatively low baseline joint counts observed in our cohort may reflect prior or concomitant immunosuppressive treatment and should be taken into account when interpreting the magnitude of improvement in articular outcomes.

We also explored cardiac parameters in patients with myocardial involvement. Troponin T levels significantly decreased over time, suggesting a possible impact of TCZ on myocardial inflammation. NT-proBNP levels, EF and arrhythmia burden remained stable, suggesting disease stabilisation. Unfortunately, the absence of cardiac MRI data precludes more definitive conclusions.

After 24 months, TCZ was discontinued in 32% of patients, mostly due to inefficacy or infections. Notably, PAH at baseline and age at TCZ introduction were independently associated with TCZ discontinuation, whereas elevated CRP levels predicted better persistence, in keeping with findings from post hoc analyses of RCTs. The association between PAH and TCZ discontinuation should, however, be interpreted with caution, given the wide CIs, which likely reflects the limited number of events in this subgroup. This is of crucial importance in clinical practice because it could be a first step for precision medicine in SSc. Indeed, whereas previous RCTs[10 11] selectively enrolled patients with SSc with an inflammatory phenotype, our real-life study supports the broader relevance of baseline CRP levels in predicting TCZ maintenance across the full spectrum of the disease. Moreover, in our cohort, neither disease duration nor ATA positivity was associated with treatment efficacy; but reinforce the role of CRP as a useful marker to guide physicians in the decision to initiate TCZ in patients with SSc. The lack of association between ATA positivity and lung response in our cohort should be interpreted with caution, as, predictably, there was a very high prevalence of ATA positivity among patients with SSc-ILD, which may have limited the ability to detect differences. Moreover, the real-world setting, with heterogeneous indications for TCZ initiation and frequent use of concomitant immunosuppressive therapies, particularly MMF, may have further contributed to this finding.

The overall safety profile was acceptable and consistent with prior studies.[10 11] Infections were the most frequent adverse event, particularly involving the respiratory tract, but the incidence was similar to that seen in RA cohorts.[27 28] No safety signal emerged regarding combination therapy, and discontinuation or adverse events were not significantly higher in patients receiving TCZ alongside immunosuppressants. Given the rheumatological background of all participating centres, clinicians were highly familiar with TCZ, and we did not observe any safety concerns beyond those already recognised in RA and giant cell arteritis. This likely is the result of a scrupulous selection of patients in whom the treating physicians anticipated a low risk of TCZ-related adverse effects, further contributing to the favourable safety profile observed in this cohort.

The real-world setting of our study allowed us to capture one of the key aspects of SSc management: the widespread use of combination therapy. In contrast to the faSScinate and focuSSced trials, where TCZ was administered as monotherapy, 71% of our cohort received it in combination with conventional immunosuppressants, most commonly MTX and MMF. This aligns with current clinical practice and with the therapeutic continuum proposed by the 2023 EULAR update,[5] which for the first time explicitly recommends TCZ for both ILD and skin fibrosis. However, EULAR recommendations remain organ-specific, reflecting the focus of past RCTs[10 11] on specific disease domains. Our data suggest that TCZ may offer broader multidomain benefits, particularly in patients with overlapping ILD and musculoskeletal involvement, thus potentially supporting the role of TCZ as a disease-modifying drug, especially when combined with conventional synthetic DMARDs such as MMF or MTX. This is further supported by the steroid-sparing effect of TCZ, which was shown in our cohort to have a significant impact on the mean steroid dose used. Another consideration in the real-world management of patients with SSc is the half-life of TCZ, which is significantly lower to other drugs such as RTX, and it is likely making TCZ one of the drugs of choice, thus further broadening its prescription in clinical practice.

Lastly, it should be noted that 13 patients (7%) in our cohort were also receiving nintedanib; however, the very limited number of patients (n=4) with available pulmonary function data at 12 months after TCZ initiation precluded any meaningful assessment of the potential effect of TCZ plus nintedanib combination therapy.

The study's main limitation is its retrospective design, and the absence of systematic HRCT or cardiovascular magnetic resonance follow-up, which restricts conclusions about structural changes in lung or heart. Skin improvements, although significant, did not reach the clinically meaningful threshold. Nonetheless, the real-world nature of this cohort enhances the validity of our findings. Also, pulmonary function data were not available for all patients at all

time points, which may have introduced selection bias and could have influenced the interpretation of lung function changes over time. Lastly, the absence of a control group represents a limitation of this study, as changes in mRSS and lung function may, at least in part, reflect the natural course of the disease rather than a direct treatment effect, although comparison with the pretreatment trajectory provides supportive evidence.

In conclusion, our study provides real-world evidence supporting the multidomain effectiveness of TCZ in SSc. The drug demonstrated long-term stabilisation of lung function, sustained improvement in arthritis, modest benefit on skin and some clues for effects on myocardial disease. These findings complement existing trial data and suggest that, when combined with background immunosuppressants, TCZ offers a valuable therapeutic option for patients with complex and progressive SSc.

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